Synthesis of Some Novel Azido/Tetrazolothienopyrimidines and their Reduction to 2,4-Diaminothieno[2,3-*d*]pyrimidines

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Received October 1, 1991

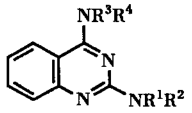
A variety of novel 2,4-diaminothieno[2,3-*d*]pyrimidines has been prepared through the reduction of the corresponding azido/tetrazolothienopyrimidines under acidic conditions.

J. Heterocyclic Chem., **29**, 883 (1992).

2,4-Diaminopyridines and condensed 2,4-diaminopyrimidines have exhibited promising antifolate activities. Some of these antifolate compounds namely, methotrexate, trimethoprim and pyrimethamine are widely used in therapy as potential anticancer, antibacterial and antimalarial drugs, respectively [1]. Antimalarial activity has also been reported in some 2,4-substituted-diaminoquinazolines, **1** and their bioisosteric 2,4-diaminothieno[2,3-*d*]pyrimidines **2** by Elslager and co-workers [2,3]. As part of our continuing program on the synthesis of antifolate antimalarial compounds, we have earlier prepared a series of 2,4-diaminopyrimidines and 2,4-substituted-diaminothieno[2,3-*d*]pyrimidines **3** [4]. We now required the derivatives of the types **4-6** for completing the SAR studies of the antimalarial 2,4-diaminothieno[2,3-*d*]pyrimidines.

The synthesis of condensed 2,4-diaminopyrimidines **8** and **9** through sequential nucleophilic displacement reactions of an appropriately substituted condensed pyrimidine substrate **7** is of limited utility as the displacement reactions involving ammonia require very drastic conditions like heating under elevated pressures and temperatures [5].

Azides and tetrazoles can be viewed as latent amino functionalities. While azides undergo facile reduction to yield amines, tetrazoles are highly resistant to reduction [6]. Heterocyclic azides especially the azidoazomethines, are known to exist in equilibrium with their tetrazolo tautomers. The azidoazomethine-tetrazole equilibrium is the subject of many reviews [7-9]. This equilibrium is influenced by many factors, notably the nature of the sub-



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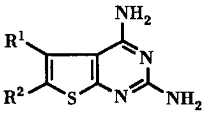

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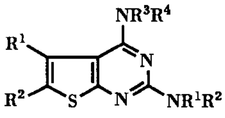

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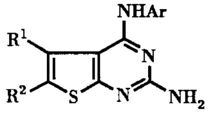
NR^{1}R^2, NR^{3}R^4 = ArNH
R$_2$N(CH$_2$)$_n$-NH-



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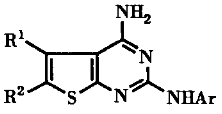

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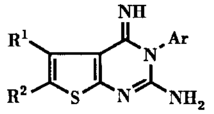

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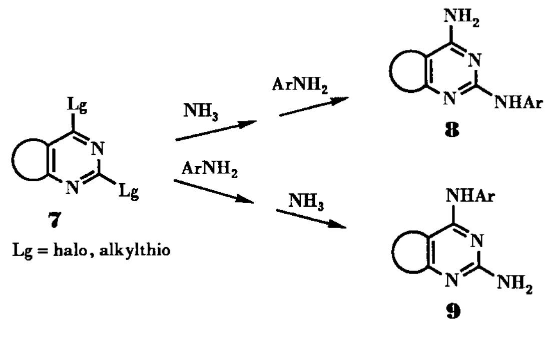
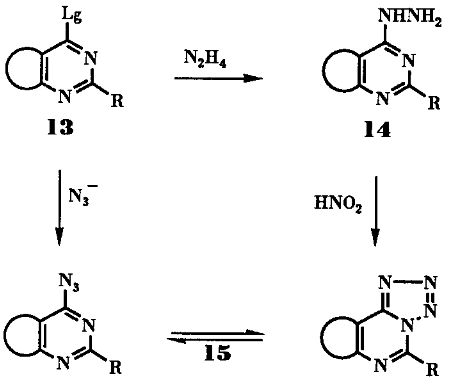


stituents around the C = N bond of the azidoazomethine, the nature of the solvent system, *p*H and temperature [7-9] and therefore, can be shifted in either direction by manipulating these factors. The well studied influence of acidic *p*H to shift the azide-tetrazole equilibrium to the more reactive azido tautomer has been successfully utilized [10-12] not only in the reduction reactions to obtain amines, but also in the photolysis of tetrazoles to obtain reactive nitrenes. Thus it is possible to effect the reduction of tetrazoles by shifting this equilibrium to the side of the more labile and reactive azides prior to the reduction step.

This report describes our approach to the synthesis of aminothieno[2,3-*d*]pyrimidines **4-6** by the reduction of the appropriate precursor azido/tetrazolothienopyrimidines **10-12** (Scheme I). The azido/tetrazolothienopyrimidines have been synthesized by different routes and their structural assignments are based on spectral data.

In general, azido/tetrazolopyrimidines **15** can be obtained through the nitrosation of the corresponding hydrazinopyrimidines with nitrous acid. The hydrazinopyrimidines **14** in turn can be synthesized by the nucleophilic displacement of a labile halogen atom or an alkylthio group of the corresponding substrate **13** by hydrazine. Alternatively, the synthesis of azido/tetrazolopyrimidines involves the direct nucleophilic displacement of the leaving group of **13** with the azide ion. This later route is more attractive and was, therefore, adopted in the present work.

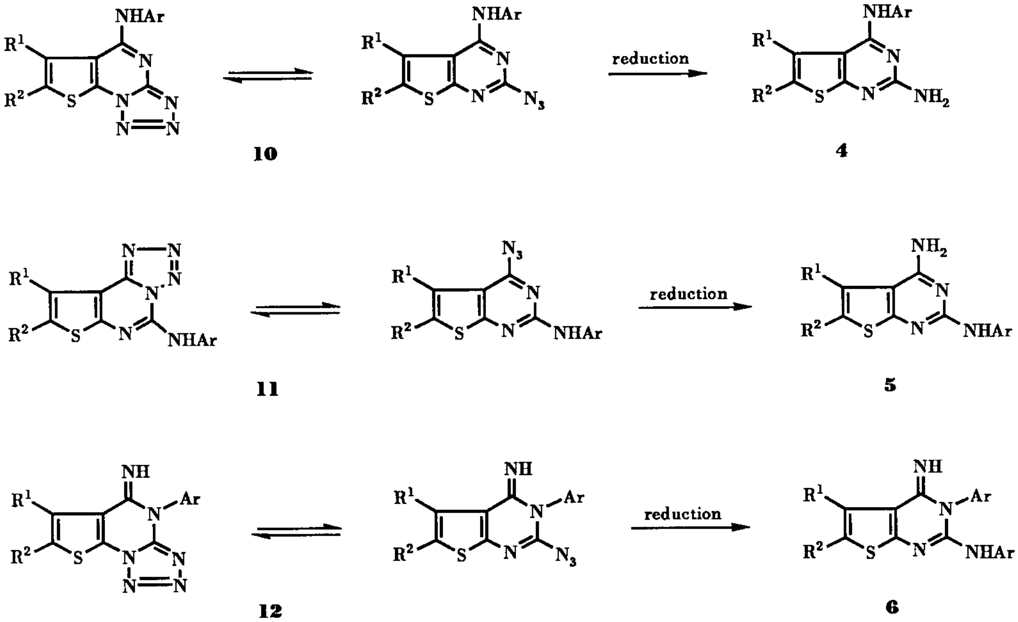
The 4-arylamino-2-azidothieno[2,3-*d*]pyrimidines **10a-e** were prepared by the route depicted in Scheme II.



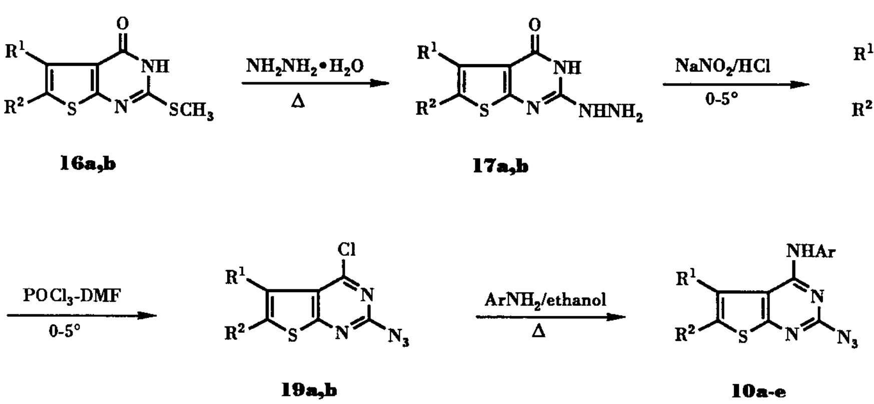
The 2-methylthiothieno[2,3-*d*]pyrimidin-4(3*H*)-one, **16** [13] was refluxed with excess hydrazine hydrate to afford 2-hydrazinothieno[2,3-*d*]pyrimidin-4(3*H*)-one, **17**, which was then nitrosated to the 2-azidothieno[2,3-*d*]pyrimidin-4(3*H*)-one **18** at 0-5°. Reaction of **18** with phosphorus oxychloride yielded the 2-azido-4-chlorothieno[2,3-*d*]pyrimidine **19**. Displacement of the 4-chlorine atom of **19** with various arylamines under mild conditions afforded a series of the desired 4-arylamino-2-azidothieno[2,3-*d*]pyrimidines **10a-e** characterized by their spectral and analytical data.

The 5-arylaminotetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines **11a-e** were synthesized from the same starting material **16**. The 2-methylthio group of **16** was displaced with arylamines at 180-200°. Reaction of **20** with phosphorus oxychloride in presence of a catalytic amount of *N*,*N*-dimeth-

Scheme I

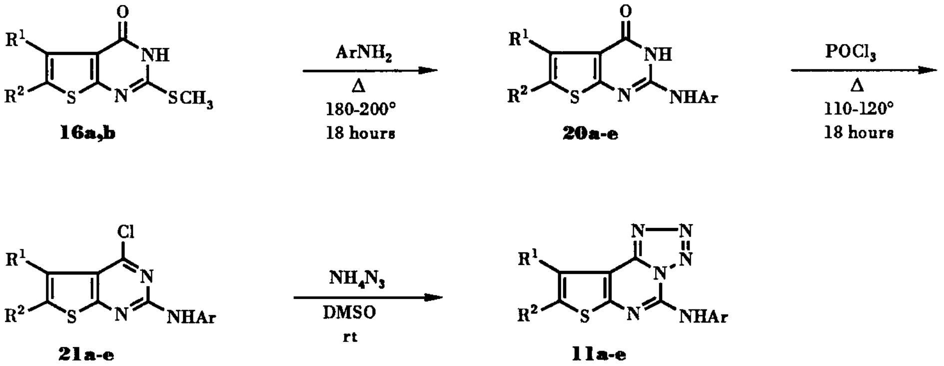


Scheme II



16-19a, $R^1, R^2 = -(CH_2)_4-$; **b,** $R^1 = R^2 = CH_3$
10a, $R^1, R^2 = -(CH_2)_4-$, $Ar = C_6H_5$
10b, $R^1, R^2 = -(CH_2)_4-$, $Ar = 4\text{-}CH_3C_6H_4$
10c, $R^1, R^2 = -(CH_2)_4,-$ $Ar = 4\text{-}CH_3OC_6H_4$
10d, $R^1, R^2 = -(CH_2)_4-$, $Ar = 4\text{-}ClC_6H_4$
10e, $R^1 = R^2 = -CH_3$, $Ar = 4\text{-}ClC_6H_4$

Scheme III

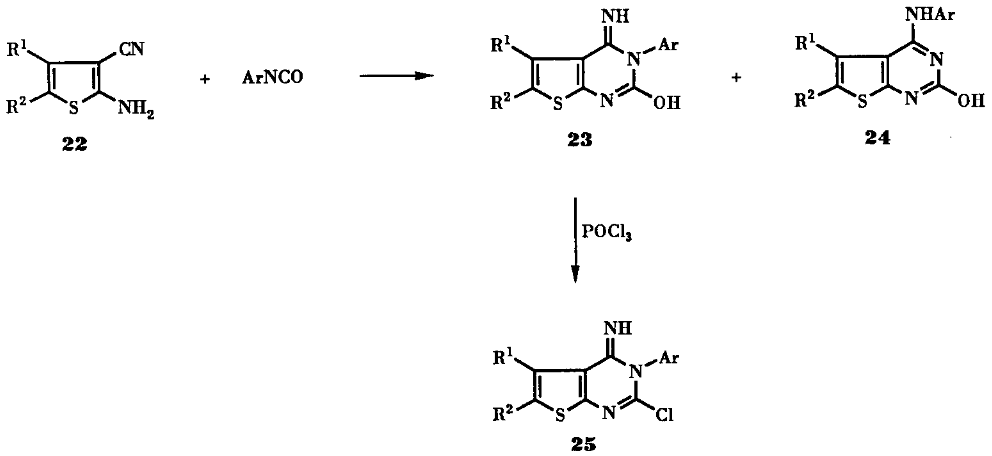


a, $R^1, R^2 = -(CH_2)_4-$, $Ar = C_6H_5$
b, $R^1, R^2 = -(CH_2)_4-$, $Ar = 4\text{-}CH_3C_6H_4$
c, $R^1, R^2 = -(CH_2)_4-$, $Ar = 4\text{-}CH_3OC_6H_4$
d, $R^1, R^2 = -(CH_2)_4-$, $Ar = 4\text{-}ClC_6H_4$
e, $R^1, R^2 = -CH_3$, $Ar = 4\text{-}ClC_6H_4$

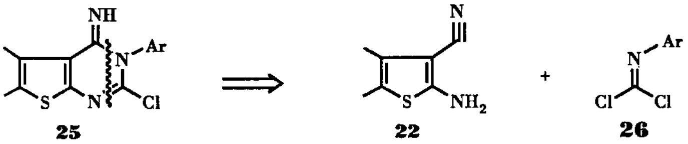
ylaniline at reflux temperatures yielded **21**. The displacement of the 4-chlorine atom of **21** could be achieved by using an equimolar mixture of sodium azide and ammonium chloride in a dipolar aprotic solvent like dimethyl sulfoxide at room temperature. This not only reduced the reaction time drastically but also gave better yields and purity of the desired products **11a-e** [14] (Scheme III).

For the synthesis of 4-aryl-5-iminotetrazolo[1,5-*a*]thieno[3,2-*e*]pyrimidines **12** the direct approach was the nucleophilic displacement of the 2-chlorine atom of the corresponding 3-aryl-2-chloro-4-iminothieno[2,3-*d*]pyrimidines **25** with sodium or ammonium azide. At the outset **25** was thought to be preparable by the chlorination of the corresponding 3-aryl-2-hydroxy-4-iminothieno[2,3-*d*]pyrimidine

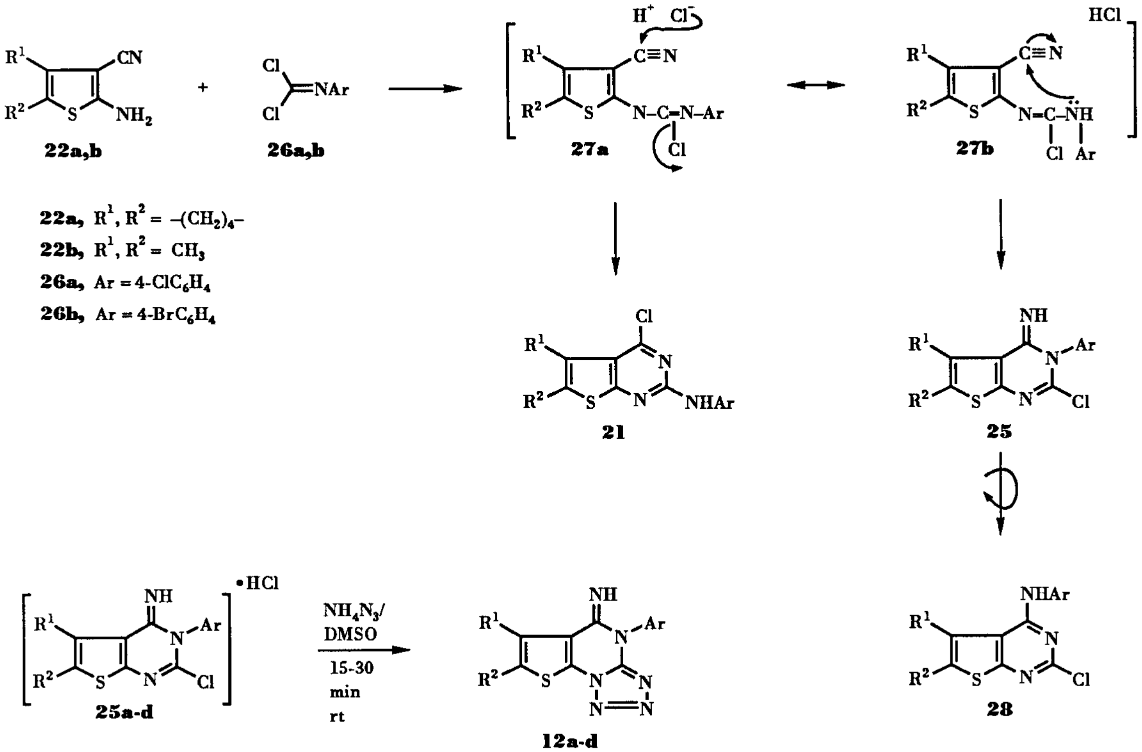
Scheme IV



Scheme V



Disconnection approach



22a, R^1, R^2 = $-(CH_2)_4-$
22b, R^1, R^2 = CH_3
26a, Ar = 4-ClC_6H_4
26b, Ar = 4-BrC_6H_4

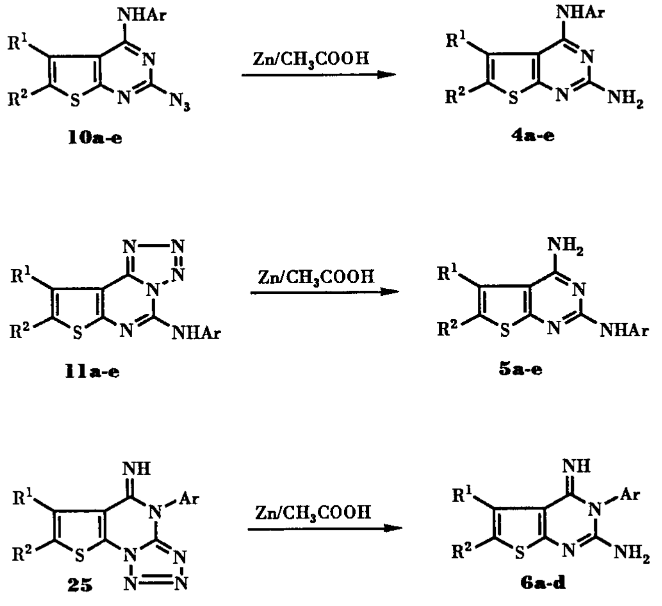
a, R^1, R^2 = $-(CH_2)_4-$, Ar = 4-ClC_6H_4
b, R^1, R^2 = $-(CH_2)_4-$, Ar = 4-BrC_6H_4
c, R^1, R^2 = CH_3, Ar = 4-ClC_6H_4
d, R^1, R^2 = CH_3, Ar = 4-BrC_6H_4

23 which can be prepared by the route, analogous to the one adopted by Taylor and Ravindranathan for the preparation of 3-aryl-2-hydroxy-4-iminoquinazolines [15]. However, the simultaneous formation of the isomeric 4-arylamino-2-hydroxythieno[2,3-*d*]pyrimidine **24** made this route less attractive (Scheme IV).

Therefore, an alternate approach was devised to obtain the desired 3-aryl-2-chloro-4-iminothieno[2,3-*d*]pyrimidine **25**. The disconnection of the pyrimidine framework of **25** was considered [16]. The C_4 of the pyrimidine ring along with its imino substituent can be derived from a cyano functionality, while the N_1 atom of the pyrimidine can be obtained from an amino group. Thus 2-aminothiophene-3-nitrile **22** became one of the recognizable fragments, while *N*-aryl isocyanide dichloride **26** was the other fragment. This approach indeed led to an elegant synthesis of 3-aryl-2-chloro-4-iminothieno[2,3-*d*]pyrimidines **25** isolable as their hydrochloride salts in good yields and purity under very mild conditions. The reaction presumably proceeds through the chloroformamidine intermediates **27a** or **27b** to yield either or both of the isomeric chlorothieno[2,3-*d*]pyrimidines **21** and **25**. At the same time, the rearrangement of **25** under the reaction conditions to the third isomer **28** cannot be overlooked. However, in actual experiments, only the desired product, 3-aryl-2-chloro-4-iminothieno[2,3-*d*]pyrimidine **25** was obtained exclusively, as its hydrochloride salt. The formation of the other two isomeric chlorothieno[2,3-*d*]pyrimidines **21** and **28** was ruled out by comparison with the authentic samples prepared through unequivocal syntheses.

The next step, involved the displacement of the 2-chlorine atom of **25** with the azide ion. The hydrochloride salts of **25a-d** as such, on stirring with ammonium azide (generated *in situ*) in dimethyl sulfoxide at room temperature for 15-30 minutes afforded the final products **12a-d** (Scheme V).

Scheme VI



Tetrazoles in general are difficult to reduce. Protic solvents and higher temperatures are known to shift the azide-tetrazole equilibrium in favour of the azide tautomer [7-9]. The use of activated zinc dust in acetic acid was found to be suitable for this purpose and best results were obtained when the reaction mixture was heated on a boiling water bath for 2-3 hours. All the azido/tetrazolothienopyrimidines **10-12** were reduced successfully by adopting the above procedure (Scheme VI).

The azido/tetrazolothienopyrimidines **10-12** synthesized are colorless to pale yellow crystalline compounds generally melting with decomposition at temperatures below 200°. The 2,4-diaminothieno[2,3-*d*]pyrimidines **4-6** melt at higher temperatures. The azido/tetrazolothienopyrimidines are insoluble in polar solvents like ethanol but soluble in non-polar solvents like benzene and chloroform. The diaminothieno[2,3-*d*]pyrimidines are sparingly soluble in both ethanol and benzene but highly soluble in chloroform. Both the above types of compounds are practically insoluble in *n*-hexane.

The ir spectra of all the azido/tetrazolothienopyrimidines were recorded in potassium bromide discs as well as in chloroform solution. A strong absorption in the region 2180-2110 cm^{-1} characterizes the azido group (ν_{as} $N=N=N$) in the spectra of the 2-azidothieno[2,3-*d*]pyrimidines **10a-e**, **15a,b** and **16a,b**. The ir spectra of the tetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines **11a-c** and tetrazolo[1,5-*a*]thieno[3,2-*e*]pyrimidines **12a-d** are generally devoid of such azido absorption peaks. However, the ir spectra of the chloroform solutions of **12a-d** occasionally reveal an azide band of moderate intensity indicative of the existence of the azide-tetrazole equilibrium in chloroform solution of this system. The ir spectra of the tetrazolothieno[3,2-*d*]pyrimidines **11** and **12** exhibit one or two absorption bands between 1100-1000 cm^{-1} which are characteristic of the tetrazolo moiety [17]. Besides a single N-H stretching band of moderate intensity at around 3500-3280 cm^{-1}, the ir spectra of all the 2,4-diaminothieno[2,3-*d*]pyrimidines show multiple absorption bands of medium to strong intensities around 3500-3200 cm^{-1} due to asymmetric and symmetric N-H stretching vibrations.

The ^1H nmr spectra of the 2-azido-4-arylaminothieno[2,3-*d*]pyrimidines **10** exhibit a deuterium oxide-exchangeable singlet corresponding to the 4-arylamino proton in the region δ 6.9-7.1. The position of this signal indicates that the amino proton is not deshielded. In the ^1H nmr spectra of the 5-arylaminotetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines **11** the position of the deuterium oxide-exchangeable singlet corresponding to the N-H proton is as far downfield as δ 10.5-11.5 indicating that this proton is deshielded due to the presence of the electron withdrawing tetrazolo moiety [6,18]. In the ^{1}H nmr spectra of 4-aryl-5-iminotetrazolo[1,5-*a*]thieno[3,2-*e*]pyrimidines **12** this NH singlet may be still downfield as it is not observed up to 15 ppm. In the spectra of the 2-amino-4-arylaminothieno[2,3-*d*]pyrimidines **4**, two distinct deuterium oxide-exchangeable signals appear at δ 4.8-5.0 and δ 7.0, for the 2-amino and 4-arylamino protons, respectively. These signals of primary and secondary amino protons appear at δ 6.5 and 8.6 in the spectra of 4-amino-2-arylaminothieno[2,3-*d*]pyrimidines **5**. The amino as well as imino protons of 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidines **6** give a single deuterium oxide-exchangeable singlet at δ 5.0 integrating for three protons.

The 4-arylamino-2-azidothieno[2,3-*d*]pyrimidines **10** exhibit a prominant daughter ion peak in their mass spectra arising due to the loss of 26 amu from the molecular ion. This is a characteristic fragmentation pattern of organic azides [19]. The spectra of tetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidines **11** on the other hand exhibit prominant [M-28] peaks, a characteristic mode of fragmentation of the tetrazole moiety [19]. However, the mass spectra of the tetrazolo[1,5-*a*]thieno[3,2-*e*]pyrimidines **12** are characterized by intense [M-26] peaks and total absence of the molecular ion [M$^+$] peaks. This may be due to the existence of the azide-tetrazole equilibrium in this system.

The mass spectra of all the 2,4-diaminothieno[2,3-*d*]pyrimidines are characterized by intense molecular ion peaks [M$^+$] and daughter ion peaks arising due to the loss of $NH_2^{\cdot}$, NH_2CN and ArNHCN from the molecular ion.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were recorded in potassium bromide or chloroform on a Perkin Elmer 841 Grating Spectrophotometer. The ^{1}H nmr spectra were taken on a Varian A-60 spectrometer using tetramethylsilane as the internal standard. The mass spectra were obtained on a Varian Atlas CH-7 spectrometer at 70 eV ionizing beam using a direct insertion probe.

The 2-methylthiothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **16a** and **16b** [13], *N*-aryl isocyanide dichloride, **26a,b** [20] and 2-aminothiophene-3-nitriles **22a,b** [23] were prepared by literature methods. Commercially available sodium azide (Loba) and zinc dust (Loba) were used.

I. General Procedure for the Reaction of 2-Methylthiothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **16a** and **16b** with Hydrazine Hydrate.

A suspension of dry **16** (0.01 mole) in hydrazine hydrate (99-100%) (25 ml) was refluxed gently. The insoluble solid went into solution within 5 minutes with copious evolution of methylmercaptan to form a clear solution. After 15 minutes when the solid product started separating out, heating was discontinued and the reaction mixture was allowed to cool to room temperature. The solid which separated was filtered, washed with water, ethanol and dried.

2-Hydrazino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4-(3*H*)-one (**17a**).

In this case **16a** upon refluxing with hydrazine hydrate afforded the product as colorless crystals (dimethylformamide), mp 277-279°, yield 76%; ir (potassium bromide): 3320, 3250 (NH), 2940, 1650 (CONH), 1600, 1490 cm^{-1}.

2-Hydrazino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**17b**).

In this case **16b** was used as the starting material. The product was obtained as colorless crystals (dimethylformamide), mp 270-272°, yield 71%; ir (potassium bromide): 3360, 3320, 3280 (NH), 2940, 1630 (CONH) cm^{-1}.

II. General Procedure for the Nitrosation of 2-Hydrazinothieno-[2,3-*d*]pyrimidin-4(3*H*)-ones **17a** and **17b**.

2-Hydrazinothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**17**) (0.01 mole) was dissolved in hydrochloric acid (30 ml, 15% v/v) and the solution was cooled to 5°. An aqueous solution of sodium nitrite (0.76 g, 0.01 mole) was added portionwise to the above cooled solution, with stirring. The solid which separated was filtered after 1 hour of stirring, washed with cold water, dried and crystallized.

2-Azido-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**18a**).

In this case **17a** was used as the starting material. The compound was obtained as brown crystals (benzene), mp 200-202° dec, yield 71%; ir (potassium bromide): 2930, 2140 (N=N=N), 1650 (CONH), 1560, 1300, 1200, 1140, 1040, 970, 930 cm^{-1}; ir (chloroform): 3000, 2940, 2850, 2140 (N=N=N), 1630 (CONH), 1550, 1500, 1400, 1180, 1130, 1020, 900, 850 cm^{-1}.

Anal. Calcd. for $C_{10}H_9N_5OS$: C, 48.56; H, 3.68. Found: C, 48.84; H, 3.88.

2-Azido-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**18b**).

In this case **17b** was used as the starting material. The compound was obtained as pale brown crystals (benzene), mp 198-200° dec, yield 69%; ir (potassium bromide): 2940, 2170 (N=N=N), 1670 (CONH), 1580, 1400, 1220, 1040, 920 cm^{-1}; ir (chloroform): 2940, 2180 (N=N=N), 1660 (CONH), 1580, 1400, 1220, 1030, 910 cm^{-1}.

Anal. Calcd. for $C_8H_7N_5OS$: C, 43.45; H, 3.20. Found: C, 43.62; H, 3.01.

III. General Procedure for the Chlorination of 2-Azidothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **18a** and **18b**.

Phosphorus oxychloride (5 ml) was added dropwise with stirring to an ice-cold solution of **18** (0.01 mole) in dimethylformamide (30 ml). The reaction mixture was further stirred for 1 hour at 0-5° and allowed to stand overnight at room temperature. The yellow syrupy mixture was poured on crushed ice with stirring. The solid which separated was filtered after 30 minutes, dried and recrystallized.

2-Azido-4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**19a**).

In this case **18a** was chlorinated. The product was obtained as light yellow crystals (*n*-hexane), mp 105-107° dec, yield 66%; ir (potassium bromide): 2960, 2150 (N=N=N), 1580, 1500, 1350, 1220, 1140, 1020, 920, 840 cm^{-1}.

Anal. Calcd. for $C_{10}H_8ClN_5S$: C, 45.19; H, 3.04. Found: C, 45.10; H, 3.08.

2-Azido-4-chloro-5,6-dimethylthieno[2,3-*d*]pyrimidine (**19b**).

In this case **18b** was chlorinated. The product was obtained as a light yellow crystalline solid (*n*-hexane), mp 105-107° dec, yield 67%; ir (potassium bromide): 2160 (N = N = N), 1570, 1500, 1420, 1330, 1220, 1060, 930, 850 cm^{-1}.

Anal. Calcd. for $C_8H_6ClN_5S$: C, 40.08; H, 2.53. Found: C, 40.41; H, 2.93.

IV. General Procedure for the Reaction of 19 with Arylamines.

In a warm solution of **19** (0.01 mole) in ethanol (30 ml) was added the freshly distilled arylamine (0.01 mole) and 2-3 drops of concentrated hydrochloric acid. The reaction mixture was refluxed for 2 hours, cooled and the solid obtained was filtered, washed with water, dried and recrystallized.

For the products **10a-d** the starting material used was **19a** while **19b** was the starting material used to obtain **10e**.

2-Azido-4-phenylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]-pyrimidine (**10a**).

The compound was obtained as light brown shining crystals (cyclohexane), mp 174-175° dec, yield 74%; ir (potassium bromide): 3490 (NH), 2980, 2150 (N = N = N), 1620, 1530, 1400, 1150, 1080, 1010, 830 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_6S$: C, 59.60; H, 4.39. Found: C, 59.82; H, 4.68.

2-Azido-4-[4-methylphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**10b**).

The compound was obtained as pale brown crystals (cyclohexane), mp 150-152° dec, yield 69%; ir (potassium bromide): 3440 (NH), 2940, 2180 (N = N = N), 1610, 1510, 1380, 1300, 1140, 1100, 920 cm^{-1}; ir (chloroform): 3450 (NH), 3000, 2940, 2130 (N = N = N), 1600, 1560, 1510, 1350, 1240, 1050, 960, 910 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.8-1.9 (m, 4H, CH_2 at 6 and 7), 2.2 (s, 3H, Ar-CH_3), 2.7-2.9 (m, 4H, CH_2 at 5 and 8), 6.9 (s, 1H, N*H*, deuterium oxide-exchangeable), 7.1-7.6 (m, 4H, phenyl protons).

Anal. Calcd. for $C_{17}H_{16}N_6S$: C, 60.68; H, 4.80. Found: C, 61.16; H, 5.09.

2-Azido-4-[4-methoxyphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**10c**).

The compound was obtained as pale brown crystals (cyclohexane), mp 168-170° dec, yield 67%; ir (potassium bromide): 3440 (NH), 2960, 2140 (N = N = N), 1600, 1560, 1500, 1380, 1260, 1150, 1030, 910, 830 cm^{-1}; ir (chloroform): 3460 (NH), 3000, 2940, 2140 (N = N = N), 1600, 1570, 1510, 1390, 1250, 1220, 1040, 830 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.8-1.9 (m, 4H, CH_2 at 6 and 7), 2.0 (s, 3H, Ar-OCH_3), 2.7-2.9 (m, 4H, CH_2 at 5 and 8), 7.0 (s, 1H, N*H*, deuterium oxide-exchangeable), 6.8-7.6 (m, 4H, phenyl protons); ms: (m/z) 352 (M^+), 326, 324, 323, 309, 296, 291, 283, 281, 137, 122, 108, 107, 94, 79, 77.

Anal. Calcd. for $C_{17}H_{16}N_6OS$: C, 57.93; H, 4.59. Found: C, 58.34; H, 4.74.

2-Azido-4-[4-chlorophenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**10d**).

This compound was obtained as pale brown crystals (cyclohexane), mp 177-178° dec, yield 73%; ir (potassium bromide): 3460 (NH), 2940, 2130 (N = N = N), 1590, 1560, 1500, 1480, 1240, 1090, 1010, 920, 840 cm^{-1}; ir (chloroform): 3460 (NH), 2940, 2130 (N = N = N), 1600, 1560, 1520, 1480, 1100, 920, 830 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.8-1.9 (m, 4H, CH_2 at 6 and 7), 2.8-3.0 (m, 4H, CH_2 at 5 and 8), 7.1-7.7 (m, 5H, phenyl protons and N*H*, deuterium oxide-exchangeable).

Anal. Calcd. for $C_{16}H_{13}ClN_6S$: C, 53.86; H, 3.67. Found: C, 54.24; H, 4.08.

2-Azido-4-[4-chlorophenyl]amino-5,6-dimethylthieno[2,3-*d*]pyrimidine (**10e**).

This compound was obtained as pale brown crystals (cyclohexane), mp 145-147° dec, yield 67%; ir (potassium bromide): 3460 (NH), 2980, 2120 (N = N = N), 1610, 1560, 1500, 1360, 1310, 1240, 1100, 1010, 910, 840 cm^{-1}; ir (chloroform): 3460 (NH), 3000, 2120 (N = N = N), 1600, 1560, 1520, 1490, 1380, 1310, 1230, 1090, 1010, 910, 820 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.3-2.5 (d, 6H, CH_3 at 5 and 6), 7.2-7.7 (m, 5H, phenyl protons and N*H*, deuterium oxide-exchangeable).

Anal. Calcd. for $C_{14}H_{11}ClN_6S$: C, 50.83; H, 3.36. Found: C, 51.28; H, 3.47.

V. General Procedure for the Reaction of 2-Methylthiothieno[2,3-*d*]pyrimidin-4(3*H*)-one 16 with Arylamines.

To an intimate mixture of **16** (0.01 mole) and the appropriate freshly distilled arylamine (0.01 mole) was added concentrated hydrochloric acid (2-3 drops). The mixture was heated in an oil bath at 180-200° for 18 hours whereupon the evolution of methyl mercaptan gradually ceased. The fused reaction mixture was triturated with aqueous hydrochloric acid (10% v/v, 150 ml) followed by water and warm ethanol. The insoluble residue was filtered, dried and recrystallized. For compounds **20a-d** the starting material used was **16a** while **16b** was used to obtain **20e**.

2-Phenylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**20a**).

This compound was obtained as light brown crystals (ethanol-dimethylformamide), mp 280-282° (lit [13] mp 277-278°, lit [21] mp 274°, lit [22] mp 284-286°), yield 51%; ir (potassium bromide): 3380 (NH), 2930, 1670 (CONH), 1630, 1590, 1560, 1490, 1440, 1330, 1250, 960 cm^{-1}.

2-[4-Methylphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**20b**).

This compound was obtained as colorless crystals (ethanol-dimethylformamide), mp 310-311° (lit [13] mp 303-304°, lit [21] mp 297°), yield 62%; ir (potassium bromide): 3440 (NH), 2970, 1670 (CONH), 1620, 1570, 1420, 1340, 1260, 1210, 1030, 970, 820 cm^{-1}.

2-[4-Methoxyphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**20c**).

This compound was obtained as light pink colored crystals (ethanol-chloroform), mp 280-282° (lit [21] mp 273°), yield 46%; ir (potassium bromide): 3400 (NH), 3080, 2940, 2830, 1680 (CONH), 1520, 1450, 1250, 1180, 1150, 1030, 820 cm^{-1}.

2-[4-Chlorophenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (**20d**).

This compound was obtained as colorless crystals (ethanol-dimethylformamide), mp 318-320° (lit [21] mp > 300°), yield 67%; ir (potassium bromide): 3400 (NH), 2980, 1670 (CONH), 1580, 1500, 1410, 1300, 1210, 970, 870, 830 cm^{-1}; ms: (m/z) 333 (M + 2), 331 (M^+), 316, 305, 303, 268, 180, 152, 134, 123, 111, 109.

2-[4-Chlorophenyl]amino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**20e**).

This compound was obtained as colorless crystals (ethanol-dimethylformamide), mp 315-317°, yield 56%; ir (potassium bromide): 3420, 3300 (NH), 1650 (CONH), 1540, 1470, 1350, 1240, 1080, 1000, 810 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 2.3-2.6 (d, 6H, CH_3 at 5 and 6), 7.2-7.7 (m, 4H, phenyl protons), 10.5 (s, 1H, N*H*, deuterium oxide-exchangeable).

Anal. Calcd. for $C_{14}H_{12}ClN_3OS$: C, 54.98; H, 3.99. Found: C, 54.57; H, 3.68.

VI. General Procedure for the Chlorination of 2-Arylaminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **20a-e**.

A mixture of **20** (0.01 mole), freshly distilled *N*,*N*-dimethylaniline (1.0 ml) and phosphorus oxychloride (50 ml) was refluxed at 110-120° for 18 hours. The excess of phosphorus oxychloride was removed under reduced pressure. The gummy residue left in the distillation flask was poured on crushed ice and the aqueous mixture was neutralized (*p*H 7) with sodium bicarbonate. The neutralized mixture was allowed to stand at room temperature for 4-5 hours. The solid which separated was filtered, washed with water and dried. The crude solid was extracted with cyclohexane in a soxhlet extractor to yield a light colored solid which was recrystallized.

4-Chloro-2-phenylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**21a**).

This compound was obtained as a light yellow colored crystalline solid (*n*-hexane), mp 161-163°, yield 48%; ir (potassium bromide): 3360 (NH), 2980, 1610, 1570, 1510, 1430, 1190, 980, 820 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}ClN_3S$: C, 60.85; H, 4.47. Found: C, 60.50; H, 4.83.

4-Chloro-2-(4-methylphenyl)amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**21b**).

This compound was obtained as light yellow crystals (*n*-hexane), mp 172-175°, yield 52%; ir (potassium bromide): 3320 (NH), 2940, 1600, 1560, 1500, 1420, 1180, 1130, 820 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}ClN_3S$: C, 61.90; H, 4.89. Found: C, 61.54; H, 4.80.

4-Chloro-2-(4-methoxyphenyl)amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**21c**).

This compound was obtained as light yellow crystals (*n*-hexane), mp 102-105°, yield 48%; ir (potassium bromide): 3350 (NH), 2940, 1600, 1570, 1510, 1440, 1370, 1250, 1200, 1140, 1040, 830 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}ClN_3OS$: C, 59.04; H, 4.66. Found: C, 58.87; H, 4.28.

4-Chloro-2-(4-chlorophenyl)amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**21d**).

This compound was obtained as shining yellow crystals (*n*-hexane), mp 189-191°, yield 61%; ir (potassium bromide): 3320 (NH), 2940, 1600, 1560, 1500, 1420, 1190, 1130, 1010, 830 cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}Cl_2N_3S$: C, 54.86; H, 3.74. Found: C, 55.08; H, 3.82.

4-Chloro-2-(4-chlorophenyl)amino-5,6-dimethylthieno[2,3-*d*]pyrimidine (**21e**).

This compound was obtained as light yellow crystals (*n*-hexane), mp 180-185°, yield 56%; ir (potassium bromide): 3320 (NH), 2860, 1600, 1560, 1500, 1400, 1250, 1100, 1020, 830, 800 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}Cl_2N_3S$: C, 51.86; H, 3.42. Found: C, 51.68; H, 3.82.

VII. General Procedure for the Reaction of 2-Arylamino-4-chlorothieno[2,3-*d*]pyrimidines (**21**) with Ammonium Azide.

To a well stirred solution of dry ammonium chloride (0.59 g, 0.011 mole) and sodium azide (0.72 g, 0.01 mole) in dry dimethyl sulfoxide (30 ml) was added portionwise **21** (0.01 mole). The reaction mixture was stirred for 15-20 minutes, when a clear solution resulted. The reaction mixture was thereafter heated on a water bath at 50-60° for 2-3 hours. The progress of the reaction was followed by tlc. Heating was discontinued as soon as the reaction went to completion. The reaction mixture was cooled to room temperature and poured on an ice-water mixture. The solid which separated was filtered, washed with water, dried and recrystallized.

5-Phenylamino-8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**11a**).

This compound was obtained as colorless shining crystals (ethanol-chloroform), mp 200-202° dec, yield 72%; ir (potassium bromide): 3360 (NH), 2940, 1630, 1570, 1475, 1300, 1160, 1080, 980, 950 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.5-2.3 (broad s, 4H, CH_2 at 9 and 10), 2.4-2.9 (m, 4H, CH_2 at 8 and 11), 7.0-8.0 (m, 5H, phenyl protons), 10.4 (s, 1H, N*H*, deuterium oxide-exchangeable); ms: (m/z) 323 (M + 1), 322 (M$^+$), 296, 295, 294, 293, 292, 279, 267, 266, 265, 253, 251, 241, 239, 226, 188, 177, 175, 164, 161, 150, 148, 136, 127, 118, 94, 92, 91.

Anal. Calcd. for $C_{16}H_{14}N_6S$: C, 59.61; H, 4.38. Found: C, 59.43; H, 4.55.

5-[4-Methylphenyl]amino-8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**11b**).

This compound was obtained as colorless needles (ethanol-chloroform), mp 202-204° dec, yield 71%; ir (potassium bromide): 3350 (NH), 2940, 1630, 1570, 1370, 1240, 1080, 960, 820 cm^{-1}; ir (chloroform): 3400 (NH), 3000, 2940, 2120 (N=N=N), 1630, 1560, 1380, 1220, 1070, 1030, 950 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.9-2.2 (broad s, 4H, CH_2 at 9 and 10), 2.5 (s, 3H, Ar-CH_3), 2.8-3.0 (m, 4H, CH_2 at 8 and 11), 7.3-8.1 (m, 4H, phenyl protons), 10.3 (s, 1H, N*H*, deuterium oxide-exchangeable); ms: (m/z) 336 (M$^+$), 309, 308, 307, 293, 281, 280, 265, 255, 253, 202, 177, 175, 165, 164, 146, 132, 131, 91.

Anal. Calcd. for $C_{17}H_{16}N_6S$: C, 60.69; H, 4.79. Found: C, 61.05; H, 4.84.

5-[4-Methoxyphenyl]amino-8,9,10,11-tetrahydro[1]benzothieno-[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**11c**).

The compound was obtained as colorless crystals (ethanol-chloroform), mp 210-212° dec, yield 65%; ir (potassium bromide): 3350 (NH), 2940, 1630, 1570, 1520, 1360, 1300, 1240, 1070, 830 cm^{-1}; ir (chloroform): 3400 (NH), 3000, 2940, 2120 (N=N=N), 1630, 1570, 1520, 1250, 1220, 1070, 1030, 830 cm^{-1}; ^{1}H nmr (deuteriochloroform + dimethyl sulfoxide-d$_6$): δ 2.0 (s, 4H, CH_2 at 9 and 10), 2.4 (s, 3H, Ar-OCH_3), 2.7-3.2 (m, 4H, CH_2 at 8 and 11), 7.3-8.1 (m, 4H, phenyl protons), 10.5 (s, 1H, N*H*, deuterium oxide-exchangeable).

Anal. Calcd. for $C_{17}H_{16}N_6OS$: C, 57.94; H, 4.58. Found: C, 57.98; H, 4.81.

5-[4-Chlorophenyl]amino-8,9,10,11-tetrahydro[1]benzothieno[3,2-*e*]tetrazolo[1,5-*c*]pyrimidine (**11d**).

The compound was obtained as colorless shining crystals (ethanol-chloroform), mp 199-201° dec, yield 67%; ir (potassium bromide): 3400 (NH), 2960, 1630, 1560, 1460, 1390, 1230, 1090, 1080, 950, 820 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.8-2.1 (broad s, 4H, CH_2 at 9 and 10), 2.5-3.0 (m, 4H, CH_2 at 8 and 11), 7.2-8.0 (m, 4H, phenyl protons), 10.4 (s, 1H, N*H*, deuterium oxide-exchangeable); ms: (m/z) 358 (M + 2), 356 (M$^+$), 330, 328, 327, 313, 302, 301, 300, 293, 265, 233, 222, 217, 202, 197, 195, 191, 189, 177, 174, 164, 154, 152, 138, 136, 134, 126, 125, 113, 111.

Anal. Calcd. for $C_{16}H_{13}ClN_6S$: C, 53.85; H, 3.67. Found: C, 53.80; H, 3.90.

5-[4-Chlorophenyl]amino-8,9-dimethyltetrazolo[1,5-*c*]thieno[3,2-*e*]pyrimidine (**11e**).

This compound was obtained as colorless crystals (ethanol-chloroform), mp 195-200° dec, yield 69%; ir (potassium bromide): 3360 (NH), 2960, 1650, 1590, 1490, 1350, 1300, 1090, 1030, 820 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}ClN_6S$: C, 50.83; H, 3.35. Found: C, 50.82; H, 3.61.

VIII. General Procedure for the Reaction of a 2-Aminothiophene-3-nitrile **22** with *N*-Aryl Isocyanide Dichlorides **26**.

To a well stirred solution of an appropriate *N*-aryl isocyanide dichloride **26** (0.01 mole) in dichloromethane (30 ml) was added portionwise **22** (0.01 mole). A clear solution resulted within 30 minutes. Stirring was continued for an additional 8 hours, whereupon a colorless solid separated. The crude solid was filtered, washed with dichloromethane, dried and recrystallized.

2-Chloro-3-[4-chlorophenyl]-4-imino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine Hydrochloride (**25a**).

This compound was obtained by the reaction of **22a** and **26a** as colorless flakes (benzene-methanol), mp 237-238° dec, yield 83%; ir (potassium bromide): 3420 (NH), 2930, 1640, 1530, 1510, 1470, 1420, 1300, 1230, 1070, 1000, 970, 810 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.0-2.2 (m, 4H, CH_2 at 6 and 7), 3.0-3.4 (m, 4H, CH_2 at 5 and 8), 7.5-8.0 (m, 4H, phenyl protons); ms: (m/z) 351 (M + 2), 350 (M + 1), 349 (M$^+$), 348, 340, 336, 334, 324, 323, 321, 316, 315, 314, 313, 312, 311, 288, 287, 285, 279, 278, 251, 238, 224, 202, 177, 162, 143, 137, 134.

Anal. Calcd. for $C_{16}H_{13}Cl_2N_3S \cdot HCl$: C, 49.69; H, 3.65. Found: C, 49.60; H, 3.80.

3-[4-Bromophenyl]-2-chloro-4-imino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine Hydrochloride (**25b**).

This compound was obtained by the reaction of **22a** and **26b** as pale brown crystals (benzene-methanol), mp 284-286°, yield 79%; ir (nujol): 2980, 2120, 1640, 1550, 1520, 1460, 1370, 1300, 1240, 1010, 980, 850, 820 cm^{-1}; ms: (m/z) 395 (M + 1), 393, 375, 373, 359, 357, 354, 352, 350, 329, 327, 325, 279, 278, 266, 264, 251, 238, 224, 218, 216, 197, 175, 171, 162, 157, 155, 143, 134, 122, 94.

Anal. Calcd. for $C_{16}H_{13}BrClN_3S \cdot HCl$: C, 44.57; H, 3.28. Found: C, 44.51; H, 3.62.

2-Chloro-3-[4-chlorophenyl]-4-imino-5,6-dimethylthieno[2,3-*d*]pyrimidine Hydrochloride (**25c**).

This compound was obtained by the reaction of **22b** and **26a** as colorless crystals (benzene-methanol), mp 177-179°, yield 76%; ir (nujol): 3440 (NH), 1620, 1550, 1460, 1370, 1250, 1090, 1010, 890, 830 cm^{-1}; ms: (m/z) 325 (M + 2), 324 (M + 1), 323 (M$^+$), 322, 310, 308, 290, 288, 287, 274, 272, 262, 254, 253, 252, 238, 179, 176, 172, 162, 152, 151, 137, 136, 135, 113, 111.

Anal. Calcd. for $C_{14}H_{11}Cl_2N_3S \cdot HCl$: C, 46.62; H, 3.35. Found: C, 46.44; H, 3.57.

3-[4-Bromophenyl]-2-chloro-4-imino-5,6-dimethylthieno[2,3-*d*]pyrimidine Hydrochloride (**25d**).

This compound was obtained by the reaction of **22b** and **26b** as pale brown crystals (benzene-methanol), mp 210-215°, yield 74%; ir (potassium bromide): 3450 (NH), 1610, 1560, 1240, 1080, 1010, 890, 810 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}BrClN_3S \cdot HCl$: C, 41.50; H, 2.90. Found: C, 41.36; H, 3.30.

IX. General Procedure for the Reaction of 3-Aryl-2-chloro-4-iminothieno[2,3-*d*]pyrimidine Hydrochloride (**25**) with Ammonium Azide.

An intimate mixture of dry ammonium chloride (0.59 g, 0.011 mole) and sodium azide (0.72 g, 0.011 mole) was dissolved in dry dimethyl sulfoxide (30 ml) with stirring. To this solution was added portionwise with stirring **25** (0.01 mole). The solution became clear within 15-20 minutes. After 30 minutes of continuous stirring, the reaction mixture turned cloudy in appearance. The progress of the reaction was monitored by tlc. After completion of the reaction (additional 15 minutes stirring), stirring was discontinued and the reaction mixture was diluted with cold water (150 ml). The insoluble solid which separated was filtered, dried and recrystallized.

4-[4-Chlorophenyl]-5-imino-6,7,8,9-tetrahydro[1]benzothieno[3,2-*e*]tetrazolo[1,5-*a*]pyrimidine (**12a**).

This compound was obtained as colorless crystals (ethanol-chloroform), mp 161-162° dec, yield 69%; ir (potassium bromide): 3340 (NH), 2960, 1660, 1550, 1480, 1380, 1230, 1080, 1010, 970, 830 cm^{-1}; ir (chloroform): 3340 (NH), 2940, 2130 (N = N = N), 1620, 1540, 1490, 1460, 1360, 1010, 970, 830 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.8-2.2 (m, 4H, CH_2 at 7 and 8), 2.8-3.3 (m, 4H, CH_2 at 6 and 9), 7.2-7.8 (m, 4H, phenyl protons); ms: (m/z) 332, 330, 329, 315, 313, 301, 293, 287, 285, 278, 203, 178, 177, 175, 162, 160, 154, 152, 151, 150, 143, 134, 111, 94, 91.

Anal. Calcd. for $C_{16}H_{13}ClN_6S$: C, 53.86; H, 3.67. Found: C, 53.89; H, 4.08.

4-[4-Bromophenyl]-5-imino-6,7,8,9-tetrahydro[1]benzothieno[3,2-*e*]tetrazolo[1,5-*a*]pyrimidine (**12b**).

This compound was obtained as pale brown crystals (ethanol-chloroform), mp 165-166° dec, yield 70%; ir (potassium bromide): 3280 (NH), 2980, 1590, 1530, 1460, 1380, 1230, 1160, 1030, 990, 820 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.7-1.8 (m, 4H, CH_2 at 7 and 8), 2.7-2.9 (m, 4H, CH_2 at 6 and 9), 6.9-7.9 (m, 4H, phenyl protons).

Anal. Calcd. for $C_{16}H_{13}BrN_6S$: C, 47.89; H, 3.27. Found: C, 48.17; H, 3.68.

4-[4-Chlorophenyl]-5-imino-6,7-dimethyltetrazolo[1,5-*a*]thieno[3,2-*e*]pyrimidine (**12c**).

This compound was obtained as shining colorless crystals (ethanol-chloroform), mp 170-175° dec, yield 70%; ir (potassium bromide): 3360 (NH), 2960, 1670, 1580, 1500, 1460, 1270, 1150, 1100, 1080, 1020, 890, 840 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}ClN_6S$: C, 50.83; H, 3.35. Found: C, 50.94; H, 3.41.

4-[4-Bromophenyl]-5-imino-6,7-dimethyltetrazolo[1,5-*a*]thieno[3,2-*e*]pyrimidine (**12d**).

This compound was obtained as pale brown crystals (ethanol-chloroform), mp 155-160° dec, yield 64%; ir (potassium bromide): 3280 (NH), 2980, 1580, 1520, 1460, 1380, 1240, 1180, 1020, 980, 920, 840 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}BrN_6S$: C, 44.80; H, 2.96. Found: C, 45.00; H, 3.06.

X. General Procedure for the Reduction of Azido and Tetrazolothienopyrimidines **10-12** to Obtain the Aminothieno[2,3-*d*]pyrimidines **4-6**.

To a well stirred solution the appropriate azido or tetrazolothienopyrimidine (0.01 mole) in glacial acetic acid (30 ml) was added portionwise activated zinc dust (5.0 g) at room temperature over a period of 30 minutes. Stirring was continued for additional 3 hours. Thereafter the reaction mixture was heated on a waterbath (80-90) for 3 hours. The progress of reduction was monitored by tlc. After allowing the reaction mixture to cool to room temperature, it was poured onto cold water (150-200 ml). The insoluble solid which separated was filtered, washed with water and dried. The crude solid was extracted with hot benzene and the solid obtained after the removal of benzene under reduced pressure was recrystallized.

2-Amino-4-phenylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**4a**).

This compound obtained by the reduction of **10a** was a colorless crystalline product (benzene), mp 238-240°, yield 54%; ir (potassium bromide): 3440, 3270, 3120 (NH), 2920, 1640, 1560, 1520, 1480, 1430, 1300, 1240 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.8-2.3 (m, 4H, CH_2 at 6 and 7), 2.8-3.2 (m, 4H, CH_2 at 5 and 8), 5.0 (s, 3H, NH_2 at 2 and NH at 4, deuterium oxide-exchangeable), 7.1-7.6 (m, 5H, phenyl protons).

Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44. Found: C, 65.07; H, 5.56.

2-Amino-4-[4-methylphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**4b**).

The compound obtained by the reduction of **10b** was a colorless crystalline product (benzene), mp 193-194°, yield 58%; ir (potassium bromide): 3500, 3470, 3280, 3130 (NH), 1660, 1570, 1510, 1460, 1430, 1260, 820 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.7-2.0 (m, 4H, CH_2 at 6 and 7), 2.3 (s, 3H, Ar-CH_3), 2.5-3.0 (m, 4H, CH_2 at 5 and 8), 4.8-5.0 (s, 2H, NH_2 at 2, deuterium oxide-exchangeable), 7.0 (s, 1H, Ar-NH, deuterium oxide-exchangeable), 7.2-7.6 (m, 4H, phenyl protons).

Anal. Calcd. for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.84. Found: C, 65.88; H, 6.04.

2-Amino-4-[4-methoxyphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**4c**).

This compound was obtained by the reduction of **10c**, as colorless crystals (benzene), mp 235-237°, yield 54%; ir (potassium bromide): 3500, 3480, 3200 (NH), 2920, 1680, 1570, 1500, 1450, 1260, 820 cm^{-1}; ms: (m/z) 326 (M$^+$), 325, 311, 297, 283, 267, 266, 255, 253, 219, 218, 217, 205, 204, 192, 177, 175, 163, 142, 133, 127.

Anal. Calcd. for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56. Found: C, 62.35; H, 5.52.

2-Amino-4-[4-chlorophenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**4d**).

This compound obtained by the reduction of **10d** was a pale brown colored crystalline product (benzene), mp 219-221°, yield 56%; ir (potassium bromide): 3480, 3320, 3180 (NH), 2920, 1620, 1580, 1500, 1410, 1330, 1270, 1240, 1150, 1040, 1010, 970, 810 cm^{-1}; ms: (m/z) 332 (M + 2), 330 (M$^+$), 329, 317, 315, 303, 302, 301, 295, 294, 289, 287, 280, 279, 270, 267, 266, 260, 253, 225, 219, 217, 205, 193, 192, 177, 175, 165, 137, 135, 129, 127.

Anal. Calcd. for $C_{16}H_{15}ClN_4S$: C, 58.09; H, 4.57. Found: C, 57.95; H, 4.84.

2-Amino-4-[4-chlorophenyl]amino-5,6-dimethylthieno[2,3-*d*]pyrimidine (**4e**).

This compound obtained by the reduction of **10e** was a colorless crystalline product (benzene), mp 205-207°, yield 56%; ir (potassium bromide): 3480, 3340, 3200 (NH), 2940, 1630, 1580, 1500, 1350, 1280, 1160, 1050, 1000, 970, 800 cm^{-1}.

Anal. Calcd. for $C_{14}H_{13}ClN_4S$: C, 55.16; H, 4.31. Found: C, 55.01; H, 4.74.

4-Amino-2-phenylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**5a**).

This compound obtained by the reduction of **11a** was a colorless crystalline product (benzene-*n*-hexane), mp 150-152°, yield 61%; ir (nujol): 3500, 3320, 3180 (NH), 2920, 1630, 1560, 1500, 1460, 1360, 1240, 1160, 1040, 930, 890 cm^{-1}; ms: (m/z) 296 (M$^+$), 295, 281, 280, 268, 267, 252, 246, 197, 177, 176, 175, 151, 150, 149, 137, 127, 94.

Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44. Found: C, 64.96; H, 5.33.

4-Amino-2-[4-methylphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**5b**).

This compound obtained by the reduction of **11b** was a colorless crystalline solid (benzene-*n*-hexane), mp 220-222°, yield 63%; ir (potassium bromide): 3360, 3320, 3180 (NH), 2940, 2840, 1650, 1520, 1440, 1280, 1020, 940, 780 cm^{-1}; ms: (m/z) 310 (M$^+$), 309, 294, 282, 281, 267, 265, 218, 202, 179, 177, 155, 150, 140, 134, 133, 94, 91, 85, 83, 81, 71.

Anal. Calcd. for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.85. Found: C, 65.50; H, 5.46.

4-Amino-2-[4-methoxyphenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**5c**).

This compound obtained by the reduction of **11c** was a pale brown crystalline solid (benzene-*n*-hexane), mp 185-187°, yield 57%; ir (potassium bromide): 3500, 3280, 3130 (NH), 2920, 1640, 1540, 1510, 1440, 1380, 1310, 1240, 1140, 1010, 860, 840 cm^{-1}; ^{1}H nmr (deuteriochloroform + dimethyl sulfoxide-d_6): δ 1.9 (s, 4H, CH_2 at 6 and 7), 2.3 (s, 3H, Ar-OCH_3), 2.7-2.9 (m, 4H, CH_2 at 5 and 8), 6.2 (s, 2H, NH_2 at 4, deuterium oxide-exchangeable), 6.8-7.8 (m, 4H, phenyl protons), 8.5 (s, 1H, Ar-NH, deuterium oxide-exchangeable).

Anal. Calcd. for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56. Found: C, 62.19; H, 5.83.

4-Amino-2-[4-chlorophenyl]amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**5d**).

This compound obtained by the reduction of **11d** was a colorless shining crystalline solid (benzene-*n*-hexane), mp 213-215°, yield 63%; ir (potassium bromide): 3500, 3420, 3300, 3180 (NH), 2920, 1640, 1570, 1530, 1480, 1450, 1410, 1310, 1220, 1080, 940, 810 cm^{-1}; ^{1}H nmr (deuteriochloroform + dimethyl sulfoxide-d$_6$): δ 1.8-2.1 (m, 4H, CH_2 at 6 and 7), 2.6-3.0 (m, 4H, CH_2 at 5 and 8), 6.5 (s, 2H, NH_2 at 4, deuterium oxide-exchangeable), 7.2-8.1 (m, 4H, phenyl proton), 9.2 (s, 1H, Ar–N*H*, deuterium oxide-exchangeable).

Anal. Calcd. for $C_{16}H_{15}ClN_4S$: C, 58.09; H, 4.57. Found: C, 57.78; H, 4.80.

4-Amino-2-[4-chlorophenyl]amino-5,6-dimethylthieno[2,3-*d*]pyrimidine (**5e**).

This compound obtained by the reduction of **11e** was a colorless crystalline product (benzene-*n*-hexane), mp 230-235°, yield 57%; ir (potassium bromide): 3520, 3420, 3300, 3180 (NH), 2920, 1640, 1570, 1540, 1490, 1420, 1270, 1170, 1080, 1010, 940, 840 cm^{-1}; ^{1}H nmr (deuteriochloroform + dimethyl sulfoxide-d$_6$): δ 2.0-2.7 (m, 6H, CH_3 at 5 and 6), 6.1 (s, 2H, NH_2 at 4, deuterium oxide-exchangeable), 7.2-7.8 (m, 4H, phenyl protons), 8.6 (s, 1H, Ar–N*H*, deuterium oxide-exchangeable).

Anal. Calcd. for $C_{14}H_{13}ClN_4S$: C, 55.17; H, 4.30. Found: C, 54.84; H, 4.41.

2-Amino-3-[4-chlorophenyl]-4-imino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**6a**).

This compound obtained by the reduction **12a** was a colorless crystalline solid (benzene), mp 185-188°, yield 33%; ir (potassium bromide): 3480, 3350, 3300 (NH), 3090, 2940, 1640, 1550, 1230, 1020 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.6-1.8 (s, 4H, CH_2 at 6 and 7), 2.5-2.8 (m, 4H, CH_2 at 5 and 8), 5.1 (s, 3H, N*H* at 4 and NH_2 at 2, deuterium oxide-exchangeable), 7.1-7.6 (m, 4H, phenyl protons); ms: (m/e) 332 (M + 2), 330 (M$^+$), 329, 303, 301, 217, 215, 269, 177, 108, 107, 94, 78, 77.

Anal. Calcd. for $C_{16}H_{15}ClN_4S$: C, 58.09; H, 4.57. Found: C, 57.97; H, 4.40.

2-Amino-3-[4-bromophenyl]-4-imino-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidine (**6b**).

This compound obtained by the reduction of **12b** was a brown colored crystalline solid (benzene), mp 168-169°, yield 36%; ir (potassium bromide): 3450, 3380, 3200 (NH), 3090, 2960, 1660, 1550, 1230, 1020, 840 cm^{-1}; ms: (m/z) 375 (M$^+$), 374, 373, 361, 359, 348, 346, 345, 295, 279, 267, 233, 185, 173, 171, 157, 155, 151, 150, 149, 147.5*, 133.5*, 127, 103, 94, 87.

Anal. Calcd. for $C_{16}H_{15}BrN_4S$: C, 51.21; H, 4.04. Found: C, 50.89; H, 4.11.

Acknowledgements.

We are grateful to Hindustan Ciba-Geigy Research Centre, Bombay for microanalysis and spectra and the Principal of the L. M. College of Pharmacy, Ahmedabad for providing facilities to carry out this work.

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