The Synthesis of β-Heteroarylamino-α,β-dehydro-α-amino Acid Derivatives *via* Thiazolones

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2-Alkoxy-4-heteroarylaminomethylene-5(4*H*)-thiazolones **4** were converted with various nucleophiles into β-heteroarylamino-α,β-dehydro-α-amino acid derivatives **11, 14, 15, 16, 17, 18**, and **19**. Reduction of **4** with sodium borohydride in ethanol saturated with gaseous ammonia afforded the corresponding β-heteroarylamino substituted alanyl amides **20**. Thiazoledione derivative **7a** was transformed with sodium methoxide in methanol into 1-(4,6-dimethylpyrimidinyl-2)-4-mercaptocarbonylimidazol-2(3*H*)-one (**8a**).

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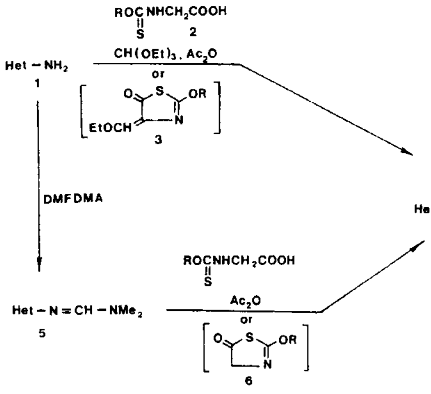
The synthesis of α,β-dehydro-α-amino acid derivatives and dipeptides are of considerable interest because of their pharmacological importance and as components of microbial metabolites [1-3].

Recently, heteroaryl substituted α,β-dehydro-α-amino acid derivatives have been prepared in our laboratory using either properly substituted 4-methylene-2-phenyl-5(4*H*)-oxazolone intermediates or methyl 2-benzoylamino-3-dimethylaminopropenoate which react with an amino or active methylene or potential methylene group [4-7]. However, one of the weak points is deprotection of the benzoylamino group, since the benzoyl group can be removed only under more drastic reaction conditions.

In order to avoid these difficulties, we selected the corresponding sulfur analogues. In this connection, 2-alkoxy-4-ethoxymethylene-5(4*H*)-thiazolones **3** were prepared *in situ* from *N*-alkoxythiocarbonylglycines **2a-d** and triethyl orthoformate in acetic anhydride [8]. These compounds react with heterocyclic amines **1** to give 2-alkoxy-4-heteroarylaminomethylene-5(4*H*)-thiazolones **4a-d** in good yields. Alternatively, compounds **4a-d** can be prepared from *N*-heteroarylformamidines **5** and 2-alkoxy-5(4*H*)-thiazolones **6** prepared *in situ* from *N*-alkoxythiocarbonylglycines **2** in acetic anhydride (Scheme 1).

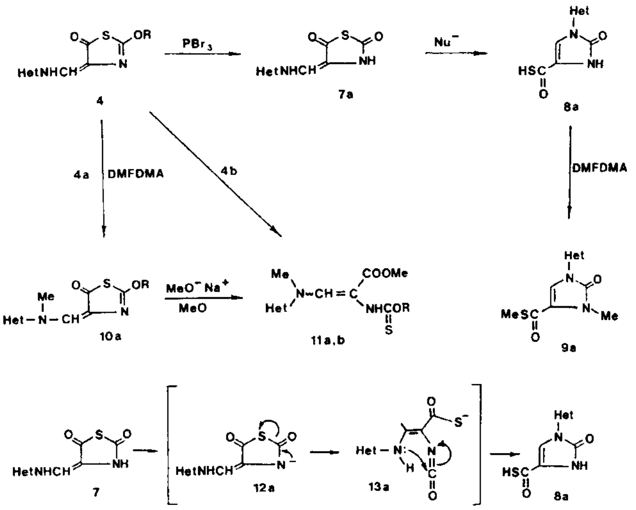
Scheme 1



4 a R = Me ; Het = 4,6 – dimethylpyrimidinyl – 2
b R = CH$_2$Ph ; Het = 4,6 – dimethylpyrimidinyl – 2
c R = Me ; Het = 4 – methylpyrimidinyl – 2
d R = Et ; Het = 4,6 – dimethylpyrimidinyl – 2

Compound **4a** reacts with phosphorus tribromide in pyridine resulting in the cleavage of the ether linkage producing thiazoledione derivative **7a**. This compound seems to be a suitable intermediate for the synthesis of α,β-dehydro-α-amino acid derivatives. However, the reactions with nucleophiles takes a different course. When compound **7a** is treated with methanol in the presence of potassium carbonate or sodium methoxide, ammonia in ethanol or hydrazine in ethanol, the same product is formed. It was shown on the basis of elemental analysis and ^{1}H nmr spectra to be 1-heteroarylimidazol-2-one-4-thiocarboxylic acid **8a**. This rearrangement can be explained with the formation of the anion **12a** followed by the S-C$_2$ bond cleavage and cyclization of the intermediary isocyanate **13a** into **8a**. Compound **8a** can be methylated with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) at the ring nitrogen atom and at the sulfur atom to give the ester **9a**. Similarly, the methylation of **4a** with DMFDMA gives the corresponding *N*-methyl derivative **10a**. This is then further transformed with sodim methoxide in methanol into methyl 2-alkoxythiocarbonylamino-(*N*-heteroaryl-*N*-methyl)propenoates **11a,b** (Scheme 2).

Scheme 2

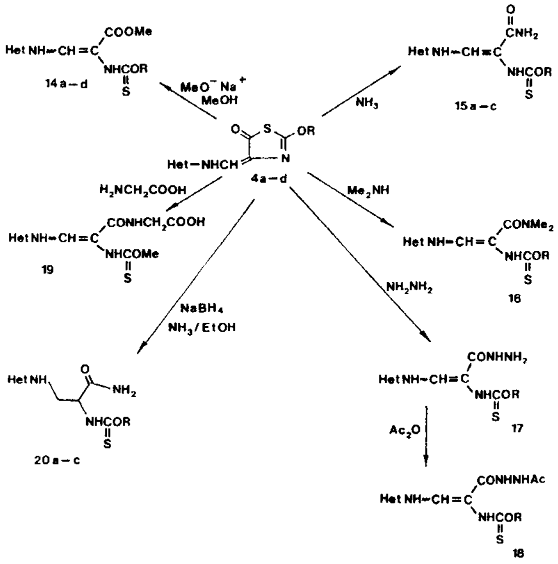


a R = Me ; Het = 4,6 – dimethylpyrimidinyl – 2
b R = CH$_2$Ph ; Het = 4,6 – dimethylpyrimidinyl – 2

Similarly, compounds **4a-d** react with sodium methoxide in methanol at room temperature to give esters **14a-d**. Other *N*-nucleophiles react analogously. For example, **4a**, with ammonia in methanol or tetrahydrofuran gives the corresponding amides **15a-c**, with dimethylamine the corresponding dimethylamide **16**, with hydrazine hydrate the hydrazide **17**, and **4a** and with glycine the dipeptide **19**.

Reduction of the exocyclic double bond in the compounds **4a-c** was successful only with sodium borohydride in ethanol saturated with ammonia to give the corresponding methyl β-heteroaryl substituted alanyl amides **20a-c** (Scheme 3).

Scheme 3



a R = Me ; Het = 4,6-dimethylpyrimidinyl-2
b R = CH₂Ph ; Het = 4,6-dimethylpyrimidinyl-2
c R = Me ; Het = 4-methylpyrimidinyl-2
d R = Et ; Het = 4,6-dimethylpyrimidinyl-2

The structures of the new compounds were determined by elemental analyses for C, H, and N, and by ^{1}H nmr spectra.

Further studies about the orientation of groups around the double bond in β-heteroarylamino-α,β-dehydro-α-amino acid derivatives **11, 14, 15, 16, 17, 18,** and **19** are in progress.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were recorded on a Varian E-360 spectrometer and microanalyses for C, H, and N on a Perkin-Elmer Analyser 2400.

N-(4,6-Dimethylpyrimidinyl-2)-*N,N*-dimethylformamidine (**5**) was prepared according to the procedure described in the literature [6].

4-(4,6-Dimethylpyrimidinyl-2)aminomethylene-2-methoxy-5(4*H*)-thiazolone (**4a**) was prepared according to the modified procedure described in the literature [9] for some pyridinyl derivatives [9].

Method a).

A mixture of equivalent amounts of 2-amino-4,6-dimethylpyrimidine (**1**) *N*-methoxythiocarbonylglycine **2** (R = Me) and triethyl orthoformate in acetic anhydride (5 ml/mmole) was heated in an oil bath at 110° for 3 hours. The volatile components were evaporated *in vacuo* and the solid residue recrystallized from ethanol to give **4a** in 78% yield, mp 178-180°; ^{1}H nmr (deuteriochloroform): δ 2.4 (s, 6H, 4'-Me, 6'-Me), 4.07 (s, 3H, OMe), 6.7 (s, 1H, 5'-H), 8.15-8.4 (m, 2H, N*H*C*H*).

Anal. Calcd. for $C_{11}H_{12}N_4O_2S$: C, 49.99; H, 4.58; N, 21.20. Found: C, 49.87; H, 4.63; N, 21.23.

Method b).

A mixture of equivalent amounts of *N'*-(4,6-dimethylpyrimidinyl-2)-*N,N*-dimethylformamidine (**5**) and methoxythiocarbonylglycine **2** (R = Me) in acetic anhydride (5 ml/mmole) was heated on an oil bath at 100° for 2 hours. The product was, after cooling, collected by filtration to give **4a** in 88% yield.

In this manner the following compounds were prepared:

2-Benzyloxy-4-(4,6-dimethylpyrimidinyl-2)aminomethylene-5(4*H*)-thiazolone (**4b**).

This compound was prepared from 2-amino-4,6-dimethylpyrimidine (**1**) and *N*-benzyloxythiocarbonylglycine **2** (R = CH₂Ph) according to method a) in 78% yield, 205-208° (from a mixture of DMF and ethanol); ^{1}H nmr (deuteriochloroform): δ 2.4 (s, 6H, 4'-Me, 6'-Me), 5.48 (s, 2H, CH₂), 6.7 (s, 1H, 5'-H), 7.45 (s, 5H, Ph), 8.2-8.4 (m, 2H, N*H*C*H*).

Anal. Calcd. for $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46. Found: C, 59.75; H, 4.68; N, 16.19.

4-(4-Methyl-2-pyrimidinylamino)methylene-2-methoxy-5(4*H*)-thiazolone (**4c**).

This compound was prepared from 2-amino-4-methylpyrimidine and *N*-methoxythiocarbonylglycine according to method a) in 68% yield, mp 185-188° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 2.48 (s, 3H, 4'-Me), 4.1 (s, 3H, OMe), 6.83 (d, 1H, 5'-H), 8.25 (m, 2H, N*H*C*H*), 8.38 (d, 1H, 6'-H), $J_{5'\text{-H},6'\text{-H}}$ = 5.5 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, 4.02; N, 22.47.

2-Ethoxy-4-(4,6-dimethyl-2-pyrimidinylamino)methylene-5(4*H*)-thiazolone (**4d**).

This compound was prepared from **1** according to method a) in 61% yield, mp 133-138° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.43 (t, 3H, CH₂C*H*₃), 2.40 (s, 6H, 4'-Me, 6'-Me), 4.54 (q, 2H, C*H*₂CH₃), 6.66 (s, 1H, 5'-H), 8.00 (d, 1H, N*H*CH), 8.22 (d, 1H, NHC*H*), J_{MeCH_2} = 7.1 Hz, J_{NHCH} = 12.5 Hz.

Anal. Calcd. for $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07; N, 20.13. Found: C, 51.91; H, 5.14; N, 20.53.

4-(4,6-Dimethylpyrimidinyl-2)aminomethylenethiazole-2,5-(3*H*,4*H*)-dione (**7a**).

To a suspension of **4a** (396 mg, 0.0015 mole) in chloroform (8 ml) phosphorus tribromide (0.27 ml) in pyridine (0.18 ml) was added and the mixture was left at room temperature for 1 hour. The solvent was evaporated *in vacuo*, ethanol (5 ml) was added to the residue, the suspension was heated to the boiling and the precipitate was collected by filtration to give **7a** in 67% yield, mp 230-240° (from a mixture of DMF and ethanol); ^{1}H nmr DMSO-

d_6): δ 2.38 (s, 6H, 4'-Me, 6'-Me), 6.9 (s, 1H, 5'-H), 7.77 (d, 1H, NHC*H*), 9.98 (d, 1H, N*H*CH), 10.55 (br s, 1H, NHCO), J_{NHCH} = 12.5 Hz.

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 48.28; H, 4.06; N, 22.41.

1-(4,6-Dimethylpyrimidinyl-2)-4-mercaptocarbonylimidazol-2(3*H*)-one (**8a**).

To a suspension of **7a** (250 mg, 0.001 mole) in methanol (8 ml) solid potassium carbonate (100 mg) was added and the mixture was stirred for 12 hours at room temperature. The precipitate was collected by filtration. The precipitate was dissolved in water and acidified with hydrochloric acid to *p*H 3. The precipitate was collected by filtration to give **8a** in 71% yield, mp 220° dec (from a mixture of ethanol and water; ^{1}H nmr DMSO-d_6): δ 2.45 (s, 6H, 4'-Me, 6'-Me), 3.25-3.80 (br s, 1H, COSH), 7.23 (s, 1H, 5'-H), 8.39 (s, 1H, 4-H), 11.48 (br s, 1H, NHCO); ms: m/e 250 (100%, M^+), 217 (90%, M^+-SH), 189 (15%, M^+-COSH).

Anal. Calcd. for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.02; N, 22.39. Found: C, 47.87; H, 4.09; N, 22.46.

1-(4,6-Dimethylpyrimidinyl-2)-3-methyl-4-methylmercaptocarbonylimidazo-2(3*H*)-one (**9a**).

A mixture of **8a** (125 mg, 0.0005 mole) and DMFDMA (0.15 ml) in toluene (4 ml) was heated under reflux for 1 hour. The product was purified by chromatothrone (silica gel and chloroform as eluent) to give **9a** in 56% yield, mp 150-155° (from a mixture of toluene and cyclohexane); ^{1}H nmr (deuteriochloroform): δ 2.45 (s, 3H, SMe), 2.55 (s, 6H, 4'-Me, 6'-Me), 3.55 (s, 3H, NMe), 6.95 (s, 1H, 5'-H), 8.12 (s, 1H, 5-H).

Anal. Calcd. for $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07; N, 20.13. Found: C, 52.08; H, 5.17; N, 20.09.

4-[*N*-Methyl-(4,6-dimethylpyrimidinyl-2)amino]methylene-2-methoxythiazol-5(4*H*)-one (**10a**).

A mixture of 4-(4,6-dimethylpyrimidinyl-2)aminomethylene-2-methoxythiazol-5(4*H*)-one **4a** (264 mg, 0.001 mole) and DMFDMA (0.15 ml) in toluene (5 ml) was heated under reflux for 3 hours. The solvent was evaporated *in vacuo* and the solid residue recrystallized from a mixture of DMF and ethanol to give **10a** in 48% yield, mp 184-185°; ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 6H, 4'-Me, 6'-Me), 3.97 (s, 3H, NMe), 4.07 (OMe), 6.7 (s, 1H, 5'-H), 8.88 (s, 1H, CH).

Anal. Calcd. for $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07; N, 20.13. Found: C, 51.62; H, 5.08; N, 20.19.

Methyl 3-[*N*-Methyl-(4,6-dimethylpyrimidinyl-2)amino]-2-methoxythiocarbonylaminopropenoate (**11a**).

A solution of **10a** (93 mg, 0.00033 mole) and sodium methoxide prepared from sodium (15 mg) in methanol (4 ml) was left at room temperature for 12 hours. The volume of the solution was reduced *in vacuo* to 1 ml, water (4 ml) was added and the mixture was adjusted to *p*H 4 with hydrochloric acid (10%). The precipitate was collected by filtration to give **11a** in 87% yield, mp 180-183° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 2.42 (s, 6H, 4'-Me, 6'-Me), 3.54 (s) and 3.59 (s) (3H each, NMe_2), 3.82 (s, 3H, COOMe), 4.04 and 4.08 (2 s, 3H, CSOMe), 6.7 (s, 1H, 5'-H), 7.77 (br s, 1H, NHCS), 8.92 and 9.05 (s, 1H, CH).

Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.31; H, 5.85; N, 18.05. Found: C, 50.19; H, 5.93; N, 18.12.

Methyl 2-Benzyloxythiocarbonylamino-3-[(*N*-methyl-(4,6-dimethylpyrimidinyl-2)amino]propenoate (**11b**).

A mixture of **4b** (340 mg, 0.001 mole), and DMFDMA (0.15 ml) in toluene (5 ml) was heated under reflux for 3 hours. The solvent was evaporated *in vacuo*. A solution of sodium methoxide, prepared from sodium (25 mg) in methanol (5 ml) was added and the mixture was left at room temperature for 24 hours. Water (15 ml) was added and the solution was adjusted to *p*H 5 with hydrochloric acid (10%). The precipitate was collected by filtration to give **11b** in 82% yield, mp 175-178° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): δ 2.34 (s, 6H, 4'-Me, 6'-Me), 3.67 (s, 3H, CSOMe), 6.82 (s, 1H, 5'-H), 8.38 (d, 1H, NHC*H*), 9.5-9.85 (m, 2H, N*H*CH, NHCS), J_{NHCH} = 12.5 Hz.

Anal. Calcd. for $C_{12}H_{16}N_4O_3S$: C, 48.64; H, 5.44; N, 18.91. Found: C, 48.87; H, 5.52; N, 19.11.

Methyl 3-Heteroarylamino-2-methoxythiocarbonylaminopropenoates.

General Procedure.

A mixture of 4-heteroarylamino-2-alkoxy-5(4*H*)-thiazolone (**4**, 0.01 mole) and sodium methoxide, prepared from sodium (300 mg) in methanol (70 ml) was stirred at room temperature for two hours. Water (50 ml) was added and the mixture was acidified with hydrochloric acid (10%) to *p*H 5. The precipitate was collected by filtration and recrystallized from apropriate solvent.

In this manner the following compounds were prepared:

Methyl 3-(4,6-Dimethylpyrimidinyl-2)amino-2-methoxythiocarbonylaminopropenoate (**14a**).

This compound was prepared from **4a** in 82% yield, mp 175-178° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): δ 2.34 (s, 6H, 4-Me, 6-Me), 3.67 (s, 3H, CSOMe), 6.82 (s, 1H, 5'-H), 8.38 (d, 1H, NHC*H*), 9.5-9.85 (m, 2H, N*H*CH, NHCS), J_{NHCH} = 12.5 Hz.

Anal. Calcd. for $C_{12}H_{16}N_4O_3S$: C, 48.64; H, 5.44; N, 18.91. Found: C, 48.87; H, 5.52; N, 19.11.

Methyl 2-Benzyloxythiocarbonylamino-3-(4,6-dimethylpyrimidinyl-2)aminopropenoate (**14b**).

This compound was prepared from **4b** in 92% yield, mp 147-150° (from a mixture of ethanol and water); ^{1}H nmr (deuteriochloroform): δ 2.4 (s, 6H, 4'-Me, 6'-Me), 3.8 (s, 3H, COOMe), 5.52 (s, 3H, CH_2), 6.68 (s, 5'-H), 7.4 (s, 5H, Ph), 7.8 (br d, 2H, NHC*H*, NHCS), 8.62 (d, 1H, N*H*CH), J_{NHCH} = 12.5 Hz.

Anal. Calcd. for $C_{18}H_{20}N_4O_3S$: C, 58.05; H, 5.41; N, 15.04. Found: C, 58.35; H, 5.72; N, 15.35.

Methyl 3-(4-Methylpyrimidinyl-2)amino-2-methoxythiocarbonylaminopropenoate (**14c**).

This compound was prepared from **4c** in 73% yield, mp 165-166° (from 1-propanol); ^{1}H nmr (deuteriochloroform): δ 2.45 (s, 3H, 4'-Me), 3.8 (s, 3H, COOMe), 6.8 (d, 1H, 5'-H), 7.5-8.0 (m, 2H, N*H*CH, N*H*CS), 8.35 (d, 1H, 6'-H), 8.65 (d, 1H, NHC*H*), J_{H_5,H_6} = 5.5 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd. for $C_{11}H_{14}N_4O_3S$: C, 46.80; H, 5.00; N, 19.84. Found: C, 46.85; H, 5.10; N, 19.56.

Methyl 3-(4,6-Dimethylpyrimidinyl-2)amino-2-ethoxythiocarbonylaminopropenoate (**14d**).

This compound was prepared from **4d** in 68% yield, mp 135-140° (from a mixture of ethanol and water); ^{1}H nmr (deuteriochloroform): δ 1.33 (t, 3H, *Me*CH_2), 2.38 (s, 6H, 4'-Me, 6'-Me), 3.80 (s, 3H, COOMe), 4.52 (q, 2H, Me*C*H_2), 6.64 (s, 1H, 5'-H), 7.42-7.96

(br s, 1H, NHCS), 7.66 (d, 1H, N*H*CH), 8.56 (d, 1H, NHC*H*), J_{MeCH_2} = 7.08 Hz, J_{NHCH} = 13.0 Hz.

Anal. Calcd. for $C_{13}H_{18}N_4O_3S$: C, 50.31; H, 5.85; N, 18.05. Found: C, 50.50; H, 5.90; N, 18.52.

3-Heteroarylamino-2-methoxythiocarbonylpropenoic Acid Amides.

General Procedure.

Heteroarylaminomethylene-2-alkoxy-5(4*H*)-thiazolone (0.001 mole) was suspended in ethanol saturated with ammonia (10 ml) and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated *in vacuo* and the solid residue was recrystallized from appropriate solvent.

In this manner the following compounds were obtained:

3-(4,6-Dimethylpyrimidinyl-2)amino-2-methoxythiocarbonylpropenoic Acid Amide (**15a**).

This compound was prepared from **4a** in 71% yield, mp 185-187° (from 1-propanol); ^{1}H nmr (DMSO-d$_6$): δ 2.3 (s, 6H, 4'-Me, 6'-Me), 6.8 (br s, 3H, CONH$_2$, 5'-H), 8.22 (d, 1H, NHC*H*), 9.05 (d, 1H, N*H*CH), 9.45-9.65 (br s, 1H, NHCS), J_{NHCH} = 12.5 Hz.

Anal. Calcd. for $C_{11}H_{15}N_5O_2S$: C, 46.97; H, 5.38; N, 24.90. Found: C, 47.16; H, 5.53; N, 25.01.

2-Benzyloxycarbonylamino-3-(4,6-dimethylpyrimidinyl-2)aminopropenoic Acid Amide (**15b**).

This compound was prepared from **4b** in 53% yield, mp 179-182° (from ethanol); ^{1}H nmr (DMSO-d$_6$): δ 2.33 (s, 6H, 4'-Me, 6'-Me), 5.44 (s, 2H, CH$_2$), 6.76 (s, 1H, 5'-H), 6.7-6.9 (br s, 2H, CONH$_2$), 7.3-7.5 (m, 5H, Ph), 8.2 (d, 1H, N*H*CH), 9.08 (d, 1H, N*H*CH), J_{NHCH} = 12.2 Hz.

Anal. Calcd. for $C_{17}H_{19}N_5O_2S$: C, 57.13; H, 5.36; N, 19.59. Found: C, 57.03; H, 5.44; N, 19.88.

3-(4-Methylpyrimidinyl-2)amino-2-methoxythiocarbonylaminopropenoic Acid Amide (**15c**).

This compound was prepared from **4c** in 30% yield, mp 190-191° (from ethanol); ^{1}H nmr (DMSO-d$_6$): δ 2.4 (s, 3H, 4'-Me), 4.95 (s, 3H, CSOMe), 6.8 (br s, 2H, CONH$_2$), 6.95 (d, 1H, 5'-H), 8.25 (d, 1H, NHC*H*), 8.45 (d, 1H, 6'-H), 9.2 (d, 1H, N*H*CH), 9.7 (br s, 1H, N*H*CS), J_{H_5,H_6} = 5.0 Hz, J_{NHCH} = 12.4 Hz.

Anal. Calcd. for $C_{10}H_{13}N_5O_2S$: C, 44.93; H, 4.90; N, 26.20. Found: C, 45.03; H, 5.18; N, 26.30.

N,N-Dimethyl 3-(4,6-Dimethylpyrimidinyl-2)amino-2-methoxythiocarbonylaminopropenoic Acid Amide (**16**).

A mixture of compound **4a** (264 mg, 0.001 mole) and a solution of dimethylamine (33% in methanol, 3 ml) was left at room temperature for 1 hour. The precipitate was collected by filtration to give **16** in 64% yield, mp 167-170° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d$_6$): δ 2.32 (s, 6H, 4'-Me, 6'-Me), 2.95 (s, 6H, NMe$_2$), 3.92 (s, 3H, CSOMe), 6.75 (s, 1H, 5'-H), 7.35 (d, 1H, NHC*H*), 9.15 (d, 1H, N*H*CH), 10.17 (br s, 1H, N*H*CS), J_{NHCH} = 11.0 Hz.

Anal. Calcd. for $C_{13}H_{19}N_5O_2S$: C, 50.47; H, 6.19; N, 22.64. Found: C, 50.60; H, 6.28; N, 22.91.

2-Benzyloxythiocarbonylamino-3-(4,6-dimethylpyrimidinyl-2)aminopropenoic Acid Hydrazide (**17**).

To a mixture of **4b** (340 mg, 0.001 mole) in chloroform (6 ml) and ethanol (1 ml) hydrazine hydrate (80%, 0.1 ml) was added and the mixture was left at room temperature for 1 hour. The precipitate was then collected by filtration to give **17** in 75% yield, mp 196-199° (from a mixture of DMF and ethanol), ^{1}H nmr (DMSO-d$_6$): δ 2.32 (s, 6H, 4'-Me, 6'-Me), 3.35 (br s, 3H, H$_2$O, CON*H*NH$_2$), 4.00-4.44 (br s, 2H, CONHN*H*$_2$), 5.43 (s, 2H, CH$_2$), 6.75 (s, 1H, 5'-H), 7.27-7.51 (m, 5H, Ph), 8.15 (d, 1H, N*H*CH), 8.56-8.76 (br s, 1H, NHCS), 9.07 (d, 1H, HN*H*CH), J_{NHCH} = 12.0 Hz.

Anal. Calcd. for $C_{17}H_{20}N_6O_2S$: C, 54.82; H, 5.41; N, 22.56. Found: C, 54.82; H, 5.52; N, 22.25.

N'-Acetyl-2-benzyloxythiocarbonylamino-3-(4,6-dimethylpyrimidinyl-2)aminopropenoic Acid Hydrazide (**18**).

A mixture of **17** (186 mg, 0.0005 mole) and acetic anhydride (4 ml) was left at room temperature for 30 minutes. The precipitate was collected by filtration to give **18** in 83% yield, mp 207-210° (from ethanol); ^{1}H nmr (DMSO-d$_6$): δ 1.86 (s, 3H, COMe), 2.34 (s, 6H, 4'-Me, 6'-Me), 5.44 (s, 2H, CH$_2$), 6.78 (s, 1H, 5'-H), 7.27-7.40 (m, 5H, Ph), 8.24 (d, 1H, NHC*H*), 9.04-9.48 (m, 2H, N*H*CH, NHCS), 9.64-9.83 (m, 2H, CONHHNCO), J_{NHCH} = 12.2 Hz.

Anal. Calcd. for $C_{19}H_{22}N_6O_3S$: C, 55.06; H, 5.36; N, 20.28. Found: C, 55.31; H, 5.48; N, 20.58.

3-(4,6-Dimethylpyrimidinyl-2)amino-*N*-carboxymethyl-2-methoxythiocarbonylaminopropenoic Acid Amide (**19**).

A mixture of **4a** (194 mg, 0.0008 mole), glycine (60 mg, 0.0008 mole) and sodium carbonate (106 mg, 0.001 mole) in acetonitrile (5 ml) and water (2 ml) was heated under reflux for 2 hours. The solvents were evaporated, water (5 ml) was added to the residue and the solution was adjusted with hydrochloric acid (10%) to *p*H = 5. The precipitate was collected by filtration and washed with water to give **19** in 43% yield, mp 150-153° (from a mixture of DMF and water); ^{1}H nmr (DMSO-d$_6$): δ 2.32 (s, 4'-Me, 6'-Me), 3.70-4.00 (m, 6H, CH$_2$, CSOMe, NHCS), 6.80 (s, 1H, 5'-H), 7.40-7.70 (t, 1H, CONHCH$_2$), 8.22 (d, 1H, NHC*H*), 9.18 (d, 1H, N*H*CH), 9.70 (br s, 1H, COOH), J_{NHCH_2} = 5.5 Hz, J_{NHCH} = 12.5 Hz.

Anal. Calcd. for $C_{13}H_{17}N_5O_4S$: C, 46.01; H, 5.05; N, 20.64. Found: C, 45.73; H, 5.26; N, 20.37.

The Synthesis of β-Heteroarylamino-α-aminopropanoic Acid Amides.

General Procedure.

To a solution of **4** (0.001 mole) in ethanol saturated with gaseous ammonia (10 ml) sodium borohydride (50 mg, 0.0013 mole) was added. The suspension was stirred at room temperature for 24 hours. The precipitate was collected by filtration and recrystallized from an appropriate solvent.

In this manner the following compounds were prepared:

3-(4,6-Dimethylpyrimidinyl-2)amino-2-methoxythiocarbonylaminopropanecarboxamide (**20a**).

This compound was prepared from **4a** in 48% yield, mp 215° (from ethanol); ^{1}H nmr (DMSO-d$_6$): δ 2.21 (s, 6H, 4'-Me, 6'-Me), 3.63 (dd, 2H, CHCH$_2$), 3.87 (s, 3H, OMe), 4.63 (t, 1H, C*H*CH$_2$), 6.1-6.4 (br s, 2H, CONH$_2$), 6.36 (s, 1H, 5'-H), 6.47-7.01 (m, 2H, NHCH$_2$, NHCS), J_{CHCH} = 5.7 Hz.

Anal. Calcd. for $C_{11}H_{17}N_5O_2S$: C, 46.63; H, 6.05; N, 24.72. Found: C, 46.97; H, 6.00; N, 24.83.

2-Benzoyloxythiocarbonylamino-3-(4,6-dimethylpyridinyl-2)aminopropanecarboxamide (**20b**).

This compound was prepared from **4b** in 72% yield, mp 227-229° (from a mixture of DMSO and water); ^{1}H nmr (DMSO-d_6): δ 2.22 (s, 4'-Me, 6'-Me), 3.5-3.8 (m, 2H, $CHCH_2$), 4.35-4.85 (m, 1H, $\mathrm{C}H\mathrm{CH_2}$), 5.45 (s, 2H, CH_2), 6.42 (s, 1H, 5'-H), 6.8-7.35 (m, 3H, $\mathrm{CON}H_2$, $\mathrm{N}H\mathrm{CH_2}$), 7.45 (br s, 5H, Ph), 9.6-9.8 (m, 1H, NHCS).

Anal. Calcd. for $C_{17}H_{21}N_5O_2S$: C, 56.81; H, 5.87; N, 19.48. Found: C, 56.78; H, 6.02; N, 19.59.

2-Methoxythiocarbonylamino-3-(4-methylpyrimidinyl-2)aminopropanecarboxamide (**20c**).

This compound was prepared from **4c** in 57% yield, mp 208-210° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 2.25 (s, 3H, 4'-Me), 3.5-3.8 (s, 3H, 4'-Me), 3.5-3.8 (s, 3H, CSOMe), 4.55-4.80 (m, 1H, $\mathrm{C}H\mathrm{CH_2}$), 6.52 (d, 1H, 5'-H), 6.7-7.05 (t, 1H, $\mathrm{N}H\mathrm{CH_2}$), 7.15 (br s, 1H, $CONH_2$), 7.4 (br s, 1H, $CONH_2$), 8.18 (d, 1H, 6'-H), 8.8-9.6 (br s, 1H, NHCSOMe).

Anal. Calcd. for $C_{10}H_{15}N_5O_2S$: C, 44.60; H, 5.61; N, 26.00. Found: C, 44.68; H, 5.64; N, 25.89.

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