Synthesis of 2,4-Dioxo-, 2-Oxo-4-thioxo-, 4-Oxo-, and 4-Thioxo-pyrimidine-5-carbonitriles

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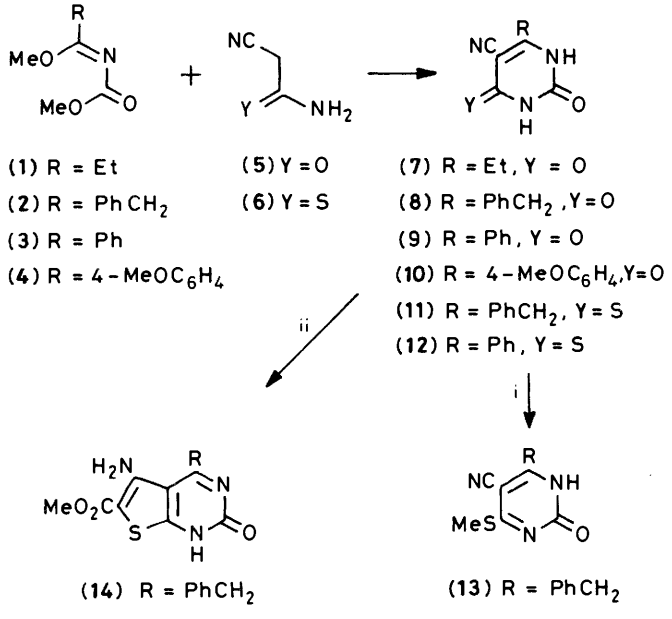
Methyl *N*-methoxycarbonylimidates (**1**)—(**4**) cyclized readily with 2-cyanoacetamide (**5**) or 2-cyanoethanethioamide (**6**) to 2,4-dioxopyrimidine-5-carbonitriles (**7**)—(**10**) or 2-oxo-4-thioxopyrimidine-5-carbonitriles (**11**) and (**12**). In analogous reactions with alkyl *N*-acylimidates (**15**)—(**19**) 4-oxopyrimidine-5-carbonitriles (**20**)—(**23**) or 4-thioxopyrimidine-5-carbonitrile (**24**) were obtained. Representatives of 4-thioxopyrimidine-5-carbonitriles (**11**), (**24**) were methylated to 4-methylthiopyrimidine-5-carbonitriles (**13**) and (**25**) or cyclized with methyl chloroacetate to give methyl thieno[2,3-*d*]pyrimidine-6-carboxylates (**14**) and (**26**)

N-Acylamides can be modified to enhance the reactivity of one carbonyl group so as to achieve regioselectivity under dinucleophilic attack. Although the synthetic utility of some modified *N*-acylamides, such as *N*-acylamidines,[1,2] *N*-thioacylamides,[3] and a *N*-acylcarbamimidoyl chloride,[4] is of current interest, the synthetic potential of alkyl *N*-acylimidates remains almost unexplored.[5] We have already studied the regioselective cyclization of alkyl *N*-acylimidates with hydrazines and hydroxylamine.[6] Now we wish to communicate the reaction of these compounds with 2-cyanoacetamide and 2-cyanoethanethioamide to afford substituted 4-oxo- and 4-thioxo-pyrimidine-5-carbonitriles.

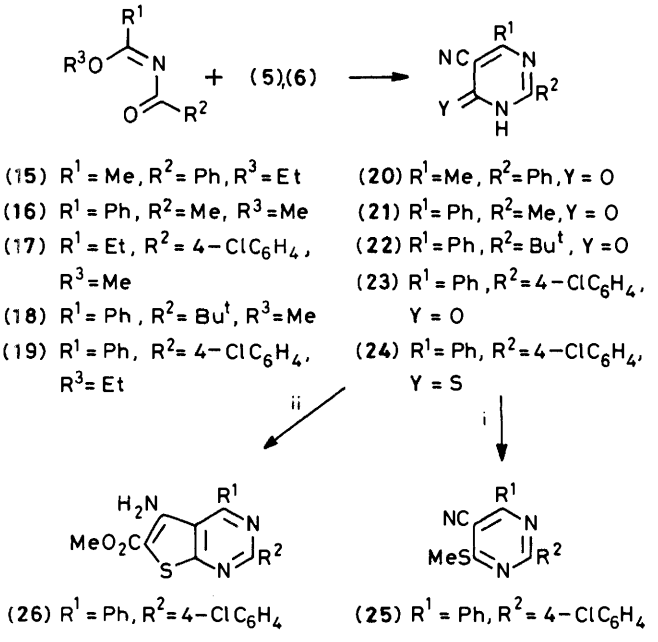
Results and Discussion

Methyl *N*-(methoxycarbonyl)imidates (**1**)—(**4**) were prepared from methyl imidates and an excess of methyl chloroformate in refluxing dry hexane in the presence of 2,4,6-trimethylpyridine.[6] Less sterically hindered bases reacted with methyl chloroformate.

By refluxing equimolar amounts of the methyl *N*-methoxycarbonylimidates (**1**)—(**4**) and 2-cyanoacetamide (**5**) with 1.1 molar equivalents of sodium methoxide in dry methanol, the 2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**7**)—(**10**) were obtained in good to excellent yields. An analogous reaction of the methyl *N*-(methoxycarbonyl)imidates (**2**) and (**3**) and 2-cyanoethanethioamide (**6**) afforded the yellow 2-oxo-4-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**11**) and (**12**) after a simple work-up. Methylation of the sodium salt of the 2-oxo-4-thioxopyrimidine-5-carbonitrile (**11**) with an excess of iodomethane yielded the colourless 4-methylthio-2-oxo-1,2-dihydropyrimidine-5-carbonitrile (**13**). On the other hand, the reaction of the sodium salt of the pyrimidine (**11**) with methyl chloroacetate led to the methyl 5-amino-2-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylate (**14**) *via* nucleophilic substitution and intramolecular cyclization.



Reagents: i, MeS; ii, $ClCH_2CO_2Me$



Reagents: i, MeS; ii, $ClCH_2CO_2Me$

Alkyl *N*-acylimidates (**15**)—(**19**) were obtained by a reported procedure.[6,7] The reaction of equimolar amounts of these imidates, 2-cyanoacetamide (**5**), and sodium methoxide in methanol afforded the 4-oxo-3,4-dihydropyrimidine-5-carbonitriles (**20**)—(**23**). A similar cyclocondensation of the imidate (**19**) and 2-cyanoethanethioamide (**6**) with an excess of sodium methoxide led to the yellow 4-thioxo-3,4-dihydropyrimidine-5-carbonitrile (**24**). On treating a solution of the sodium salt of

(**24**) with an excess of iodomethane at room temperature the colourless 4-methylthiopyrimidine-5-carbonitrile (**25**) was obtained. The sodium salt of the pyrimidine (**24**) cyclized with methyl chloroacetate to the methyl 5-aminothieno[2,3-*d*]-pyrimidine-6-carboxylate (**26**). The structure of the products was established on the basis of spectral evidence. The structure of several pyrimidines was also further confirmed by comparison with known representatives.[8-12] The yellow methyl 5-aminothieno[2,3-*d*]pyrimidine-6-carboxylates (**14**) and (**26**) showed a strong fluorescence. Low ester carbonyl stretching frequencies around 1 660 cm^{-1} were found in the i.r. spectra of both compounds as a result of intramolecular hydrogen bonding with the *ortho* amino group.

Experimental

U.v. spectra were recorded for ethanol solutions on a Perkin Elmer 124 spectrophotometer. I.r. spectra were obtained as KBr pellets on a Perkin Elmer 257 spectrophotometer. ^1H N.m.r. spectra were recorded on a Varian T-60A spectrometer with $SiMe_4$ as an internal standard in the solvents as indicated. The alkyl *N*-acylimidates (**15**), (**16**), and (**19**) were prepared as reported.[6]

Preparation of Methyl N-*Methoxycarbonylimidates* (**1**)—(**4**).—A mixture of the appropriate methyl imidate (0.15 mol), methyl chloroformate (21.27 g, 0.225 mol), and 2,4,6-trimethylpyridine (24.24 g, 0.20 mol) in dry hexane (100 ml) was refluxed for 24 h. The precipitate was filtered off and washed with hexane (200 ml). The combined filtrates were evaporated and the residue was distilled to yield the following methyl *N*-(methoxycarbonyl)imidates (**1**)—(**4**). Methyl *N*-methoxycarbonylpropanimidate (**1**) (57%), b.p. 65—67 °C/18 mbar; $\delta_H(CDCl_3)$ 1.13 (3 H, t, *J* 7.6 Hz, Me), 2.37 (2 H, q, *J* 7.6 Hz, CH_2), 3.62 (3 H, s, MeO), and 3.67 (3 H, s, MeO) [lit.,[13] δ_H 1.16 (3 H, t, *J* 7.9 Hz), 2.37 (2 H, q, *J* 7.9 Hz), 3.68 (3 H, s), and 3.71 (3 H, s)]. *Methyl* N-*methoxycarbonyl*-2-*phenylethanimidate* (**2**) (51%), b.p. 86—88 °C/0.03 mbar (Found: C, 64.1; H, 6.2; N, 6.6. $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.3; N, 6.8%); $\nu_{max.}$ 1 710 (CO) and 1 660 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 3.49, 3.50 (6 H, 2 s, 2 MeO), 3.55 (2 H, s, CH_2), and 6.93 (5 H, s, ArH). *Methyl* N-*methoxycarbonylbenzenecarboximidate* (**3**) (76%), b.p. 72—74 °C/0.03 mbar (Found: C, 62.3; H, 5.6; N, 7.4. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.3%); $\nu_{max.}$ 1 710 (CO) and 1 660 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 3.57 (3 H, s, MeOCO), 3.77 (3 H, s, MeOC=N), and 7.1—7.5 (5 H, m, ArH). *Methyl* 2-*methoxy*-N-*methoxycarbonylbenzenecarboximidate* (**4**) (62%), b.p. 134—136 °C/0.4 mbar (Found: C, 59.3; H, 5.8; N, 6.4. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.9; N, 6.3%); $\nu_{max.}$ 1 720 (CO) and 1 660 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 3.63 (3 H, s, MeO), 3.73 (3 H, s, MeO), 3.80 (3 H, s, MeO), and 6.6—7.4 (4 H, m, ArH).

Preparation of 2,4-*Dioxo*-1,2,3,4-*tetrahydropyrimidine*-5-*carbonitriles* (**7**)—(**10**).—A solution of methyl *N*-methoxycarbonylimidate (**1**)—(**4**) (10 mmol), 2-cyanoacetamide (**5**) (0.85 g, 10 mmol), and sodium methoxide (11 mmol) in dry methanol (30 ml) was heated under reflux for 12 h. To the reaction mixture at room temperature concentrated (*ca.* 18 molar) sulphuric acid (0.5 ml, *ca.* 9 mmol) was added and the solvent was evaporated. The residue was washed with water (200 ml), collected by filtration, and recrystallized to yield the following 2,4-dioxopyrimidine-5-carbonitriles (**7**)—(**10**). 2,4-Dioxo-6-ethyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**7**) (43%), m.p. 284—285 °C (from ethanol) (lit.,[8] m.p. 280—281 °C); $\nu_{max.}$ 3 200—3 040 (NH + OH), 2 230 (conj. CN), and 1 710 and 1 660 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 1.20 (3 H, t, *J* 7.0 Hz, Me), 2.50 (2 H, q, *J* 7.0 Hz, CH_2), and 11.36 (2 H, br s, NH + OH, exchangeable). 6-*Benzyl*-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimidine*-5-*carbonitrile* (**8**) (93%), m.p. 259—260 °C (from ethanol) (Found: C, 63.3; H, 3.7; N, 18.5. $C_{12}H_9N_3O_2$ requires C, 63.4; H, 4.0; N, 18.5%); $\nu_{max.}$ 3 330—2 700 (NH + OH), 2 230 (conj. CN), and 1 700 and 1 650 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 3.80 (2 H, s, CH_2), 7.17 (5 H, s, Harom), and 11.4 (2 H, br s, NH + OH, exchangeable). 2,4-Dioxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**9**) (98%), m.p. 297—299 °C (from methanol) (lit.,[9] m.p. 296—298 °C). 6-(4-*Methoxyphenyl*)-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimidine*-5-*carbonitrile* (**10**) (90%), m.p. 333—334 °C (from ethanol) (Found: C, 59.1; H, 3.4; N, 17.2. $C_{12}H_9N_3O_3$ requires C, 59.2; H, 3.7; N, 17.3%); $\nu_{max.}$ 3 110, 3 000, and 2 810 (NH + OH), 2 240 (conj. CN), and 1 735 and 1 670 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 3.85 (3 H, s, MeO), 7.36 (4 H, m, ArH), and 11.7 (2 H, br s, NH + OH, exchangeable).

Preparation of 2-*Oxo*-4-*thioxo*-1,2,3,4-*tetrahydropyrimidine*-5-*carbonitriles* (**11**) *and* (**12**).—A solution of methyl *N*-methoxycarbonylimidate (**2**) and (**3**) (10 mmol), 2-cyanoethanethioamide (**6**) (1.0 g, 10 mmol), and sodium methoxide (11 mmol) in dry methanol (30 ml) was refluxed for 12 h. To the reaction mixture at room temperature concentrated (*ca.* 18 molar) sulphuric acid (0.5 ml, *ca.* 9 mmol) was added and the solvent was evaporated. The residue was washed with water (200 ml), collected by filtration, and recrystallized to yield the following 2-oxo-4-thioxopyrimidine-5-carbonitriles (**11**) and (**12**) 6-*Benzyl*-2-*oxo*-4-*thioxo*-1,2,3,4-*tetrahydropyrimidine*-5-*carbonitrile* (**11**) (78%), m.p. 256—258 °C (decomp.) (from ethanol–water) (Found: C, 59.0; H, 3.7; N, 17.6; S, 13.3. $C_{12}H_9N_3OS$ requires C, 59.2; H, 3.7; N, 17.3; S, 13.2%); $\nu_{max.}$ 3 180 (NH), 2 240 (conj. CN), and 1 740 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 3.93 (2 H, s, CH_2), 7.3 (5 H, s, ArH), and 12.9 (2 H, br s, NH + OH, exchangeable). 2-Oxo-6-phenyl-4-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**12**) (35%), m.p. 290—291 °C (decomp.) (from dioxane) [lit.,[10] m.p. 291 °C (decomp.)].

Preparation of 6-*Benzyl*-4-*methylthio*-2-*oxo*-1,2-*dihydropyrimidine*-5-*carbonitrile* (**13**).—To a solution of the 4-thioxopyrimidine (**11**) 0.73 g, 3 mmol) and sodium methoxide (3 mmol) in dry methanol (15 ml), iodomethane (0.71 g, 5 mmol) was added. The mixture was stirred for 6 h at room temperature. The precipitate thus formed was collected, washed with water, and recrystallized from methanol to yield 4-*methylthiopyrimidine* (**13**) (0.54 g, 70%), m.p. 279—280 °C (decomp.) (Found: C, 60.5; H, 4.6; N, 16.6. $C_{13}H_{11}N_3OS$ requires C, 60.7; H, 4.3; N, 16.3%); $\nu_{max.}$ 3 150—2 400 (NH + OH), 2 220 (conj. CN) and 1 650 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 2.53 (3 H, s, MeS), 4.00 (2 H, s, CH_2), and 7.33 (3 H, s, ArH).

Preparation of Methyl 5-*Amino*-4-*benzyl*-2-*oxo*-1,2-*dihydrothieno*[2,3-d]*pyrimidine*-6-*carboxylate* (**14**).—To a solution of the 4-thioxopyrimidine (**11**) (0.49 g, 2 mmol) and sodium methoxide (4 mmol) in dry methanol (10 ml), methyl chloroacetate (0.22 g, 2 mmol) was added. The mixture was heated under reflux for 24 h. To the reaction mixture at room temperature concentrated (*ca.* 18 molar) sulphuric acid (0.1 ml, *ca.* 1.8 mmol) was added. The precipitate was collected and washed with water, methanol, and diethyl ether to yield the *thieno*[2,3-d]*pyrimidine* (**14**) (0.34 g, 54%), m.p. 229—230 °C (Found: C, 56.9; H, 4.2; N, 13.4; S, 10.5. $C_{15}H_{13}N_3O_3S$ requires C, 57.1; H, 4.2; N, 13.3; S, 10.2%); $\lambda_{max.}$(ethanol) 288 (ε 22 400 $dm^3\ mol^{-1}\ cm^{-1}$) and 320 nm (11 000); $\nu_{max.}$ 3 450, 3 330, and 3 060—2 400 (NH + OH) and 1 650 cm^{-1} (CO_2Me hydrogen-bonded with *o*-NH_2); $\delta_H[(CD_3)_2SO]$ 3.75 (3 H, s, MeO), 4.45 (2 H, s, CH_2), 6.85 (2 H, br s, NH_2, exchangeable), and 7.30 (5 H, s, ArH).

Preparation of Methyl N-*Acylimidates* (**17**)—(**18**).—To an ice-cold solution of the appropriate methyl imidate (0.3 mol) and triethylamine (33 g, 0.33 mol) in dry hexane (300 ml), the acyl chloride (0.33 mol) diluted with hexane (25 ml) was added dropwise over 1 h. Stirring was continued for 24 h. The precipitate was filtered off and washed with dry hexane (200 ml). The combined filtrates were evaporated and the residue was distilled under reduced pressure to yield the following methyl *N*-acylimidates (**17**) and (**18**). *Methyl* N-(4-*chlorobenzoyl*)*propanimidate* (**17**) (52%), b.p. 70—72 °C/0.01 mbar (Found: C, 58.3; H, 5.4; Cl, 15.9; N, 6.2. $C_{11}H_{12}ClNO_2$ requires C, 58.5; H, 5.4; Cl, 15.7; N, 6.2%); $\nu_{max.}$ 1 660 (CO) and 1 630 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 1.13 (3 H, t, *J* 7.0 Hz, Me), 2.43 (2 H, q, *J* 7.0 Hz, CH_2), 3.87 (3 H, s, MeO), and 7.67 (4 H, m, ArH). *Methyl* N-(*t-butylcarbonyl*)*benzenecarboximidate* (**18**) (70%), b.p. 116—119 °C/0.7 mbar (Found: C, 70.9; H, 8.0; N, 6.6. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%); $\nu_{max.}$ 1 690 (CO) and 1 660 cm^{-1} (C=N); $\delta_H(CDCl_3)$ 1.10 (9 H, s, Bu^t), 3.72 (3 H, s, MeO), 7.0—7.2 (3 H, m, *m,p*-ArH), and 7.3—7.5 (2 H, m, *o*-ArH).

Preparation of 4-*Oxo*-3,4-*dihydropyrimidine*-5-*carbonitriles* (**20**)—(**23**).—A solution of alkyl *N*-acylimidate (**15**)—(**19**) (10 mmol), 2-cyanoacetamide (**5**) (0.85 g, 10 mmol), and sodium methoxide (10 mmol) in dry methanol (50 ml) was heated under reflux for 4 h or stirred at room temperature for 8 h (**22**). To the reaction mixture at room temperature concentrated (*ca.* 18 molar) sulphuric acid (0.5 ml, *ca.* 9 mmol) was added and the solvent was evaporated. The residue was washed with water (200 ml), collected by filtration, and recrystallized to yield the following 4-oxopyrimidine-5-carbonitriles (**20**)—(**23**). 6-Methyl-4-oxo-2-phenyl-3,4-dihydropyrimidine-5-carbonitrile (**20**) (52%), m.p. 295—296 °C (from methanol) (lit.,[11] m.p. 290—291 °C); $\delta_H[(CD_3)_2SO]$ 2.53 (3 H, s, Me), 7.4—7.7 (3 H, m, *m,p*-ArH), and 8.0—8.3 (2 H, m, *o*-ArH). 2-Methyl-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile (**21**) (48%), m.p. 238—239 °C (from ethyl acetate) (lit.,[12] m.p. 242—244 °C). 4-*Oxo*-6-*phenyl*-2-*t-butyl*-3,4-*dihydropyrimidine*-5-*carbonitrile* (**22**) (50%), m.p. 278—279 °C (from ethyl acetate) (Found: C, 71.4; H, 6.0; N, 16.9. $C_{15}H_{15}N_3O$ requires C, 71.1; H, 6.0; N, 16.6%); $\nu_{max.}$ 3 300—2 800 (NH + OH), 2 220 (conj. CN), and 1 655 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 1.33 (9 H, s, Bu^t), 7.3—7.5 (3 H, m, *m,p*-ArH), 7.7—7.9 (2 H, m, *o*-ArH), and 12.7 (1 H, br s, NH + OH). 2-(4-*Chlorophenyl*)-4-*oxo*-6-*phenyl*-3,4-*dihydropyrimidine*-5-*carbonitrile* (**23**) (77%), m.p. 341—342 °C (decomp.) (from dioxane) (Found: C, 66.0; H, 3.3; Cl, 11.3; N, 13.3. $C_{17}H_{10}ClN_3O$ requires C, 66.3; H, 3.3; Cl, 11.5; N, 13.6%); $\nu_{max.}$ 3 200—2 700 (NH + OH), 2 220 (conj. CN), and 1 650 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 7.4—8.4 (m, ArH).

Preparation of 2-(4-*Chlorophenyl*)-6-*phenyl*-4-*thioxo*-3,4-*dihydropyrimidine*-5-*carbonitrile* (**24**).—A solution of the imidate (**19**) (1.37 g, 5 mmol), 2-cyanoethanethioamide (**6**) (0.50 g, 5 mmol), and sodium methoxide (20 mmol) in dry methanol (20 ml) was stirred at room temperature for 5 h and refluxed for additional 4 h. To the reaction mixture at room temperature concentrated (*ca.* 18 molar) sulphuric acid (0.8 ml, *ca.* 15 mmol) was added and the solvent was evaporated. The residue was washed with water (200 ml), collected by filtration, and recrystallized from methanol to yield 4-*thioxopyrimidine*-5-*carbonitrile* (**24**) (0.79 g, 49%), m.p. 230—231 °C (decomp.) (Found: C, 63.4; H, 3.0; N, 13.1. $C_{17}H_{10}ClN_3S$ requires C, 63.1; H, 3.1; N, 13.0%); $\lambda_{max.}$(ethanol) 270 (ε 29 100 dm^3 mol^{-1} cm^{-1}) and 316 nm (17 000); $\nu_{max.}$ 3 200—3 060 (NH) and 2 220 cm^{-1} (conj. CN); $\delta_H[(CD_3)_2SO]$ 7.4—8.4 (m, ArH).

Preparation of 2-(4-*Chlorophenyl*)-4-*methylthio*-6-*phenylpyrimidine*-5-*carbonitrile* (**25**).—To a solution of the 4-thioxopyrimidine (**24**) (0.32 g, 1 mmol) and sodium methoxide (1 mmol) in dry methanol (20 ml), iodomethane (0.28 g, 2 mmol) was added. The mixture was stirred for 2 h at room temperature. The precipitate thus formed was collected, washed with water, and recrystallized from ethanol to yield 4-*methylthiopyrimidine* (**25**) (0.25 g, 75%), m.p. 170—171 °C (Found: C, 64.1; H, 3.6; N, 12.5. $C_{18}H_{12}ClN_3S$ requires C, 64.0; H, 3.6; N, 12.4%); $\nu_{max.}$ 2 220 cm^{-1} (conj. CN); $\delta_H[(CD_3)_2SO]$ 2.73 (3 H, s, MeS) and 7.3—8.5 (9 H, m, ArH).

Preparation of Methyl 5-*Amino*-2-(4-*chlorophenyl*)-4-*phenylthieno*[3,2-d]*pyrimidine*-6-*carboxylate* (**26**).—To a solution of the 4-thioxopyrimidine (**24**) (0.12 g, 0.37 mmol) and sodium methoxide (0.4 mmol) in dry methanol (10 ml), methyl chloroacetate (0.40 g, 0.37 mmol) was added. The mixture was heated under reflux for 4 h. The precipitate thus formed was collected by filtration and washed with water, methanol, and diethyl ether to yield the *thieno*[2,3-d]*pyrimidine* (**26**) (0.12 g, 80%), m.p. 202—204 °C (Found: C, 60.8; H, 3.3; Cl, 9.3; N, 10.3; S, 8.3. $C_{20}H_{14}ClN_3O_2S$ requires C, 60.7; H, 3.6; Cl 9.0; N, 10.6; S, 8.1%); $\lambda_{max.}$(ethanol) 265 (ε 35 000 dm^3 mol^{-1} cm^{-1}), 300 (47 500), and 395 nm (8 260); $\nu_{max.}$ 3 490 and 3 350 (NH), and 1 670 cm^{-1} (CO_2Me hydrogen-bonded with *o*-NH_2); $\delta_H(CDCl_3)$ 3.90 (3 H, s, MeO), 5.9 (2 H, br s, NH_2, exchangeable), and 7.3—8.5 (9 H, m, ArH).

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