SYNTHESIS AND REACTIONS OF SOME NEW PYRIMIDINE THIONES

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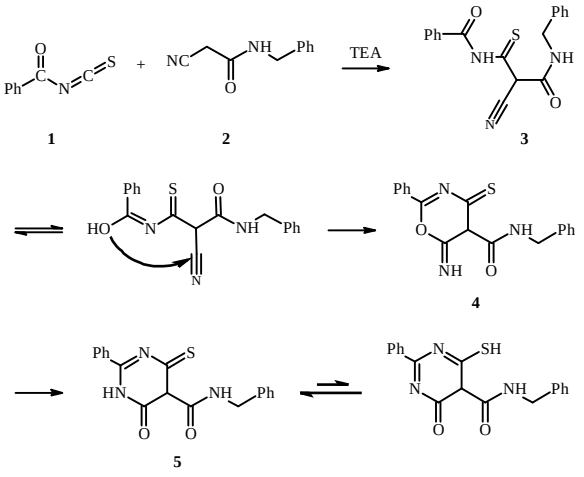
ABSTRACT: The addition of cyanomethylene derivative **2** to aroyl isothiocyanate **1** afforded mercaptopyrimidine derivative **5**. Mercaptopyrimidine **11** was prepared and transformed upon alkylation with chloroacetamide to thienopyrimidine **13**. Oxidation of **11** using I_2/AcOH yielded the disulphide **14**, while oxidation using H_2O_2/AcOH gave pyrimidine derivative **15**. Reaction of aldehydes with aminothiouracil **16** yielded 5-aroyl-2,8-dithioxo-2,3,5,8,9,10-hexahydropyrimido[5',4':5,6]pyrido[2,3-*d*]pyrimidine derivatives **19a,b**. Addition of **16** to chalcone afforded pyridopyrimidine **20**. Reaction of urea, 1-naphthaldehyde and aminothiouracil afforded pyrimidopyrimidine **21**. Reaction of **16** with NH_4SCN afforded compound **22** that oxidized to bis-isothiazolopyrimidine bisulphide **23**. [Journal of American Science 2010; 6 (6): 10-15]. (ISSN: 1545-1003).
KEY WORDS: mercaptopyrimidine, oxazine, thienopyrimidine, pyrimidine, pyridopyrimidine, pyrimidopyrimidine and isothiazolopyrimidine.

Introduction

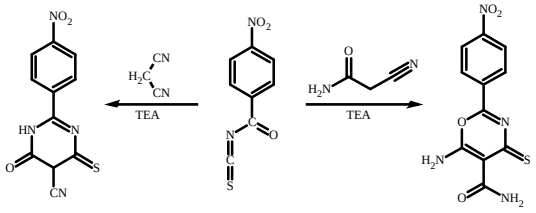
Pyrimidine derivatives comprise adverse and interested group of drugs **[Chabner et al., 2001]** and **[Hardman et al., 2001]**. Earlier a comprehensive review concerning pyrimidines had been published by Brown **[Brown et al., 1984]**. Pyrimidines in general are extremely important for their biological activities, for example, some are antiviral agents **[Nasr et al., 2002]**. The others, are selective cholecystokinine subtype receptor antagonists **[Bartolome-Nebreda et al., 2001]**, anti-inflammatory [**Santagati et al., 2002]**, **[Unangst et al., 1995**] and **[Tozkoparan et al., 1999]**, antihypertensive, diuretics, antimalarials, antithrombics, anticoagulants, antimicrobial **[Dubey et al., 2007]**, **[Learmonth et al., 2004]**, **[DeClercq et al., 2005]**, **[Demirayak et al., 2004]**, **[Ungureanu et al., 2006]**, **[Caprosu et al., 2005]** and **[Bahner et al., 1962]**.

As a part of a programme directed towards the synthesis of suitably functionalized heterocyclic systems of potential biological activity. [**Assy, et al., 1995]**, **[Assy et al., 2008]**, **[Sheriff et al., 2008]**, **[Sherif et al., 2008]**, **[Abdelghani., 2001]**, **[Abdelghani**., **1999]**. A new synthetic route for pyrimidine thione from aroyl isothiocyanate was undertaken.

The synthetic strategy towards the synthesis of pyrimidinethione involves the addition of cyanomethylene **2** to the electrophilic carbon of heteroallene **1** to give *N*-[3-(benzylamino)-2-cyano-3-oxopropanethioyl]benzamide **3** followed by intramolecular cyclization via the addition of enolic form to cyano function affording N-benzyl-6-imino-2-phenyl-4-thioxo-5,6-dihydro-4*H*-1,3-oxazine-5-carboxamide **4** which in turn undergoes ring transformation and rearrangement to give pyrimidinethione as the final product. But on base induced addition of *N*-benzyl-2-cyanoacetamide to benzoyl isothiocyanate, it afforded mercapto-pyrimidine **5**. The formation of **5** was potentiated by disappearance of CN group in its IR spectrum. The formation of **5** from addition of **2** to **1** may be proceeded presumably via the following mechanism:

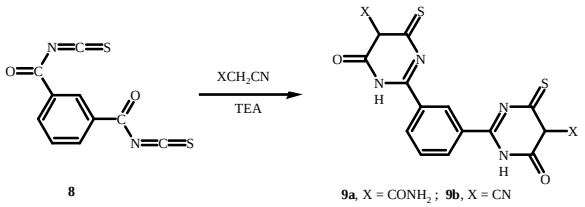


Depending on the reaction condition, p-nitrobenzoylisothiocyanate was reacted with malononitrile to give pyrimidinethione **6** upon heating. While, the addition of cyanoacetamide to p-nitrobenzoylisothiocyanate afforded 1,3-oxazine derivative **7** (Scheme I).



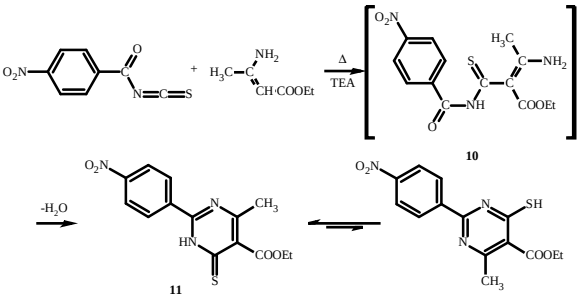
Scheme I

Addition of isophthaloyldiisothiocyanate **8** to cyanoacetamide and/or malononitrile derivative in the presence of TEA produced pyrimidine thione **9a** and **9b**, respectively (Scheme II).



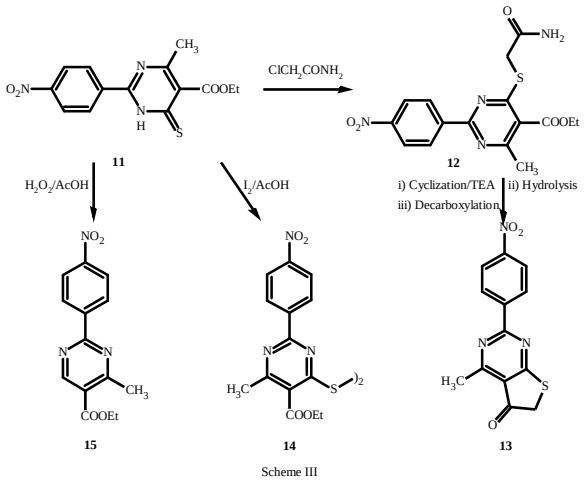
Scheme II

3-Aminocrotonate was added to p-nitrobenzoyl isothiocyanate to produce mercaptopyrimidine **11** presumably via the nonisolable intermediate **10** that undergo intramolecular cyclization followed by dehydration affording the final product **11**.



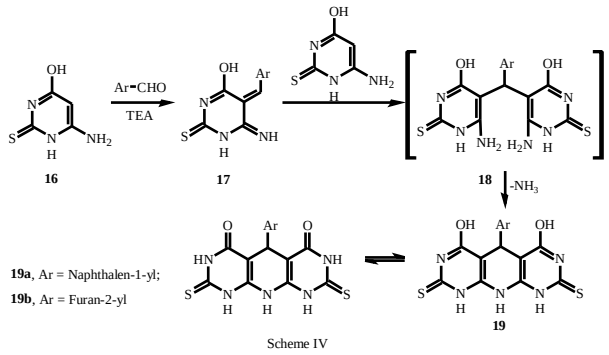
Compound **11** seemed to be of suitable located functionality for further functionalization and heterocyclization. Thus, alkylation of compound **11** using chloroacetamide in the presence of TEA afforded the alkylated derivative **12** that underwent intramolecular cyclization followed by hydrolysis and finally decarboxylated to give thienopyrimidine **13**.

Oxidation of compound **11** using I_2/AcOH it afforded the disulphide **14**. While, on oxidation using H_2O_2/AcOH it gave the desulphurized pyrimidine derivative **15** (Scheme III).



Scheme III

The synthesis of dihydropyridopyrimidine **19a,b** was achieved by refluxing of aminothiouracil **16** with aldehydes. The formation of **19** from **16** and aldehydes may be proceeded via the formation of Michael acceptors **17** followed by the addition of nucleophilic carbon of **16** and finally losing NH_3. Thus, reaction of pyrimidine derivative **16** and aldehydes namely 1-naphthaldehyde and/or furfural afforded the 2,3,5,8,9,10-hexahydropyrimido[5`,4`:5,6]pyrido[2,3-*d*]pyrimidine-4,6(1*H*,7*H*)-dione derivatives **19a,b** (Scheme IV). ^{1}H NMR spectra of **19a** showed complex spectra containing signals for each tautomeric form.

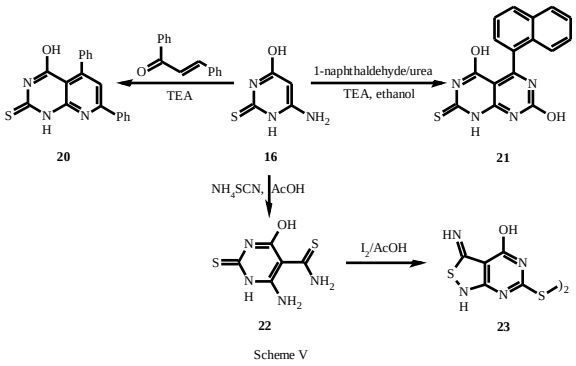


Scheme IV

Refluxing of compound **16** and 1,3-diphenylprop-2-en-1-one in the presence of TEA resulted in heterocyclization affording pyridopyrimidine **20**, while on refluxing with 1-naphthaldehyde and urea in presence of TEA, pyrimidopyrimidine **21** was obtained.

Finally, addition of enaminic carbon of aminothiouracil **16** to electrophilic carbon of isothiocyanate in acetic acid afforded pyrimidine

derivative **22**, which on treatment with iodine in acetic acid, it afforded the bis isothiazolopyrimidine disulphide **23** (Scheme V).



20 **16** **21** **22** **23**

Scheme V

Experimental

Mps are uncorrected. IR spectra (KBr discs) were recorded on a FT/IR-400 spectrophotometer (Perkin-Elmer). ^{1}H NMR spectra were recorded on a Varian 300 MHz (DMS-d_6) solutions. Chemical shifts are reported as δ values relative to tetramethylsilane (TMS) as internal reference. The elemental analysis were carried out at Micro analytical center, Cairo University.

N-[3-(benzylamino)-2-cyano-3-oxopropanethioyl]-benzamide (3):

A mixture of N-benzyl cyanoacetamide **2** (0.01 mole), benzoyl isothiocyanate **1** (0.01 mole) and TEA (3 drops) in (10 ml) acetone was stirred for 2 hours. The solid was filtered off, dried, to give **3**: yield 78%, as yellow crystals from benzene; m.p. 120-122 ^{o}C; its IR spectra: 3302, 3054 (NH), 1680 (C=O), 1648 (C=O), 2260 (CN), 1390 (C=S). Analysis for $C_{18}H_{15}N_3O_2S$ of mol. wt. 337.40, cal. C, 64.08; H, 4.48; N, 12.45; found C, 64.00; H, 4.44; N, 12.40.

***N*-benzyl-6-oxo-2-phenyl-4-thioxo-1,4,5,6-tetrahydropyrimidine-5-carboxamide (5):**

Compound **3** (0.01 mole) was dissolved in (20 ml) aqueous sodium hydroxide solution 10% and stirred for 1 hour at room temperature. The reaction mixture was neutralized by HCl, and the precipitated solid was filtered off, dried to give **5**: yield 76%, as white crystals from benzene; m.p. 170-172 ^{o}C; its IR spectra: 3302, 3034 (NH), 1690 (C=O), 1660 (C=O), 1350 (C=S); its ^{1}H NMR: δ = 4.47(d, 2H, J = 6.3 Hz, $PhCH_2$), 7.26-7.98(m, 11H, ArH's + CH methinyl), 9.06 (t, 1H, NH), 10.73(s, 1H, NH). Analysis for $C_{18}H_{15}N_3O_2S$ of mol. wt. 337.40, cal. C, 64.08; H, 4.48; N, 12.45; found C, 64.00; H, 4.44; N, 12.40.

Preparation of 6, 7, 9a and 9b.

General method:

A mixture of p-nitrobenzoylisothiocyanate (0.01 mole), cyanoacetamide and/or malononitrile (0.01 mole) and TEA (3 drops) in acetone (10 ml) was heated under reflux for 6-12 hours. The solid product obtained upon cooling, poured on ice and acidified by acetic acid, was filtered off, dried, and recrystallized from the proper solvent.

2-(4-nitrophenyl)-6-oxo-4-thioxo-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (6): yield 86%, as white crystals from water; m.p. 235-237 ^{o}C; its IR spectra: 3268 (NH), 2278 (CN), 1696 (C=O), 1604 (C=N), 1350 (C=S); its ^{1}H NMR: δ = 7.70(s, 1H, CH), 8.38-8.17(m, 4H, ArH's), 13.64(s, 1H, NH). Analysis for $C_{11}H_6N_4O_3S$ of mol. wt. 274.26: cal. C, 48.17; H, 2.21; N, 20.43; found C, 48.10; 2.19; N, 20.40.

6-amino-2-(4-nitrophenyl)-4-thioxo-4*H*-1,3-oxazine-5-carboxamide (7): yield 86%, as white crystals from water; m.p. 190-192 ^{o}C; its IR spectra: 3168, 3308 (NH_2), 1712 (C=O), 1604 (C=N), 1344 (C=S); its ^{1}H NMR: δ = 7.69(s, 2H, NH_2), 8.07-8.33(m, 6H, ArH's + NH_2). Analysis for $C_{11}H_8N_4O_4S$ of mol. wt. 292.27: cal. C, 45.20; H, 2.76; N, 19.17; found C, 45.17; H, 2.71; N, 19.12.

2,2'-benzene-1,3-diylbis(6-oxo-4-thioxo-1,4,5,6-tetrahydropyrimidine-5-carboxamide) (9a): yield 77%, as yellow crystals from dimethyl formamide; m.p. 245-247 ^{o}C; its IR spectra: 3376, 3246 (NH_2), 3450 (NH) 1684 (C=O), 1608 (C=N), 1328 (C=S); ^{1}H NMR: δ = 2.09(s, 2H, 2CH), 7.64-8.44(m, 4H, ArH's), 9.65, 9.82(s, 4H, 2CON$\underline{H}_2$), 11.20(s, 2H, 2NH). Analysis for $C_{16}H_{12}N_6O_4S_2$ of mol. wt. 416.43: cal. C, 46.15, H, 2.90; N, 20.18; found c, 46.10; H, 2.88; N, 20.10.

2,2'-benzene-1,3-diylbis(6-oxo-4-thioxo-1,4,5,6-tetrahydropyrimidine-5-carbonitrile) (9b): yield 83%, as black crystals from methanol; m.p.265-267 ^{o}C; its IR spectra: 3246, 3378 (NH), 2284 (CN), 1682 (C=O), 1608 (C=N), 1242 (C=S). Analysis for $C_{16}H_8N_6O_2S_2$ of mol.wt. 380.40: C, 50.52; H, 2.12; N, 22.09; found C, 50.48; H, 2.10; N, 22.01.

Ethyl 4-methyl-2-(4-nitrophenyl)-6-thioxo-1,6-dihydropyrimidine-5-carboxylate (11):

A mixture of aminocrotonate (0.01 mole), p-nitrobenzoyl isothiocyanate (0.01 mole) and sodium carbonate (0.01 mole) in (20 ml) acetone was refluxed for one hour. The reaction mixture was cooled and neutralized with dilute HCl. The precipitated solid was filtered off, dried to give **11**:

yield 78%, as yellow crystals from aqueous methanol; m.p.170-172 ^{o}C; IR spectra: 3454 (NH), 1732 (C=O), 1608 (C=N), 1387 (C=S); ^{1}H NMR: δ = 1.30(t, 3H, J = 6.9 Hz, CH_3), 2.28(s, 3H, CH_3), 4.32(q, 2H, J = 7.2 Hz, CH_2), 7.64(s, 1H, NH), 8.07-8.38(m, 4H, ArH's). Analysis of $C_{14}H_{13}N_3O_4S$ of mol. wt. 319.34, cal: C, 52.66; H, 4.10; N, 13.16, found C, 52.60; H, 4.00; N, 13.11.

Ethyl 4-[(2-amino-2-oxoethyl)sulfanyl]-6-methyl-2-(4-nitrophenyl)pyrimidine-5-carboxylate (12) and 4-methyl-2-(4-nitrophenyl)thieno[2,3-*d*]-pyrimidin-5(6*H*)-one (13):

A mixture of **11** (0.01 mole), chloroacetamide (0.01 mole), and TEA (3 drops) in methanol (10 ml) was refluxed for 6 hours. The separated solid was filtered off, dissolved in water and the solid obtained after neutralization with HCl was dried and recrystallized from dimethylformamid to give **12**. The mother liquor was acidified by HCl, and the precipitated solid was filtered off, dried, and recrystallized from dimethylformamide/methanol mixture (1:1) to give **13**.

Compound 12: yield 70%, as white crystals; m.p. 253-255 ^{o}C; IR spectra: 3368, 3216 (NH_2), 1710(C=O), 1646 (C=O). Analysis for $C_{16}H_{16}N_4O_5S$ of mol. wt. 376.39, cal. C, 51.06; H, 4.28; N, 14.89, found C, 51.00; H, 4.20; N, 14.84.

Compound 13: yield 65%, as black crystals; m.p. 283-285 ^{o}C; IR spectra: 1674 (C=O); ^{1}H NMR spectrum δ = 2.89(s, 3H, CH_3), 2.95(s, 2H, CH_2), 8.35-8.69(m, 4H, ArH's). Analysis for $C_{13}H_9N_3O_3S$ of mol. wt. 287.29, cal. C, 54.35; H, 3.16; N, 14.63, found C, 54.31; H, 3.13; N, 14.60.

Preparation of 14 and 23.

General method:

Iodine (0.01 mole) was added to a suspension of **11** and/or **22** (0.01 mole) in acetic acid (20 ml) and left at room temperature with stirring for 4 hours. The resulted precipitate was poured on water and collected by filtration, washed with water, dried, and recrystallized from the proper solvent to give **14** and **23**, respectively.

Ethyl 4-{[5-(ethoxycarbonyl)-6-methyl-2-(4-nitrophenyl)-4-pyrimidinyl]disulfanyl}-6-methyl-2-(4-nitrophenyl)-5-pyrimidinecarboxylate (14): yield 85%, as yellow crystals from acetic acid, m.p. 236-238 ^{o}C; IR spectra: 1724 (C=O), 1684 (C=N); ^{1}H NMR: δ = 1.47(t, 6H, J = 6.9 Hz, $2CH_3$), 2.77(s, 6H, $2CH_3$), 4.59(q, 4H, J = 7.5 Hz, $2CH_2$), 8.34-8.20(m, 8H, 2ArH's). Analysis for $C_{28}H_{24}N_6O_8S_2$ of mol. wt. 636.66, cal. C, 52.82; H, 3.80; N, 13.20; found C, 52.78; H, 3.77; N, 13.17.

6,6'-disulfanediylbis(3-imino-1,3-dihydro-isothiazolo[3,4-*d*]pyrimidin-4-ol) (23): yield 86%, as yellow crystals from methanol, m.p. 359-360 ^{o}C; IR spectra: 3422 (OH), 3315, 3194 (NH), 1639 (C=N); ^{1}H NMR: δ = 4.69(s, 2H, 2NH), 6.35(s, 2H, 2NH), 11.57(s, 2H, 2OH). Analysis for $C_{10}H_6N_8O_2S_4$ of mol. wt. 398.47, cal. C, 30,14; H, 1.52; N, 28.12; found C, 30.10; H, 1.50; N, 28.09.

Ethyl 4-methyl-2-(4-nitrophenyl)pyrimidine-5-carboxylate (15):

To a solution of **11** (0.01 mole) in acetic acid (20 ml), H_2O_2 (0.02 mole) was added dropwise. The reaction mixture was stirred for one hour at room temperature. The separated solid was collected by filtration and dried to give **15**: yield 83%, as white crystals from acetic acid, m.p. 249-247 ^{o}C, IR spectra: 3120 (NH), 1724 (C=O), 1686 (C=N). Analysis for $C_{14}H_{13}N_3O_4$ of mol. wt. 287.27, cal. C, 58.53; H, 4.56; N,14.63; found C, 58.50; H, 4.50; N, 14.60.

Preparation of 19a and 19b.

General method:

A mixture of **16** (0.02 mole) and 1-naphthaldehyde and/or furfural (0.01 mole) in (20 ml) dimethyl formamide was refluxed for 30 hours. The solid product obtained upon cooling and pouring on ice was collected by filtration, dried, and recrystallized from the proper solvent to give **19a** and **19b**, respectively.

5-naphthalen-1-yl-2,8-dithioxo-2,3,5,8,9,10-hexa-hydropyrimido[5',4':5,6]pyrido[2,3-d]pyrimidine-4,6(1H,7H)-dione (19a): yield 75%, as yellow crystals from acetic, m.p. 350-352 ^{o}C, IR spectra: 3400 (OH enolic), 3165, 3134, 3070 (NH), 1686 (C=O), 1612(C=N), 1373 (C=S); ^{1}H NMR: δ = 7.43-8.92(m, 8H, ArH's + CH methinyl), 9.63(s, 2H, 2NH), 12.62(s, 2H, 2NH), 13.22(s, 1H, NH). Analysis for $C_{19}H_{13}N_5O_2S_2$ of mol. wt. 407.47, cal. C, 56.01; H, 3.22; N, 17.19; found C, 55.97; H, 3.19; N, 17.12 .

5-furan-2-yl-4,6-dihydroxy-5,10-dihydropyrimido-[5',4':5,6]pyrido[2,3-*d*]pyrimidine-2,8(1*H*,9*H*)-dithione (19b): yield 81%, as black crystals from methanol, m.p. 358-356 ^{o}C, IR spectra: 3397, 3323 (OH), 3180, 3089 (NH), 1622 (C=N), 1294 (C=S); Analysis for $C_{13}H_9N_5O_3S_2$ of mol. wt. 347.37, cal. C, 44.95; H, 2.61, N, 20.16; found C, 44.90; H, 2.60; N, 20.11.

4-hydroxy-5,7-diphenylpyrido[2,3-*d*]pyrimidine-2(1*H*)-thione (20):

A mixture of **16** (0.01 mole) and 1,3-diphenylprop-2-en-1-one (0.01 mole) and TEA (3 drops) in ethanol

(25 ml) was refluxed for 30 hours. The precipitated solid obtained upon cooling and neutralization with few drops of acetic acid was filtered off, dried, to give **20**: yield 77%, as yellow crystals from benzene/ethanol mixture (1:1), m.p. 200-202 ^{o}C, IR spectra: 3213 (OH), 3059 (NH), 1218 (C=S), ^{1}H NMR: δ = 7.16-8.16(m, 11H, ArH's + CH pyridine), 12.00(s, 1H, NH), 12.20(s, 1H, OH). Analysis for $C_{19}H_{13}N_3OS$ of mol. wt. 331.39, cal. C, 68.86; H, 3.95; N, 12.68, found C, 68.80; H, 3.93; N, 12.60.

4,7-dihydroxy-5-naphthalen-1-ylpyrimido[4,5-*d*]-pyrimidine-2(1*H*)-thione (21):

A mixture of **16** (0.01 mole) 1-naphthaldehyde (0.01 mole) and urea (0.01 mole) in dimethyl formamide (10 ml) was refluxed for 30 hours. The reaction mixture was cooled, poured on ice and the separated solid was collected by filtration, dried, to give **21**: yield 85%, as yellow crystals fom methanol, m.p. 330-332 ^{o}C; IR spectra: 3057 (OH), 1616(C=N), 1374 (C=S); ^{1}H NMR: δ = 7.35-9.01(m, 7H, ArH's), 9.64(s, 1H, NH), 12.00(s, 1H, OH), 12.86(s, 1H, OH). Analysis for $C_{16}H_{10}N_4O_2S$ of mol. wt. 322.34 cal. C, 59.62; H, 3.13; N, 17.38; found C, 59.55; H, 3.10; N, 17.30.

6-amino-4-hydroxy-2-thioxo-1,2-dihydro-pyrimidine-5-carbothioamide (22):

A mixture of **16** (0.01 mole) and ammonium thiocyanate (0.01 mole) in acetic acid (15 ml) was refluxed for 12 hours. The reaction mixture was cooled, poured on ice and the separated solid was collected by filtration, dried to give **22**: yield 85%, as yellow crystals from methanol, m.p. 310-312 ^{o}C; IR spectra: 3423, 3320 (NH_2), 3088 (NH), 1635 (C=N), 1292 (C=S); ^{1}H NMR: δ = 4.70(s, 2H, NH_2), 6.35(s, 2H, NH_2), 11.49(s, 1H, NH), 11.58(s, 1H, OH). Analysis for $C_5H_6N_4OS_2$ of mol. wt. 202.26, cal. C, 29.69; H, 2.99; N, 27.70; found C, 29.60; H, 2.94; N, 27.66.

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