# [1]Benzothienopyrimidines. II. Study of the Electrophilic Substitutions of [1]Benzothieno[3,2-*d*]pyrimidine and [1]Benzothieno[3,2-*d*]pyrimidin-4-(3*H*)one



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The nitration and bromination of both [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**1**) and [1]benzothieno-[3,2-*d*]pyrimidine (**2**) has been studied. Nitration of **1** at −30° afforded a mixture of 8-nitro[1]benzothieno-[3,2-*d*]pyrimidin-4(3*H*)one (**7b**) (70%) and 6-nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7a**) (30%). However when the nitration was carried out at 60°, the 6,8-dinitro derivative **8** was the result. On the contrary, the nitration of **2** at −30° gave a single nitration product, 8-nitro[1]benzothieno[3,2-*d*]pyrimidine (**11**). The bromination of both **1** and **2** gave the corresponding 8-bromo derivatives **10** and **13**. Assignment of structure of all the products was based on ir and nmr spectral studies and on unequivocal syntheses.

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In continuation of our work on the synthesis of condensed polyheterocyclic systems (1) including evaluation of their antineoplastic activity, we now report a study of the nitration and bromination of both[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)one (**1**) and [1]benzothieno[3,2-*d*]pyrimidine (**2**) (2,3,4). Nitration of benzothienopyrimidinone **1** using fuming nitric acid (d = 1.52) at −30° gave a product which analyzed for a mononitro derivative. A study of the nmr spectrum of this product showed that it contained a mixture of two mononitrated compounds. However, analysis of the total spectrum was not possible because of overlapping signals, even when the spectrum was run in two different solvents, *viz.*, deuterated dimethyl sulfoxide and deuterated trifluoroacetic acid. This prompted us to examine the nmr spectrum of the corresponding amino products, resulting from the reduction of the nitrobenzothienopyrimidones using Raney nickel in absolute ethanol containing hydrazine hydrate.

A closer study of the latter spectrum indicated quite clearly that the mixture contains two amino derivatives, since the signals corresponding to the protons of one isomer do not overlap with those of the other, owing to the observed differences in their chemical shifts.

With respect to the aromatic protons, the spectrum of the major product (70%) displayed an ABX system with a quadruplet at δ 7.70 ppm showing *ortho* and *para* coupling, a quadruplet at δ 6.95 ppm showing *ortho* and *meta* coupling and another quadruplet at δ 7.35 ppm showing *meta* and *para* coupling. These data indicate that the amino group is in the 7- or 8-position. On the other hand, the spectrum of the minor product (30%) exhibited an ABC system with a triplet centered at δ 7.26 ppm, indicative of two *ortho* coupling and two quadruplets at δ 7.48 ppm and 6.85 ppm, indicating *ortho* and *meta* couplings. Accordingly, the amino group occurs whether in the 6- or 9-position. It can be concluded, therefore, that the mixture of the nitration products contains a major isomer (70%) in which the nitro group exists in the 7- or 8-position and a minor isomer (30%) in which the nitro group exists in the 6- or 9-position.

To assign the structure of these two nitro isomers, the unequivocal synthesis of 8-nitro[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)one (**7b**) and 6-nitro[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)one (**7a**) was deemed of interest.

The nitroaminoesters **5a** and **5b** were prepared by condensing the requisite 2-chloro-3(or 5)nitrobenzonitriles (**3**) with methylthioglycolate following the method of Friedlander (5-9). The reaction proceeded *via* nucleophilic substitution by the methylthioester at the 2 position of compound **3**, giving the methyl thiophenoxyacetate intermediates (**4**).

However, by adjusting the reaction conditions the intermediate **4b** could be isolated and identified (ir and nmr spectra). The reaction of the aminoesters **5** with formic acid afforded the corresponding formamido derivatives **6**, which in turn were converted to the desired nitrobenzothienopyrimidones **7** by heating with formamide and ammonium formate, following the synthesis of quinazolones reported by Niementowski (10). Alternatively, compounds **7** were directly obtained from **5** by reacting the latter compounds with formamide.

In a similar way to that mentioned before, these two 6-and 8-nitro compounds **7a** and **7b** were reduced to the corresponding amines **9a** and **9b**, respectively. Comparison of the nmr spectra of these latter two amines with that of the amine mixture revealed that it consisted of both **9a** and **9b** in a 30:70 ratio. That is to say, the mixture of the nitration products consists of 6-nitro[1]benzothieno-[3,2-*d*]pyrimidin-4(3*H*)one (**7a**) (30%) and 8-nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7b**) (70%).

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SCHEME 1

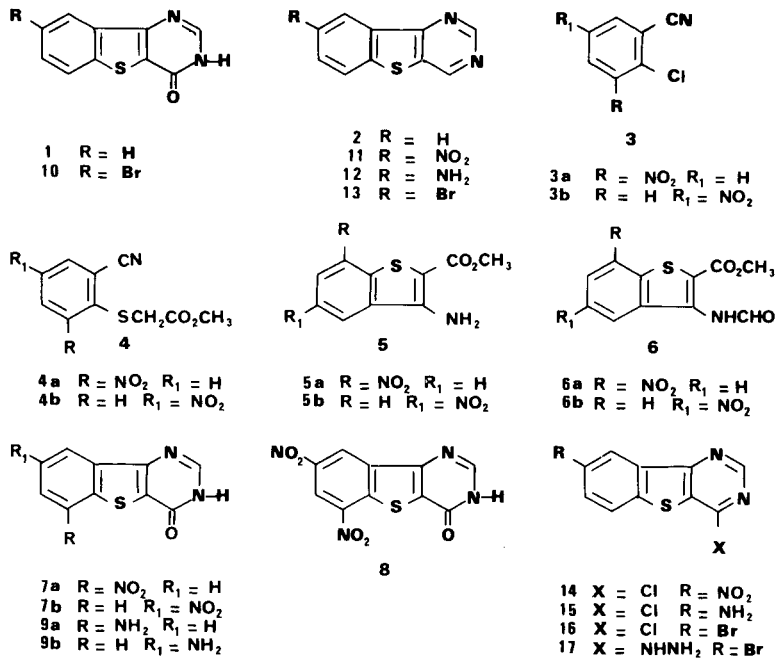
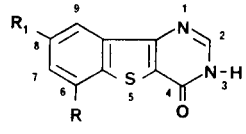



Table 1

Proton Chemical Shifts (δ) and Coupling Constants (J) of [1]Benzothieno[3,2-*d*]pyrimidin-4(3*H*)ones (a)

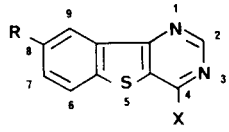


| Compound No. | R | R1 | δ H2 | δ H6 | δ H7 | δ H8 | δ H9 | δ Others Protons | Coupling Constants | Solvent |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | | | 8.40 | 8.20 | 7.70 | 7.70 | 8.20 | 12.60 (NH) | | DMSO-$d_6$ |
| **7a** | $NO_2$ | H | 8.33 | | 8.60 (8.51) | 7.76 | 8.51 (8.60) | 3.3 (NH) | $J_{7,8}$ = 7.8<br>$J_{8,9}$ = 7.8<br>$J_{7,9}$ = 1.2 | DMSO-$d_6$ |
| **7a** | $NO_2$ | H | 9.46 | | 8.89 (8.85) | 7.96 | 8.85 (8.89) | | | TFA (b) |
| **7b** | H | $NO_2$ | 8.44 | 8.44 | 8.44 | | 8.86 | | | DMSO-$d_6$ |
| **7b** | H | $NO_2$ | 9.57 | 8.35 | 8.72 | | 9.55 | | $J_{6,7}$ = 9.0<br>$J_{7,9}$ = 2.0 | TFA |
| **8** | $NO_2$ | $NO_2$ | 8.40 | | 9.10 | | 9.10 | 13.1 (NH) | | DMSO-$d_6$ |
| **8** | $NO_2$ | $NO_2$ | 9.23 | | 9.72 | | 9.51 | | $J_{7,9}$ = 2.0 | TFA |
| **9a** | $NH_2$ | H | 8.25 | | 6.85 | 7.26 | 7.48 | 5.65 ($NH_2$) | $J_{8,9}$ = 7.8<br>$J_{7,8}$ = 7.2<br>$J_{7,9}$ = 1.3 | DMSO-$d_6$ |
| **9b** | H | $NH_2$ | 8.21 | 7.70 | 6.95 | | 7.35 | 5.2 ($NH_2$) | $J_{6,7}$ = 8.7<br>$J_{7,9}$ = 2.0<br>$J_{6,9}$ = 0.5 | DMSO-$d_6$ |
| **10** | H | Br | 8.27 | 8.08 | 7.72 | | 8.27 | | $J_{6,7}$ = 8.7<br>$J_{7,9}$ = 1.9<br>$J_{6,9}$ = 0.5 | DMSO-$d_6$ |

(a) Chemical shifts are given in ppm relative to tetramethylsilane as an internal standard. Coupling constants are given in Hertz. (b) TFA = deuterated trifluoroacetic acid.

Table 2

Proton Chemical Shifts (δ) and Coupling Constants (J) of [1]Benzothieno[3,2-*d*]pyrimidines (a)



| Compound No. | X | R | δ H2 | δ H4 | δ H6 | δ H7 | δ H9 | δ Others Proton | Coupling Constants |
|---|---|---|---|---|---|---|---|---|---|
| **2** | H | H | 9.35 | 9.80 | 8.20 | 7.75 | 8.45 | 7.75 (H8) | |
| **11** | H | $NO_2$ | 9.46 | 9.75 | 8.59 | 9.20 | 8.56 | | |
| **12** | H | $NH_2$ | 9.27 | 9.46 | 7.87 | 7.21 | 7.76 | 5.51 ($NH_2$) | $J_{6,7}$ = 8.6<br>$J_{7,9}$ = 2.2 |
| **13** | H | Br | 9.29 | 9.58 | 8.20 | 7.90 | 8.54 | | $J_{6,7}$ = 8.7<br>$J_{7,9}$ = 1.9<br>$J_{6,9}$ = 0.5 |
| **14** | Cl | $NO_2$ | 8.93 | | 8.25 | 8.25 | 8.73 | | |
| **15** | Cl | $NH_2$ | 9.00 | | 7.76 | 7.06 | 7.53 | 5.53 ($NH_2$) | $J_{6,7}$ = 8.7<br>$J_{7,9}$ = 2.1 |
| **16** | Cl | Br | 9.11 | | 8.20 | 7.92 | 8.48 | | |

(a) Chemical shifts are given in ppm relative to tetramethylsilane as an internal standard. Coupling constants are given in Hertz (solvent = DMSO-$d_6$).

On the other hand, the nitration of benzothienopyrimidone (**1**) in a mixture of concentrated sulfuric acid and fuming nitric acid (d = 1.52) at 60° furnished 6,8-dinitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**8**). The same compound was obtained by nitrating the 8-nitro derivative **7b**.

It should be noted that the reaction of **7b** with phosphorus oxychloride afforded the 4-chlorobenzothienopyrimidine (**14**), which was reduced to 8-amino-4-chlorobenzothienopyrimidine (**15**) by catalytic hydrogenation over Raney nickel under pressure.

Despite the fact that a mixture was obtained from the nitration of **1**, only a monosubstituted compound was obtained when [1]benzothieno[3,2-*d*]pyrimidine (**2**) was nitrated at −30°. Evidence that the resulting material was 8-nitrobenzothienopyrimidine (**11**) was provided as follows. Reduction of this mononitro compound **11** to the corresponding amine **12** was followed by its conversion, *via* the Sandmeyer reaction, to the corresponding bromo compound **13**. Characterization of this compound was accomplished by its comparison with a sample of 8-bromo-[1]benzothieno[3,2-*d*]pyrimidine (**13**), prepared by an unequivocal route starting from 8-amino[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)one (**9b**). Thus, **9b** was converted to **10** employing the Sandmeyer reaction. Treating the latter compound with phosphoryl chloride gave **16**, which was allowed to react with hydrazine hydrate in ethanol to give the 4-hydrazino derivative **17**.

The removal of the hydrazino group by bubbling oxygen through a sodium ethoxide/ethanol solution of **17** following the method of Albert and Catterall (11) gave the 8-bromo derivative **13**. The two samples of **13** prepared from **9b** or **11** proved to be identical (m.p., ir, nmr).

Bromination of **1** with bromine at room temperature gave a monobrominated compound the nmr spectrum of which indicated that substitution may have occurred at the 7- or 8-position. This compound proved to be identical with a sample of 8-bromo[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**10**), prepared from the 8-amino compound (**9b**) *via* the Sandmeyer reaction.

Similarly, the bromination of **2** with bromine at 70° afforded the monobrominated compound. The nmr spectrum of the latter compound suggested the 7- or 8-brominated structure. Once again, comparing this compound with a sample of **13** prepared by unequivocal synthesis starting from **9b**, revealed that they are identical.

## EXPERIMENTAL

All melting points were determined on a Kofler block, or on a Maquenne block apparatus and are uncorrected. Ir spectra were recorded (potassium bromide or nujol) on a Perkin-Elmer model 157 G spectrometer. Nmr spectra were obtained with Varian EM 360 and EM 390, using TMS (tetramethylsilane) as an internal standard and chemical shifts were expressed as δ, parts per million.

Materials.

Methyl thioglycolate and 2-chloro-5-nitrobenzonitrile (**3b**) were obtained from the Aldrich-Europe Division. 2-Chloro-3-nitrobenzonitrile (**3a**) was synthesized from the 2-chloro-3-nitrobenzoic acid (Aldrich-Europe

Division) through the methyl ester and the amide.

The previously described synthesis (12) of 2-carbomethoxy-3-amino-5-nitro[1]benzothiophene (**5b**) was modified, particularly by using triethylamine instead of potassium *tert*-butylate as catalyst. [1]Benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**1**) and [1]benzothieno[3,2-*d*]pyrimidine (**2**) were prepared by procedures described in the literature (4).

Methyl 2-Cyano-4-nitrothiophenoxyacetate (**4b**).

To a stirred solution of 2-chloro-5-nitrobenzonitrile (**3b**) (5.46 g.) and methylthioglycolate (3.08 g.) in ethanol (100 ml.), heated at 60°, triethylamine (3.5 ml.) was added dropwise keeping the temperature below 60°. After stirring for 5 minutes, the crystalline compound that separated was filtered, washed thoroughly with water and crystallized from ethanol giving yellow platelets, yield 6 g. (91%), m.p. 125°; ir (potassium bromide): $\nu$ $cm^{-1}$ 2240 (C≡N), 1740 (C=O), 1595 and 1520 (C=C); nmr (DMSO-$d_6$): $\delta$ ppm 8.63 (d, H3), 8.35 (q, H5), 7.65 (d, H6), 4.33 (s, $CH_2$), 3.71 (s, $CH_3$).

*Anal.* Calcd. for $C_{10}H_8N_2O_4S$: C, 47.62; H, 3.19; N, 11.10; S, 12.71. Found: C, 47.46; H, 3.09; N, 11.09; S, 12.60.

2-Carbomethoxy-3-amino-5-nitro[1]benzothiophene (**5b**).

In the above procedure, after addition of all the triethylamine, the reaction mixture was allowed to reflux and then more triethylamine (5 ml.) was added in portions until no more fading of the red color of the reaction mixture was observed. Refluxing was continued for 3 additional hours. The orange-red crystals which separated were filtered and washed with water followed by a small amount of alcohol. Crystallization from dioxane gave orange needles, yield 6.6 g. (88%), m.p. 242°, lit. (12) m.p. 240-242°; ir (potassium bromide): $\nu$ $cm^{-1}$ 3440, 3340 and 1610 ($NH_2$), 1675 (C=O), 1590 and 1565 (C=C); nmr (DMSO-$d_6$): $\delta$ ppm 9.28 (q, H4), 8.33 (q, H6), 8.11 (q, H7), 7.48 (s, $NH_2$), 3.85 (s, $CH_3$).

*Anal.* Calcd. for $C_{10}H_8N_2O_4S$: C, 47.62; H, 3.20; N, 11.11; S, 12.71. Found: C, 47.80; H, 3.38; N, 11.25; S, 12.93.

2-Carbomethoxy-3-formamido-5-nitro[1]benzothiophene (**6b**).

A solution containing 2-carbomethoxy-3-amino-5-nitrobenzothiophene (**5b**) (3.25 g.) and sodium acetate (2.27 g.) in formic acid (16 ml.) was refluxed for 1 hour and then evaporated under reduced pressure. The solid residue was triturated with water, filtered and crystallized from ethanol (long colorless needles), yield 2.23 g. (60%), m.p. 200°; ir $\nu$ $cm^{-1}$ 3220 (NH), 1720 (C=O, ester), 1655 (C=O, amide); nmr (DMSO-$d_6$): $\delta$ ppm 8.76 (m, H4 and H6), 8.25 (m, H7 and CHO), 3.93 (s, $CH_3$), 3.40 (s, NH).

*Anal.* Calcd. for $C_{11}H_9N_3O_5S$: C, 47.15; H, 2.88; N, 10.00; S, 11.42. Found: C, 47.28; H, 2.97; N, 10.15; S, 11.42.

2-Carbomethoxy-3-formamido-7-nitro[1]benzothiophene (**6a**).

In a similar manner this compound was obtained starting with 2-carbomethoxy-3-amino-7-nitro[1]benzothiophene (**5a**) (3.25 g.). Crystallization from ethanol gave yellow needles, yield 2.7 g. (77%), m.p. 226°; ir: $\nu$ $cm^{-1}$ 3220 (NH), 1700 (C=O ester), 1660 (C=O amide), nmr (DMSO-$d_6$): $\delta$ ppm 8.58 (q, H6), 8.43 (s, CHO), 8.33 (q, H4), 7.73 (t, H5), 3.90 (s, $CH_3$), 2.06 (s, NH).

*Anal.* Calcd. for $C_{11}H_9N_3O_5S$: C, 47.15; H, 2.88; N, 10.00; S, 11.42. Found: C, 47.06; H, 2.84; N, 10.12; S, 11.41.

8-Nitro-[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7b**).

Method 1.

To a solution containing the 2-carbomethoxy-3-amino-5-nitro[1]benzothiophene (**5b**) (5 g.) and sodium ethoxide (1.36 g.) in dimethylsulfoxide (30 ml.), was added formamide (25 ml.). The resulting mixture was heated at 90° for 45 minutes. It was then cooled, poured into ice-cold water (400 ml.) and acidified with acetic acid. The precipitate was filtered washed with water and crystallized from an acetic acid-dioxane mixture (1/1) as yellow crystals, yield 3.9 g. (78%); m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 1660 (C=O), 1605, 1590 and 1535 (C=C and C=N).

*Anal.* Calcd. for $C_{10}H_5N_3O_5S$: C, 48.59; H, 2.04; N, 17.00; S, 12.69. Found: C, 48.46; H, 1.89; N, 17.16; S, 12.81.

Method 2.

A mixture of 2-carbomethoxy-3-formamido-5-nitro[1]benzothiophene (**6b**) (2.5 g.) ammonium formate (3.5 g.) and formamide (20 ml.) was heated at 140° for 5 hours. The reaction mixture was evaporated to one third of its volume and diluted with excess water. The resulting precipitate was filtered, washed with water and crystallized from an acetic acid-dioxane mixture (1/1) as yellow crystals, yield 2 g. (87%); m.p., ir and nmr spectra are identical with those of a sample prepared by Method 1.

6-Nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7a**).

This compound was prepared following one of the two procedures described for **7b**, using equivalent amounts of the requisite starting materials. Crystallization from dioxane gave dark yellow prisms, yield 2.1 g. (91%) (following Method 2), m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 1670 (C=O), 1605, 1580 and 1510 (C=C and C=N).

*Anal.* Calcd. for $C_{10}H_5N_3O_3S$: C, 48.59; H, 2.04; N, 17.00; S, 12.69. Found: C, 48.83; H, 2.16; N, 16.75; S, 12.49.

6,8-Dinitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**8**).

Method 1.

To a solution of [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**1**) (1 g.) in concentrated sulfuric acid (10 ml.), fuming nitric acid (5 ml.) was added dropwise. The reaction mixture was heated at 60° with stirring for 1 hour and then poured on crushed ice (50 g.). The precipitate was filtered, washed with water and crystallized from an acetic acid-dioxane mixture (1/1) as dark yellow crystals, yield 0.73 g. (49%); m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 3400 (NH), 3095 (CH), 1665 (C=O), 1610, 1575 and 1520 (C=C and C=N).

*Anal.* Calcd. for $C_{10}H_4N_4O_5S$: C, 41.11; H, 1.38; N, 19.18. Found: C, 41.36; H, 1.63; N, 19.31.

Method 2.

8-Nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7b**) (1 g.) was nitrated in a similar manner, however the reaction mixture was heated at 80-85° for 1.5 hours, yield 0.3 g. (20%). The ir and nmr spectra are identical with those of a sample prepared by Method 1.

6- and 8-Nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)ones (**7a** and **7b**).

[1]Benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**1**) (1 g.) was added, in portions with stirring, to cold (−30°) fuming nitric acid (10 ml.). The resulting mixture was stirred at this temperature for 1 hour and then poured onto crushed ice (50 g.). The precipitate was filtered, washed with water and crystallized from an acetic acid-dioxane mixture (1/1) as yellow crystals, yield 0.9 g. (75%), m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 1660 (C=O); the nmr spectrum showed a mixture of **7a** and **7b**, the analysis of which was impossible (in DMSO-$d_6$ or deuterated trifluoroacetic acid) because of the overlapping of signals.

*Anal.* Calcd. for $C_{10}H_5N_3O_3S$: C, 48.59; H, 2.04; N, 17.00. Found: C, 48.46; H, 1.89; N, 17.16.

8-Nitro[1]benzothieno[3,2-*d*]pyrimidine (**11**).

To a stirred solution of [1]benzothieno[3,2-*d*]pyrimidine (**2**) (1 g.) in concentrated sulfuric acid (10 ml.), cooled at −30°, fuming nitric acid (5 ml.) was added dropwise. After stirring for 1 additional hour at this temperature, the reaction mixture was poured on crushed ice. The precipitate was filtered, washed with water and crystallized from dioxane as yellow needles, yield 0.6 g. (48%), m.p. 227°; ir (potassium bromide): $\nu$ $cm^{-1}$ 3085 (C-H aromatic), 1600, 1575 and 1545 (C=N and C=C).

*Anal.* Calcd. for $C_{10}H_5N_3O_2S$: C, 51.96; H, 2.18; N, 18.18. Found: C, 51.85; H, 2.15; N, 18.04.

8-Amino[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**9b**).

Hydrazine hydrate (1 ml.) was added to a well stirred suspension of 8-nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7b**) (2 g.) in ethanol (800 ml.) and the resulting mixture was heated at 60° and stirred for 10 minutes. Raney nickel (3 g.) was then added, the heat was removed and stirring was continued for 4 additional hours at room temperature. Unreacted nickel was removed by filtration and the filtrate was

evaporated *in vacuo*. The solid residue was crystallized from ethanol as fine needles, yield 1.3 g. (87%), m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 3330 and 3205 ($NH_2$), 1670 (C=O).

*Anal.* Calcd. for $C_{10}H_7N_3OS$: C, 55.30; H, 3.25; N, 19.35; S, 14.73. Found: C, 55.03; H, 3.33; N, 19.28; S, 14.82.

6-Amino[1]benzothieno[3,2-*d*]pyrimidine-4(3*H*)one (**9a**).

In a similar manner this compound was prepared by the reduction of 6-nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7a**) (2 g.). Crystallization from ethanol gave needles, yield 1.4 g. (93%), m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 3410, 3300 and 1630 ($NH_2$), 1660 (C=O).

*Anal.* Calcd. for $C_{10}H_7N_3OS$: C, 55.30; H, 3.25; N, 19.35; S, 14.73. Found: C, 55.25; H, 3.41; N, 19.48; S, 14.95.

6- and 8-Amino[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)ones (**9a** and **9b**).

In a similar manner the mixture of compounds **7a** and **7b** (0.16 g.) was reduced to give a mixture of 6- and 8-amino[1]benzothieno[3,2-*d*]-pyrimidin-4(3*H*)ones. Crystallization from ethanol gave yellow needles, yield 0.5 g. (94%), m.p. 218°; ir (nujol): $\nu$ $cm^{-1}$ 3330 and 3220 ($NH_2$), 1670 (C=O). Comparison of the nmr spectrum (DMSO-$d_6$) of the mixture with those of **9a** and **9b**, which were obtained by unequivocal synthesis, revealed that it consisted of 70% of **9b** and 30% of **9a**; **9a** nmr: $\delta$ ppm 5.65 (s, $NH_2$), 6.85 (q, H7), 7.26 (t, H8), 7.48 (q, H9), 8.25 (s, H2), $J_{7,8}$ = 7.2 Hz, $J_{8,9}$ = 7.8 Hz, $J_{7,9}$ = 1.3 Hz; **9b** nmr: $\delta$ ppm 5.20 (s, $NH_2$), 6.95 (q, H7), 7.35 (q, H9), 7.70 (q, H6); $J_{6,7}$ = 8.7 Hz, $J_{7,9}$ = 2.0 Hz, $J_{6,9}$ = 0.50 Hz.

*Anal.* Calcd. for $C_{10}H_7N_3OS$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.03; H, 3.33; N, 19.28.

8-Amino[1]benzothieno[3,2-*d*]pyrimidine (**12**).

In a similar manner this compound was obtained by the reduction of 8-nitro[1]benzothieno[3,2-*d*]pyrimidine (**11**) (0.6 g.). Crystallization from ethanol gave orange yellow needles, yield 0.4 g. (80%), m.p. 218°; ir (potassium bromide): $\nu$ $cm^{-1}$ 3340, 3210 and 1610 ($NH_2$), 1550 and 1520 (C=N and C=C).

*Anal.* Calcd. for $C_{10}H_7N_3S$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.64; H, 3.41; N, 20.85.

8-Nitro-4-chloro[1]benzothieno[3,2-*d*]pyrimidine (**14**).

A mixture of 8-nitro[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**7b**) (1 g.), phosphoryl chloride (10 ml.) and pyridine (0.5 ml.) was refluxed for 30 minutes. After evaporation *in vacuo*, the solid residue was worked up in ice. The ammonium hydroxide mixture was filtered and crystallized from ethanol as yellow crystals, yield 0.54 g. (50%), m.p. 225°; ir (nujol): $\nu$ $cm^{-1}$ 3200 (CH), 1610, 1555 and 1515 (C=C and C=N).

*Anal.* Calcd. for $C_{10}H_4ClN_3O_2S$: C, 45.20; H, 1.55; N, 16.18; Cl, 13.36. Found: C, 45.12; H, 1.55; N, 16.09; Cl, 13.54.

8-Amino-4-chloro[1]benzothieno[3,2-*d*]pyrimidine (**15**).

8-Nitro-4-chloro[1]benzothieno[3,2-*d*]pyrimidine (**14**) (2 g.) was reduced by catalytic hydrogenation over Raney nickel (3 g.) under pressure (100 atmospheres) in a steel bomb at 80° for a 5 hour period, following the same procedure described for **9b**. Crystallization from ethanol gave yellow crystals, yield 1.6 g. (90%), m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 3380, 3300 and 1620 ($NH_2$), 1605, 1550 and 1510 (C=C and C=N).

*Anal.* Calcd. for $C_{10}H_6ClN_3S$: C, 51.05; H, 2.56; N, 17.86; Cl, 14.87. Found: C, 51.23; H, 2.68; N, 17.76; Cl, 14.68.

8-Bromo[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**10**).

Method 1.

To a cold (0-5°) solution of 8-amino[1]benzothieno[3,2-*d*]pyrimidin-4-(3*H*)one (**9b**) (2.17 g.) in hydrobromic acid (d, 1.07, 24 ml.) and water (20 ml.), was added, with stirring over a 5 minute period, a solution of sodium nitrite (0.75 g.) in water (6 ml.). The resulting diazonium solution was held at this temperature for 15 minutes and then poured, in portions with shaking, on a hot (water bath temperature) mixture of cuprous bromide (2.5 g.), hydrobromic acid (d, 1.07, 2 ml.) and water (5 ml.). When the evolution of nitrogen gas ceased the precipitate was filtered off, washed with water and crystallized from a dioxane-acetonitrile mixture (1/1) in white crystals, yield 2.3 g. (82%), m.p. > 300°; ir (potassium bromide): $\nu$ $cm^{-1}$ 1655 (C=O), 1580 (C=C).

*Anal.* Calcd. for $C_{10}H_5BrN_2OS$: C, 42.72; H, 1.79; Br, 28.42. Found: C, 42.97; H, 1.79; Br, 28.20.

Method 2.

A solution of [1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**1**) (1 g.) in bromine (5 ml.) was stirred at room temperature for 2 hours. Excess bromine was removed under reduced pressure and the solid residue was washed by boiling alcohol and dried, yield 1 g. (72%); m.p. ir and nmr spectra are identified with those of a sample prepared by Method 1.

8-Bromo-4-chloro[1]benzothieno[3,2-*d*]pyrimidine (**16**).

A mixture of 8-bromo[1]benzothieno[3,2-*d*]pyrimidin-4(3*H*)one (**10**) (1.4 g.), phosphoryl chloride (14 ml.) and pyridine (0.7 ml.) was refluxed with stirring for 0.5 hour. After evaporation of the excess phoshoryl chloride *in vacuo*, the solid residue was worked up in an ammonium hydroxide-ice mixture, filtered and washed with water. Crystallization from acetonitrile gave white crystals, yield 1.2 g. (81%), m.p. 192°; ir (potassium bromide): $\nu$ $cm^{-1}$ 1530, 1500 and 1445 (C=C).

*Anal.* Calcd. for $C_{10}H_4BrClN_2S$: C, 40.09; H, 1.34; N, 9.35. Found: C, 40.12; H, 1.44; N, 9.59.

8-Bromo-4-hydrazino[1]benzothieno[3,2-*d*]pyrimidine (**17**).

8-Bromo-4-chloro[1]benzothieno[3,2-*d*]pyrimidine (**16**) (0.56 g.) and hydrazine hydrate (0.1 ml.) in ethanol (15 ml.) was refluxed for 2 hours. The solvent was removed *in vacuo* and the precipitate was washed with water and crystallized from methanol as white needles, yield 0.4 g. (71%), m.p. > 300°; ir (nujol): $\nu$ $cm^{-1}$ 3320, 3195 and 1645 ($NHNH_2$), 1575 and 1495 (C=C and C=N).

*Anal.* Calcd. for $C_{10}H_7BrN_4S$: C, 40.49; H, 2.39; Br, 27.02; N, 18.98; S, 10.86. Found: C, 40.93; H, 2.39; Br, 27.25; N, 18.73; S, 10.76.

8-Bromo[1]benzothieno[3,2-*d*]pyrimidine (**13**).

Method 1.

To a stirred ethanolic sodium ethoxide solution (prepared from 0.06 g. of sodium and 30 ml. absolute ethanol) was added the 8-bromo-4-hydrazino[1]benzothieno[3,2-*d*]pyrimidine (**17**) and a stream of oxygen gas was allowed to bubble in the resulting solution for 3 hours. It was left overnight at room temperature. The solvent was evaporated *in vacuo* and the solid residue was washed with water and then extracted with chloroform. After washing the latter layer with water, drying over calcium chloride and filtration, the solvent was evaporated and the resulting solid product was crystallized from ethanol followed by sublimation *in vacuo*, yield 0.2 g. (46%), m.p. 208°; ir: $\nu$ $cm^{-1}$ 3080 and 3040 (CH), 1590, 1550 and 1520 (C=C and C=N).

*Anal.* Calcd. for $C_{10}H_5BrN_2S$: C, 45.30; H, 1.90; N, 10.56. Found: C, 45.33; H, 1.88; N, 10.79.

Method 2.

A solution of [1]benzothieno[3,2-*d*]pyrimidine (**2**) (0.9 g.) in bromine (13.5 ml.) was stirred for 0.5 hour at 70°. Excess bromine was removed *in vacuo* and the solid residue was washed thoroughly with boiling ethanol, dried and sublimed *in vacuo*, yield 1.03 g. (80%); m.p. mixed m.p., ir and nmr spectra are identical with those of a sample prepared by Method 1.

Method 3.

8-Amino[1]benzothieno[3,2-*d*]pyrimidine (**12**) (2 g.) was dissolved in a hot mixture of hydrobromic acid (d, 1.07, 25 ml.) and water (20 ml.), filtered and cooled to 0-5°. To this solution was slowly added, with shaking, a solution of sodium nitrite (0.69 g.) in water (7 ml.) and the resulting mixture was kept at 0-5° for 15 minutes. It was then poured onto a hot (water bath temperature) mixture of cuprous bromide (2 g.), hydrobromic acid (d, 1.07, 2 ml.) and water (3 ml.). When the evolution of nitrogen gas

ceased, the resulting precipitate was filtered, washed with water, dried and sublimed *in vacuo*, yield 1.7 g. (68%); m.p. ir and nmr spectra are identical to those of a sample prepared by Method 1.

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