Studies in the Heterocyclic Series. XVIII. Utilization of 4-Aminopyrimidine Chemistry in 1,4,7,9-Tetraazabenzo[*b*]phenothiazine Synthesis

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The synthesis of 1,4,7,9-tetraazabenzo[*b*]phenothiazine ring system from 4-aminopyrimidine is reported. This new heterocyclic ring was obtained by converting a 4-aminopyrimidine to the corresponding 5-thiocyanato derivative followed by hydrolysis and subsequent treatment with 2,3-dichloroquinoxaline. Several derivatives were obtained by using suitable substituted starting materials. Nitration with mixed nitric and sulfuric acids gave the corresponding 13-nitro derivatives. Spectral analyses are in agreement with the assigned structures.

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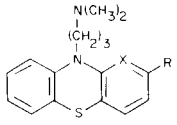
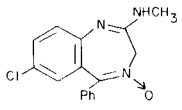
The phenothiazines (I) (2,3) and the diazepines (II and III) (4-6) are two important classes of drugs used in psychiatric medicine today. They are respectively 1,4-thiazines and 1,4-diazepines with two stabilizing benzene rings. An important drug in the phenothiazine class is chlorpromazine (I, R = Cl, X = CH) which is a household drug widely used for treating both acute and chronic schizophrenia, mania, anorexia nervosa, agitated depression and acute confusional states (7,8).

Marked improvements in the chemotherapeutic action



I



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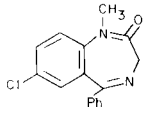
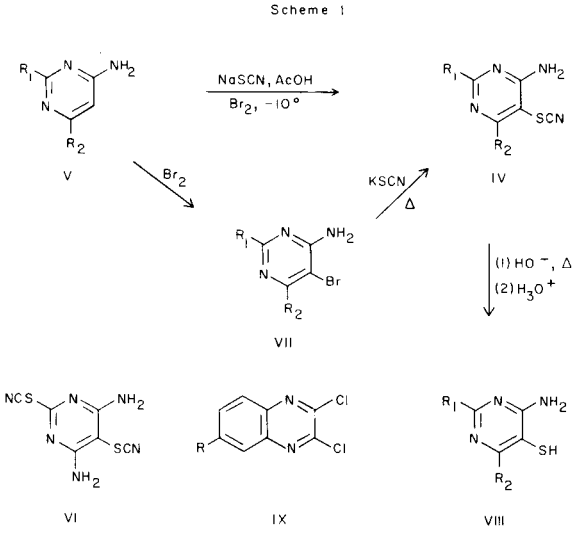


III

of chlorpromazine and other phenothiazine drugs have been achieved by modifications of the aromatic rings (9,10). Prothipendyl (I, R = H, X = N), the 1-azaphenothiazine analog of promazine (I, R = H, X = CH), is reputed as one of the best tranquilizers and is preferred to chlorpromazine in the treatment of acute psychosis particularly when there is a complication of latent epilepsy (11,12).

Further changes in the phenothiazine structure involving replacement of the benzene rings with pyrrole (13), thiophene (14), 1,3,4-triazine (15), pyridine (16,17), pyridazine (18), pyrimidine (19), pyrazine (20) and quinoxaline (21) have now been made. In the course of these studies further development of the chemistry of phenothiazine and more insight into the mechanism of Smiles rearrangement have also been achieved (9,10,22). In addition, these reactions led to new heterocyclic rings from which new chemistry has evolved. So far only four monoaza-, ten diaza- and four triaza-phenothiazine ring structures are now known. In the tetraazaphenothiazine series, Wise and Castle (23) have recently synthesized the first tetraazaphenothiazine ring and four of its structural isomers. From the remaining list of thirty unknown isomeric ring systems, we have now succeeded in preparing the 1,4,7,9-tetraazabenzo[*b*]phenothiazine ring by utilization of 4-aminopyrimidine chemistry.

Scheme I



One of the major problems encountered in these reactions is in the selection of an *ortho*-aminoheterocyclic thiol (24) and an *ortho*-dihalogenated heterocyclic compound with sufficient solubility and reactivity in the alkaline medium often employed. However, by the use of certain high boiling polar solvents such as dimethylformamide, dimethylacetamide, ethylene glycol and propylene glycol, this problem is largely circumvented. For the preparation of the desired *o*-aminopyrimidinethiols, the high reactivity of the 5-carbon centre of pyrimidine to electrophiles was exploited. The precursors, 4-amino-5-thiocyanatopyrimidine derivatives (IV), were obtained essentially by two methods. In one of them, direct thiocyanation of the 4-aminopyrimidines (V) with nascent thiocyanogen at −10° to 0° was employed. This method worked remarkably well for the thiocyanation of 4,6-diaminopyrimidine. If, however, a large excess of the thiocyanating agent were

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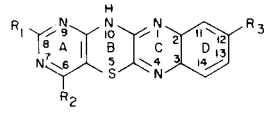
used, dithiocyanation took place resulting in the isolation of 4,6-diamino-2,6-dithiocyanatopyrimidine (VI). The second method involved the conversion of the aminopyrimidines (V) to the 5-bromo-derivatives (VII) by the action of bromine in mildly alkaline media at room temperature (25-28). The isolated products were subsequently treated with excess sodium thiocyanate solution leading to the same products IV in good yields. These reactions are summarized in Scheme I. 4,6-Diaminopyrimidine could not however, be thiocyanated by the latter method although 5-bromination took place with much ease. These 4-amino-5-thiocyanatopyrimidines (IV) were converted to 4-aminopyrimidine-5-thiols (VIII) by refluxing with 40% potassium hydroxide followed by acidification with glacial acetic acid.

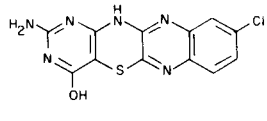
When an equimolar mixture of 4,6-diaminopyrimidine-5-thiol (VIII), R_1 = H, R_2 = NH_2 and 2,3-dichloroquinoxaline (IX, R = H) was refluxed in propylene glycol (29) in the presence of potassium hydroxide solution, a yellowish-green microcrystalline solid melting above 300° was obtained. Microanalysis and mass spectroscopy are in agreement with the molecular formula $C_9H_7N_5S$. The uv maximum absorption bands at 396, 363, 334, 261 and 222 nm and the infrared peaks at 3370 (d) (NH_2), 3130 (NH), 874 (trisubstituted benzene) (30) are in good agreement with the tetracyclic benzotetraazaphenothiazine (31) structure, X, R_1 = R_3 = H, R_2 = NH_2. Confirmatory



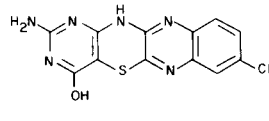
X

evidence for the assigned structure was obtained by examination of the pmr spectrum in which the four adjacent hydrogens in ring D absorbed at τ 3.36 (area 4), the 6-NH_2 protons at τ 2.37 (area 2) and the 8-H proton (area 1) at τ 2.00.

A similar reaction of 2,4-diamino-6-hydroxy pyrimidine-5-thiol, VIII, R_1 = NH_2, R_2 = OH, with 2,3-dichloroquinoxaline gave 8-amino-6-hydroxy-1,4,7,9-tetraazabenzo[*b*]phenothiazine X, R_1 = NH_2, R_2 = OH, R_3 = H. With 2,3,6-trichloroquinoxaline (IX, R = Cl), compound VIII, R_1 = NH_2, R_2 = OH gave a single product in an excellent yield. This compound has two structural possibilities, XI and XII. In order to determine the

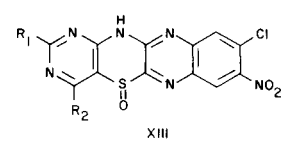


XI

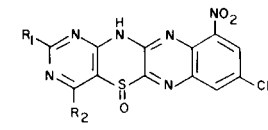


XII

correct structure, it was nitrated with mixed nitric and sulfuric acids at room temperature. Only a single product was however obtained. Elemental analysis and molecular weight determination by mass spectrometry agree with the formula $C_9H_6N_6O_3S$. The observed infrared bands at 1372 (NO_2), 1053 (S = O) and 895 cm^{-1} (1,2,4,5-tetrasubstituted benzene) are in good agreement with structure XIII, R_1 = NH_2, R_2 = OH, as the structure of the nitration product.



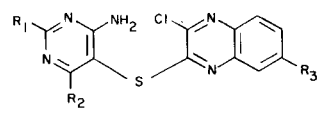
XIII



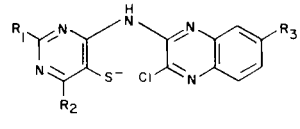
XIV

This is also the anticipated product if the directive influence of the activating group, 10-NH, is considered. Further evidence for structure XIII R_1 = NH_2, R_2 = OH is the established fact that nitration of phenothiazine with these reagents leads to *para*-nitration resulting in 3-nitrophenothiazine sulfoxide (32,33). No product is expected from the nitration of the alternative structure, XII, as the position *para* to the activating group (-N=C-NH-) is blocked by chlorine. *Ortho*-nitration is ruled out because of the mild condition employed but even if it takes place at all only a very low yield of compound XIV, R_1 = NH_2, R_2 = OH, is expected. Since only a single product was obtained and in very good yields for that matter, the structure of the nitro sulfoxide formed is therefore XIII, R_1 = NH_2, R_2 = OH. Thus, its precursor (XI) is 8-amino-12-chloro-6-hydroxy-1,4,7,9-tetraazabenzo[*b*]phenothiazine X, R_1 = NH_2, R_2 = OH, R_3 = Cl. Reaction of compound VIII, R_1 = H, R_2 = NH_2 with 2,3,6-trichloroquinoxaline similarly gave compound X, R_1 = H, R_2 = NH_2, R_3 = Cl.

The formation of these tetracyclic tetraazaphenothiazines, X, can be rationalized as proceeding *via* the sulfide XV since these reactions were run in alkaline media.



XV



XVI

The sulfides then under Smiles rearrangement to the diarylamines XVI and cyclization leading to the isolated products, X. These reactions further demonstrate the ease of Smiles rearrangement of o-amino heterocyclic sulfides which may now be considered as a reliable route to more complex azaphenothiazine ring systems.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Uv and visible spectra were recorded on a Pye Unicam SP 8000 spectrophotometer using matched 1 cm quartz cells. The solvent is methanol and the absorption maxima are always given in nanometers; the figures in parenthesis are log ϵ values. Ir spectra were obtained on a Perkin Elmer Model 137 spectrophotometer using potassium bromide discs unless otherwise stated. Pmr spectra were determined on a Varian Associates T-60 instrument. Chemical shifts are reported on the τ scale

relative to TMS used as an internal standard. The letters b, s, d, t, q, sh and m are used to indicate broad, singlet, doublet, triplet, quartet, shoulder and multiplet respectively. The mass spectra were obtained on an AE1 MS-9 double-focusing mass spectrometer at 70 eV.

4,6-Diamino-5-thiocyanatopyrimidine (IV, R_1 = H, R_2 = NH_2).

4,6-Diaminopyrimidine hemisulfate (15.92 g., 100 mmoles) was placed in a litre size three-necked flask equipped with a reflux condenser, a dropping funnel and a mechanical glass stirrer. Glacial acetic acid (200 ml.) precooled at 18° was then added and the mixture cooled in a freezing mixture of ice and salt. After about 15 minutes sodium thiocyanate dihydrate (34) (23.40 g., 200 mmoles) was added while maintaining the temperature between −5° and 0°. Bromine (8 ml., 150 mmoles) was placed in the dropping funnel and added in droplets to the stirred ice-cooled mixture during a period of about 60 minutes. The slurry turned brilliant orange yellow in colour initially but changed somewhat to deeper orange colour after about 120 minutes. Stirring was continued at near 0° for a total period of 5 hours. The slurry was left to stand overnight.

Some water (50 ml.) was added and the mixture warmed to 80° and filtered while hot. The filtrate was preserved and the deep orange residue was extracted thrice with 80 ml. of glacial acetic acid. The original filtrate was combined with the acetic acid extracts and neutralized to *p*H 6.5 with concentrated ammonia while cooling. All through the period of neutralization, the temperature was maintained below 30°.

The yellow product was then collected by filtration and recrystallized twice from methanol after treatment with activated charcoal. 2,4-Diamino-5-thiocyanatopyrimidine (IV, R_1 = H, R_2 = NH_2) (15.53 g., 93% yield) was collected as glistening yellow plates, m.p. 183°-184°; uv; λ max 270 (2.9729), 223 (4.1326); ir (potassium bromide): ν max 3425, 3387, 3300, 3166, 3070, 2145, 1628, 1570, 1529, 1473, 1316, 1350, 1295, 1160, 1023, 997, 894, 780 cm^{-1}; pmr (DMSO-d_6): τ 2.93 s (4-NH_2, 6-NH_2), 2.10 (2-CH); ms: m/e (relative intensity), 97 (31), 98 (94), 99 (13), 100 (9), 108 (9), 109 (9), 112 (16), 113 (34), 114 (75), 125 (95), 126 (23), 127 (9), 139 (6), 140 (25), 141 (38), 142 (6), 167 (M^+, 100%), 168 (28), 169 (9).

Anal. Calcd. for $C_5H_5N_5S$: C, 35.93; H, 2.99; N, 41.92; S, 19.16. Found: C, 35.84; H, 3.06; N, 42.05; S, 19.15.

4-Amino-6-hydroxy-2-methylthio-5-thiocyanatopyrimidine, (IV, R_1 = SCH_3, R_2 = OH).

4-Amino-6-hydroxy-2-methylthiopyrimidine (7.85 g., 50 mmoles) in 100 ml. of glacial acetic acid was treated at −5° to 0° with sodium thiocyanate dihydrate (12.87 g., 110 mmoles) and 4 ml. of bromine as described for 4,6-diamino-5-thiocyanatopyrimidine. Crystallization of the product from methanol-acetone mixture gave 9.10 g. (88% yield) of 4-amino-6-hydroxy-2-methylthio-5-thiocyanatopyrimidine as a yellow microcrystalline powder, m.p. > 270° dec.; uv: λ max 280 (3.8194), 227 (4.1145); ir (potassium bromide): ν max 3400 (b), 3180 (w), 2920, 2218, 1610, 1550, 1510, 1428, 1220, 1123, 1057, 980, 960, 780 cm^{-1}; pmr (DMSO-d_6): τ 6.63 s (2-SCH_3), 2.60 s (4-NH_2), 1.50 b, s (6-OH); ms: m/e (relative intensity), 216 (10), 215 (26), 214 [M^+, 36], 188 (100%), 172 (18).

Anal. Calcd. for $C_6H_6N_4OS_2$: C, 33.64; H, 2.80; N, 26.17; S, 29.91. Found: C, 33.52; H, 2.87; N, 26.20; S, 30.25.

4-Amino-5-bromo-6-hydroxy-2-methylpyrimidine, (VII, R_1 = CH_3, R_2 = OH).

4-Amino-6-hydroxy-2-methylpyrimidine (10.00 g., 80 mmoles) was placed in the reaction flask containing 120 ml. of 50% methanol. Sodium bicarbonate (12 g.) was later added. From the dropping funnel 8 ml. of bromine was added during a period of 40 minutes with constant stirring. After about 20 minutes additional 8 g. of sodium bicarbonate was added and the mixture stirred for a total period of 2 hours. The slurry was kept overnight and the product collected by filtration. Recrystallization from aqueous ethanol after treatment with activated charcoal gave 12.08 g. (74% yield) of 4-amino-5-bromo-6-hydroxy-2-methylpyrimidine (VII, R_1 = CH_3, R_2 = OH) as glistening white powder m.p. > 300° dec.; uv: λ max 288 (3.9378), 227 (4.1843); ir (potassium bromide): ν max 3460, 3348, 2912, 1630, 1600, 1567, 1534, 1453, 1418, 1227, 998, 954, 890, 754 cm^{-1}; pmr (DMSO-d_6): τ 7.60 s (2-CH_3), 3.40 s (4-NH_2); ir (potassium bromide): m/e (relative intensity), 88 (38), 110 (28), 120 (19), 128 (34), 133 (28), 135 (34), 146 (28), 148 (26), 171 (7), 170 (21), 189 (17), 188 (14), 203 (M^+, 100%) 204 (60), 205 (87), 206 (24).

Anal. Calcd. for $C_5H_6BrN_3O$: C, 29.43; H, 2.94; N, 20.60; Br, 39.18. Found: C, 29.25; H, 2.72; N, 20.88; Br, 39.15.

4-Amino-5-bromo-2-ethylthio-6-hydroxypyrimidine, (VII, R_1 = SC_2H_5, R_2 = OH).

4-Amino-2-ethylthio-6-hydroxypyrimidine (17.10 g., 100 mmoles) was converted the 5-bromoderivative by treating with a total of 25 g. of sodium bicarbonate and 9 ml. of bromine as described for 4-amino-5-bromo-6-hydroxy-2-methylpyrimidine (VII, R_1 = CH_3, R_2 = OH).

The product obtained was crystallized twice from ethanol after treatment with activated charcoal to yield 23.75 g. (95% yield) of glistening white crystals of 4-amino-5-bromo-2-ethylthio-6-hydroxypyrimidine (VII, R_1 = SC_2H_5, R_2 = OH), m.p. 218°-219° dec.; uv: λ max 287 (3.5739), 226 (3.9097); ir (potassium bromide): ν max 3455, 3268, 2916, 1610, 1570, 1540, 1450, 1424, 1380, 1283, 1224, 1065, 1050, 1034, 995, 960, 867, 757 cm^{-1}; pmr (DMSO-d_6): τ 8.75 t (J = 7.6 Hz) (2-SCH_2CH_3), 6.95 q (J = 7.6 Hz) (2-SCH_2CH_3), 3.34 (s, 4-NH_2); ms: m/e (relative intensity) 146 (19), 148 (20), 162 (21), 163 (19), 164 (21), 165 (15), 170 (8), 171 (12), 188 (38), 189 (42), 190 (40), 191 (45), 195 (12), 216 (81), 218 (80), 221 (31), 222 (8), 223 (30), 234 (28), 236 (28), 249 [M^+, 100%], 250 (19), 251 (98).

Anal. Calcd. for $C_6H_8BrN_3OS$: C, 28.81; H, 3.20; N, 16.81; S, 12.81; Br, 31.97. Found: C, 29.07; H, 3.20; N, 16.80; S, 12.68; Br, 32.00.

5-Bromo-4,6-diaminopyrimidine (VII, R_1 = H, R_2 = NH_2).

5-Bromination of 4,6-diaminopyrimidine hemisulfate (15.92 g., 100 mmoles) with 10 ml. of bromine in the presence of 20 g. of sodium bicarbonate in 150 ml. of 50% methanol was carried out as described for the preparation of 4-amino-5-bromo-6-hydroxy-2-methylpyrimidine (VII, R_1 = CH_3, R_2 = OH). 5-Bromo-4,6-diaminopyrimidine (VII, R_1 = H, R_2 = NH_2) (9.84 g., 52% yield) was obtained as a brilliant yellow microcrystalline powder, m.p. 214-216° dec.; uv spectrum λ max 280 (3.8728); (Drakeol 35): ν max 3440, 3300, 1655, 1636, 1605, 1547, 1460, 1375, 1334, 1230, 1106, 1073, 1010, 1000, 970, 936, 850, 750, 720 cm^{-1}; pmr (DMSO-d_6): τ 2.81 b, s (4-NH_2, 6-NH_2), 2.00 s (2-CH).

Anal. Calcd. for $C_4H_5BrN_4$: C, 25.41; H, 2.64; N, 29.65; Br, 42.30. Found: C, 25.50; H, 2.82; N, 29.64; Br, 42.45.

5-Bromo-2,4-diamino-6-hydroxypyrimidine, (VII, R_1 = NH_2, R_2 = OH).

This compound was obtained by treating 2,4-diamino-6-hydroxypyrimidine monohydrate (7.21 g., 50 mmoles) with sodium bicarbonate (12 g.) and bromine (5 ml.) in 50% methanolic solution as described for 4-amino-5-bromo-6-hydroxy-2-methylpyrimidine (VII, R_1 = CH_3, R_2 = OH). The desired product, 5-bromo-2,4-diamino-6-hydroxypyrimidine (VII, R_1 = NH_2, R_2 = OH) (10.83 g., 97% yield) was collected as glistening white needles after crystallization from water (Norite A) m.p. 265°; uv λ max 278 (4.2086); ir (Drakeol 35): ν max 3440, 3300, 3190, 1650, 1600, 1570, 1550, 1462, 1430, 1396, 1378, 1163, 1088, 1000, 875, 764, 730, 683 cm^{-1} pmr (DMSO-d_6): τ 3.73 s (4-NH_2), 3.58 s (2-NH_2), −0.40 (6-OH).

Anal. Calcd. for $C_4H_5BrN_4O$: C, 23.43; H, 2.44; N, 27.32; Br, 38.99. Found: C, 23.50; H, 2.42; N, 27.38; Br, 39.10.

4-Amino-6-hydroxy-2-methyl-5-thiocyanatopyrimidine, (IV, R_1 = CH_3, R_2 = OH).

4-Amino-5-bromo-6-hydroxy-2-methylpyrimidine (VII, R_1 = CH_3, R_2 = OH) (6.12 g., 30 mmoles) was placed in the reaction flask containing 500 ml. of boiling water and stirred. As the material did not dissolve, 100 ml. of dimethylsulfoxide were later added to induce dissolution. To the boiling solution was added 10 g. of sodium thiocyanate dihydrate. The stirred mixture was then refluxed for a total period of 90 minutes. Massive precipitation of the product was observed after about 10 minutes of reflux time. The solution was cooled and filtered. The residue was crystallized from aqueous ethanol-acetone mixture after treatment with activated charcoal. Glistening white needles of 4-amino-6-hydroxy-2-methyl-5-thiocyanatopyrimidine (IV, R_1 = CH_3, R_2 = OH) (3.9727),

237 (4.2258), 224 (4.2113); ir (potassium bromide): ν max 3460, 3340, 3210, 3024, 2937, 2850, 2150, 1655, 1610, 1568, 1533, 1464, 1435, 1328, 1270, 1225, 1045, 1017, 962, 883, 770 cm^{-1}; pmr (DMSO-d_6): τ 6.67 s (2-CH_3), 2.45 s (4-NH_2); ms: m/e (relative intensity), 124 (18), 156 (76), 157 (5), 166 (24), 182 [M^+, 100%], 183 (3), 184 (21).

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.56; H, 3.30; N, 30.77; S, 17.58. Found: C, 39.40; H, 3.11; N, 31.00; S, 17.59.

2,4-Diamino-6-hydroxy-5-thiocyanatopyrimidine, (IV, R_1 = NH_2, R_2 = OH).

5-Bromo-2,4-diamino-6-hydroxypyrimidine (VII, R_1 = NH_2, R_2 = OH) (20.5 g., 100 mmoles) was placed in a 3-litre three-necked flask containing 1 l. of boiled water. The mixture was boiled until all the solid dissolved. Sodium thiocyanate dihydrate (23.4 g., 200 mmoles) in 100 ml. of water was then added. The entire solution was refluxed for two hours. During the reflux period massive precipitation was observed.

At the end of the reflux period, the mixture was cooled, filtered and the residue recrystallized twice from acetone-ethanol mixture after treatment with activated charcoal, m.p. > 300° dec.; uv: λ max 267 (3.7744), 222 (4.1855); ir (potassium bromide): ν max 3430, 3360, 3300, 3140, 2900, 2144, 1650, 1590, 1535, 1480, 1465, 1396, 1155, 1086, 995, 850, 770, 707, 660 cm^{-1}; pmr (DMSO-d_6): τ 3.35 s (4-NH_2), 3.04 s (2-NH_2), −0.36 s, b (6-OH); ms: m/e (relative intensity), 85 (19), 86 (17), 87 (14), 98 (8), 113 (19), 129 (42), 140 (64), 141 (10), 142 (17), 157 (17), 158 (4), 183 [M^+, 100%], 184 (11), 185 (6).

Anal. Calcd. for $C_5H_5N_5OS$: C, 32.79; H, 2.73; N, 38.25; S, 17.49. Found: C, 33.00; H, 2.51; N, 38.40; S, 17.48.

4-Amino-2-ethylthio-6-hydroxy-5-thiocyanatopyrimidine, (IV, R_1 = SCH_2CH_3, R_2 = OH).

4-Amino-5-bromo-2-ethylthio-6-hydroxypyrimidine (VII, R_1 = SCH_2CH_3, R_2 = OH) (10 g., 40 mmoles) was treated with 16 g. of potassium thiocyanate in 750 ml. of water and 75 ml. of dimethylsulfoxide as reported for 4-amino-6-hydroxy-2-methyl-5-thiocyanatopyrimidine (IV, R_1 = CH_3, R_2 = OH).

The crude product was recrystallized twice from ethanol after treatment with activated charcoal. Glistening white light needles of 4-amino-2-ethylthio-6-hydroxy-5-thiocyanatopyrimidine (IV, R_1 = SCH_2CH_3, R_2 = OH) were obtained, m.p. 246°-247°; uv spectrum λ max 284 (3.9812), 238 (4.2153), 223 (4.25); ir (potassium bromide): ν max 3460, 3392, 3340, 3140, 2927, 2850, 2150, 1640, 1610, 1510, 1535, 1515, 1444, 1260, 1224, 1060, 1010, 958, 900, 823, 770 cm^{-1}; pmr (DMSO-d_6): τ 8.75 t (J = 7.6 Hz) (2-SCH_2CH_3), 6.92 q (J = 7.6 Hz) (2-SCH_2CH_3), 2.48 s (4-NH_2), −2.25 s, b (6-OH); ms: m/e (relative intensity), 70 (14), 85 (13), 112 (20), 113 (16), 140 (16), 141 (15), 142 (14), 152 (14), 156 (8), 157 (17), 167 (38), 168 (25), 195 (27), 200 (31), 201 (91), 202 (27), 203 (31), 213 (9), 228 [M^+, 100%], 229 (22), 230 (19).

Anal. Calcd. for $C_7H_8N_4OS_2$: C, 36.84; H, 3.51; N, 24.57; S, 28.07. Found: C, 36.80; H, 3.72; N, 24.59; S, 28.33.

2,4-Diamino-6-hydroxypyrimidine-5-thiol, (VIII, R_1 = NH_2, R_2 = OH).

2,4-Diamino-6-hydroxy-5-thiocyanatopyrimidine (IV, R_1 = NH_2, R_2 = OH) (10.98 g., 60 mmoles) was refluxed for 11 hours in 40% potassium hydroxide solution (120 ml.) as described for 4,6-diaminopyrimidine-5-thiol (VIII, R_1 = H, R_2 = NH_2). Glistening yellow crystals of 2,4-diamino-6-hydroxypyrimidine-5-thiol (VII, R_1 = NH_2, R_2 = OH) (8.72 g., 92% yield) were collected after crystallization from methanol-*N,N*-dimethylformamide mixture (Norit A), m.p. > 325°; uv: λ max 330 (3.3371), 274 (3.7427), 213 (4.0774); ir (potassium bromide): ν max 3460, 3380, 3180, 1650, 1480, 1455, 1380, 1347, 1250, 1148, 1090, 1050, 1010, 775, 706 cm^{-1}; pmr (DMSO-d_6): τ 3.44 b, s (2-NH_2, 4-NH_2), 1.94 b, s (5-SH), −0.10 very broad, s (6-OH); ms: m/e (relative intensity), 113 (4), 126 (24), 129 (9), 141 (100), 142 (14), 157 (3), 158 (M^+, 62%), 159 (3), 160 (12).

Anal. Calcd. for $C_4H_6N_4OS$: C, 30.38; H, 3.80; N, 35.44; S, 20.25. Found: C, 30.08; H, 3.98; N, 35.37; S, 20.04.

4,6-Diaminopyrimidine-5-thiol (VIII, R_1 = H, R_2 = NH_2).

4,6-Diamino-5-thiocyanatopyrimidine (IV, R_1 = H, R_2 = NH_2) (8.35 g., 50 mmoles was placed in the reaction flask to which was added 40 g. of potassium hydroxide in 100 ml. of water. The entire mixture was refluxed on a heating mantle for 12 hours.

At the end of the reflux period, it was treated with activated charcoal, boiled for 15 minutes and filtered. The filtrate was cooled and later neutralized with glacial acetic acid in an ice bath. Excessive frothing was observed during the neutralization period. This was reduced to a minimum by ensuring that the temperature never exceeded 10° during the neutralization period. It was later filtered with a buchner funnel and the residue recrystallized from methanol after treatment with Norit A. Glistening orange yellow microcrystals of 4,6-diaminopyrimidine-5-thiol (VIII, R_1 = H, R_2 = NH_2) (6.82 g., 96% yield) were obtained, m.p. > 300°; uv: λ max 330 (3.4171), 283 (3.3698), 241 (4.0554), 213 (4.0909); ir (potassium bromide): ν max 3430, 3310, 3150, 1650, 1575, 1490, 1460, 1344, 1315, 1280, 1150, 1010, 868, 780 cm^{-1}; pmr (DMSO-d_6): τ 3.60 s (4-NH_2, 6-NH_2), 2.28 (s, 2-CH); ms: m/e (relative intensity), 95 (3), 114 (25), 115 (5), 141 (100), 142 [M^+, 76], 143 (1).

Anal. Calcd. for $C_4H_6N_4S$: C, 33.80; H, 4.22; N, 39.44; S, 22.54. Found: C, 33.67; H, 4.39; N, 39.43; S, 22.83.

4-Amino-2-ethylthio-6-hydroxypyrimidine-5-thiol (VIII, R_1 = SCH_2CH_3, R_2 = OH).

4-Amino-2-ethylthio-6-hydroxy-5-thiocyanatopyrimidine (IV, R_1 = SCH_2CH_3, R_2 = OH) (2.28 g., 10 mmoles) was refluxed in 120 ml. of 40% sodium hydroxide solution for 8 hours. The resulting dark brown solution was treated with activated charcoal, boiled and filtered. The filtrate was cooled and neutralized to *p*H 5 with glacial acetic acid while cooling in an ice bath. The neutralized product was further chilled in a refrigerator for 20 hours and later filtered. On recrystallizing the residue from aqueous dimethylacetamide, green crystals of 4-amino-2-ethylthio-6-hydroxypyrimidine-5-thiol (VIII, R_1 = SCH_2CH_3, R_2 = OH) (1.93 g., 95% yield) were collected after treatment with Norit A, m.p. > 300°; uv: λ max 350 (3.50), 292 (3.71), 273 (3.72); λ infl 240 (4.20); ir (potassium bromide): ν max 3420, 2940, 1640, 1610, 1568, 1555, 1520, 1440, 1380, 1262, 1215, 1057, 958, 764 cm^{-1}; pmr (DMSO-d_6): τ 8.70 t (J = 7.4 Hz) (2-SCH_2CH_3), 6.92 q (J = 7.4 Hz) (2-SCH_2CH_3), 2.97 s, b (4-NH_2), 2.40 s, b (5-SH), −1.83 s, b (6-OH).

Anal. Calcd. for $C_6H_9N_3OS_2$: C, 35.47; H, 4.43; N, 20.69; S, 31.53. Found: C, 35.23; H, 4.45; N, 20.80; S, 31.63.

6-Amino-1,4,7,9-tetraazabenzo[*b*]phenothiazine, (X, R_1 = R_3 = H, R_2 = NH_2).

4,6-Diaminopyrimidine-5-thiol (VIII, R_1 = H, R_2 = NH_2) (2.84 g., 20 mmoles) was placed in a 250 ml. three-necked flask equipped with a dropping funnel, mechanical stirrer and a reflux condenser. Propylene glycol (80 ml.), water (24 ml.) and 5.6 g. of potassium hyroxide were then added. The mixture was warmed to dissolve. 2,3-Dichloroquinoxaline (4.38 g., 22 mmoles) was added and the mixture refluxed on a heating mantle for 6 hours. As soon as refluxing started an orange brown precipitation took place. As refluxing proceeded, the orange-brown solid turned bright yellow. The later product persisted throughout the reflux period. The mixture was poured into a beaker and the glassware thoroughly rinsed with water. The washings were poured into the beaker containing the reaction mixture. Further dilution with water was made until the total volume came to the 300 ml. mark. It was then cooled, filtered and the residue crystallized from aqueous DMF after treatment with activated charcoal. 6-Amino-1,4,7,9-tetraazabenzo[*b*]phenothiazine (X, R_1 = R_3 = H, R_2 = NH_2) (4.82 g., 90% yield) was collected as yellowish green microcrystals; m.p. > 310°; uv: λ max 396 (4.2410), 363 (3.6894), 334 (3.7555), 261 (4.2326), 222 (4.6618); ir (potassium bromide): ν max 3450, 3290, 3130, 1640, 1570, 1470, 1345, 1313, 1274, 1244, 1163, 1135, 1100, 1062, 990, 956, 874, 765 cm^{-1}; pmr (DMSO-d_6): τ 3.36 s (11-CH, 12-CH, 13-CH, 14-CH), 2.37 s (6-NH_2), 2.00 s (8-CH); 0.79 b, s (10-NH); ms: m/e (relative intensity), 73 (15), 35 (4), 88 (3), 90 (7), 95 (4), 102 (3), 110 (3), 114 (19), 115 (8), 128 (3), 129 (4), 134 (7), 141 (20), 142 (94), 143 (4), 144 (5), 152 (2), 153 (8), 209 (3), 214 (3), 226 (12), 227 (4), 236 (2),

241 (4), 242 (2), 258 (5), 267 (1), 268 [M⁺, 100%], 269 (77), 270 (15).

Anal. Calcd. for $C_{12}H_8N_6S$: C, 53.73; H, 2.99; N, 31.34; S, 11.94. Found: C, 53.80; H, 2.87; N, 31.18; S, 11.75.

8-Amino-6-hydroxy-1,4,7,9-tetraazabenzo[*b*]phenothiazine, (X, R_1 = NH_2, R_2 = OH, R_3 = H).

Propylene glycol (100 ml.) and water (50 ml.) were placed in the reaction flask. 2,4-Diamino-6-hydroxypyrimidine-5-thiol (VIII, R_1 = NH_2, R_2 = OH) (7.90 g., 50 mmoles) and 11.2 g. of potassium hydroxide pellets were later added. The mixture was warmed to dissolve. On dissolution, 10.95 g. (55 mmoles) of 2,3-dichloroquinoxaline, IX, R = H, were added and the mixture refluxed on a heating mantle for 4 hours. The reaction mixture was poured into a beaker, diluted twice with water and acidified with glacial acetic acid. It was then cooled and filtered, and the residue crystallized twice from aqueous DMF after treatment with activated charcoal (Norit A). The product, 8-amino-6-hydroxy-1,4,7,9-tetraazabenzo[*b*]phenothiazine, X, R_1 = NH_2, R_2 = OH, R_3 = H (11.93 g., 84% yield) was collected as greenish yellow microcrystalline powder, m.p. > 310°; uv: λ max 396; (3.2492), 329 (3.4533), 273 (4.1838), 213 (4.5672); ir (potassium bromide): ν max 3390, 3300, 3180, 2940, 1650, 1580, 1553, 1480, 1450, 1380, 1345, 1247, 1163, 1095, 996, 880, 770, 700 cm^{-1}; pmr (DMSO-d_6): τ 3.47 m (11-CH, 12-CH, 13-CH, 14-CH), 2.26 b, s (10-NH), 1.87 s (8-NH_2), −0.03 b, s (6-OH); ms: m/e (relative intensity), 72 (5), 73 (65), 84 (4), 85 (4), 86 (7), 98 (13), 99 (3), 102 (3), 110 (3), 126 (100), 127 (6), 158 (3), 252 (2), 284 (81), 285 (2), 286 (1).

Anal. Calcd. for $C_{12}H_8N_6OS$: C, 50.70; H, 2.82; N, 29.58; S, 11.27. Found: C, 50.97; H, 2.70; N, 29.53; S, 11.21.

8-Amino-12-chloro-6-hydroxy-1,4,7,9-tetraazabenzo[*b*]phenothiazine (X, R_1 = NH_2, R_2 = OH, R_3 = Cl).

A mixture of 2,4-diamino-6-hydroxypyrimidine-5-thiol (VIII, R_1 = NH_2, R_2 = OH) (9.48 g., 60 mmoles), propylene glycol (80 ml.) and 80 ml. of water was warmed to dissolve. 2,3,6-Trichloroquinoxaline (IX, R = Cl) (15.41 g., 66 mmoles) was then added and the mixture refluxed on a heating mantle for 4.5 hours. The mixture went into solution initially giving a reddish clear solution followed by a yellowish red precipitation after about an hour.

At the end of the reflux period, the mixture was poured into a beaker containing 100 ml. of water and cooled. The slurry was then acidified with glacial acetic acid with constant cooling. The product was then collected by filtration and recrystallized twice from aqueous DMF (Norit A) to yield 17.00 g. (89% yield) of 8-amino-12-chloro-6-hydroxy-1,4,7,9-tetraazabenzo[*b*]phenothiazine (X, R_1 = NH_2, R_2 = OH, R_3 = Cl) as a greenish yellow powder, m.p. > 310°; uv: λ max 396 (3.3783) 326 (3.5031), 275 (4.4169), 212 (4.7584); ir (potassium bromide): ν max 3480, 3380, 3130, 2920, 1650, 1535, 1475, 1445, 1346, 1170, 1070, 1006, 773, 700 cm^{-1}; pmr (DMSO-d_6): τ 3.57 m (11-CH, 13-CH, 14-CH), 2.90 b, s, (8-NH_2), 1.95 b, s (10-NH), 0.00 b, s (6-OH); ms: m/e (relative intensity), 124 (7), 177 (16), 141 (42), 283 (91), 284 (2), 318 [M⁺, 100%], 319 (2), 320 (33).

Anal. Calcd. for $C_{12}H_7ClN_6OS$: C, 45.21; H, 2.20; N, 26.37; S, 10.05; Cl, 11.15. Found: C, 45.40; H, 2.42; N, 26.29; S, 10.14; Cl, 10.96.

6-Amino-12-chloro-1,4,7,9-tetraazabenzo[*b*]phenothiazine, (X, R_1 = H, R_2 = NH_2, R_3 = Cl).

4,6-Diaminopyrimidine-5-thiol (VIII, R_1 = H, R_2 = NH_2) (7.10 g., 50 mmoles) in 80 ml. of propylene glycol was placed in 3-litre three-necked flask containing 2.6 g. of potassium hydroxide in 20 ml. of water. The mixture was warmed to dissolve. 2,3,6-Trichloroquinoxaline (IX, R = Cl) (11.68 g., 50 mmoles) was then added and the mixture refluxed on a heating mantle for 5.5 hours. The initially formed brown precipitate later turned yellow. This coloration persisted throughout the reflux period. The mixture was poured into a beaker and diluted two times with water and cooled. The yellow product was collected by filtration and recrystallized from DMF (Norit) to yield 6-amino-12-chloro-1,4,7,9-tetraazabenzo[*b*]phenothiazine X, R_1 = H, R_2 = NH_2, R_3 = Cl, (14.37 g., 95% yield) as bright greenish yellow microcrystalline powder, m.p. > 310°; uv: λ max 396 (3.4807), 358 (3.9760), 334 (3.9760), 260 (4.2902), 221 (4.7262); ir (potassium bromide): ν max 3490, 3390, 3100, 1663, 1620, 1590, 1573, 1554, 1500, 1430, 1360, 1330, 1300, 1287, 1250, 1210, 1162, 1132, 1085, 1036, 1010, 930, 877, 829, 788, 755 cm^{-1}; pmr (DMSO-d_6): τ 3.30 s (6-NH_2), 2.05 m (8-CH, 11-CH, 13-CH, 14-CH), 0.74 b, s (10-NH); ms: m/e (relative intensity), 87 (4), 112 (3), 114 (23), 135 (16), 137 (5), 141 (24), 142 (5), 151 (3), 153 (4), 161 (6), 163 (4), 196 (5), 198 (3), 212 (2), 258 (2), 259 (1), 260 (2), 276 (4), 278 (2), 301 (9), 302 [M⁺, 100%], 303 (3), 304 (22).

Anal. Calcd. for $C_{12}H_7ClN_6S$: C, 47.60; H, 2.31; N, 27.77; S, 10.58; Cl, 11.74. Found: C, 47.87; H, 2.52; N, 27.63; S, 10.31; Cl, 11.66.

8-Amino-12-chloro-6-hydroxy-13-nitro-1,4,7,9-tetraazabenzo[*b*]phenothiazine 5-Oxide, (XIII, R_1 = NH_2, R_2 = OH).

8-Amino-12-chloro-6-hydroxy-1,4,7,9-tetraazabenzo[*b*]phenothiazine, X, R_1 = NH_2, R_2 = OH, R_3 = Cl (3.19 g., 10 mmoles) was added 30 ml. of concentrated sulfuric acid pre-chilled at 0°. The dark red solution was placed in a freezing mixture of ice and salt. Concentrated nitric acid (d. 1.42, 40 ml.), also precooled, was added in drops during a period of 15 minutes ensuring that the temperature never rose beyond 5° during the process. Dissolution of the solid was only achieved after all the nitric acid had been added. The entire mixture was stirred at 0° for 1 hour. The ice bath was removed and the mixture stirred for additional two hours. It was then left to stand overnight. The clear dark red solution was poured into a beaker containing crushed ice and then neutralized to *p*H 8 with concentrated ammonia to *p*H 5 while cooling. The orange yellow product was collected by filtration, washed thoroughly with ice cold water and crystallized from aqueous ethanol (Norit A).

8-Amino-12-chloro-6-hydroxy-13-nitro-1,4,7,9-tetraazabenzo[*b*]phenothiazine 5-oxide XIII, (2.81 g., 74% yield) was obtained m.p. > 300° dec.; uv: λ max 362 (3.8917), 252 (3.9772); ir (potassium bromide): ν max 3440, 3100, 2950, 1630, 1570, 1553, 1500, 1486, 1445, 1382, 1344, 1270, 1053, 960, 895, 840, 825, 795, 784, 763, 756 cm^{-1}.

Anal. Calcd. for $C_{12}H_6ClN_7O_4S$: C, 37.95; H, 1.58; N, 25.82; Cl, 9.36; S, 8.43. Found: C, 38.09; H, 1.70; N, 25.81; Cl, 9.32; S, 8.64.

6-Amino-12-chloro-13-nitro-1,4,7,9-tetraazabenzo[*b*]phenothiazine 5-Oxide, XIII, R_1 = H, R_2 = NH_2.

Nitration of 6-amino-12-chloro-1,4,7,9-tetraazabenzo[*b*]phenothiazine (X, R_1 = H, R_2 = NH_2, R_3 = Cl) (3.03 g., 10 mmoles) was carried out using nitric acid (d. 1.42, 45 ml.) and sulfuric acid (d. 1.84, 35 ml.) as was described for 8-amino-12-chloro-6-hydroxy-13-nitro-1,4,7,9-tetraazabenzo[*b*]phenothiazine 5-oxide (XIII, R_1 = NH_2, R_2 = OH) except that neutralization continued up to *p*H 8. 6-Amino-12-chloro-13-nitro-1,4,7,9-tetraazabenzo[*b*]phenothiazine 5-oxide (XIII, R_1 = H, R_2 = NH_2) was obtained in 86% yield (3.13 g.), m.p. > 270 dec., uv: λ max 360 (4.1134), 283 (4.2974); ir: ν max 3430, 3150, 2930, 1645, 1572, 1553, 1540, 1472, 1400, 1356, 1325, 1280, 1180, 1050, 1013, 920, 885, 823, 784 cm^{-1}.

Anal. Calcd. for $C_{12}H_6ClN_7O_3S$: C, 39.62; H, 1.65; N, 26.96; Cl, 9.77; 8.80. Found: C, 39.94; H, 1.46; N, 27.01; Cl, 9.72; S, 8.99.

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