Reaction of Nitriles under Acidic Conditions. Part VII. Study on the Reaction of *o*-Aminonitriles with Cyanamides to Synthesize 2,4-Diaminothieno[2,3-*d*]pyrimidines

C. J. Shishoo* and K. S. Jain

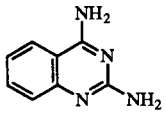
Department of Pharmaceutical Chemistry,
L. M. College of Pharmacy,
Ahmedabad 380 009, India

Received June 1, 1992

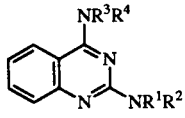
The reaction of *N*-arylcyanamides with thiophene *o*-aminonitriles under the influence of dry hydrogen chloride gas yields a mixture of two products. The major product has been identified as 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidine and the minor as 2-amino-3-arylthieno[2,3-*d*]pyrimidin-4(3*H*)-one.

J. Heterocyclic Chem., **30**, 435 (1993).

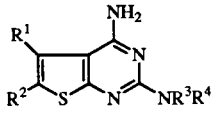
A variety of condensed pyrimidines, especially quinazolines, with primary amino groups at the 2- and 4-positions **1** as well as those with substituted amino functions at the 2- and 4-positions **2** have been synthesized and evaluated for antifolate, antimalarial activities [1-3]. As part of our continuing programme on the synthesis and antimalarial screening of 2,4-diaminopyrimidines, we have prepared a variety of 2,4-diaminopyrimidines [4] and condensed 2,4-diaminopyrimidines [5,6] through different synthetic routes. The aim of the present study was to synthesize some hitherto unexplored 4-amino-2-substituted-aminothieno[2,3-*d*]pyrimidines **3** as potential antifolate, antimalarial compounds.



1



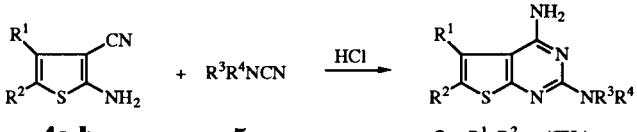
2



3

Reaction of nitriles with *o*-aminocarbonyl compounds under the influence of dry hydrogen chloride gas has been developed into a facile one-spot synthesis of condensed pyrimidines in this laboratory. *o*-Aminonitriles of benzene, thiophene and furan have been condensed with various nitriles to synthesize a series of condensed 4-aminopyrimidines [7-10].

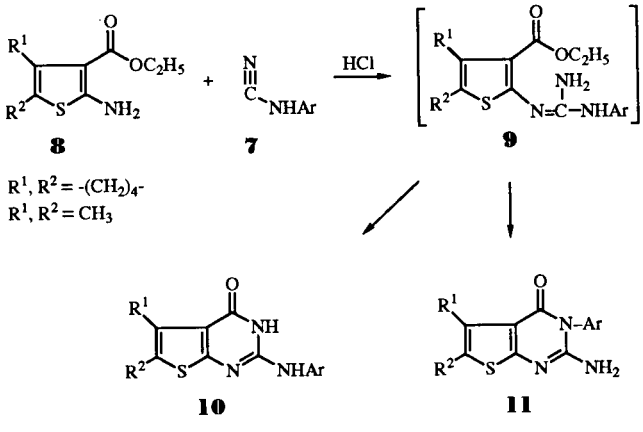
In our previous work, we described a reaction of *N,N*-dialkylcyanamides **5** with thiophene *o*-aminonitriles **4a** and **4b** leading to the corresponding 2,4-diaminothieno[2,3-*d*]-pyrimidines **6a** and **6b** [8].



4a,b **5** **6a**, $R^1, R^2 = -(CH_2)_4-$; **6b**, $R^1, R^2 = CH_3$

Reaction of monosubstituted cyanamides like *N*-arylcyanamides **7** with thiophene *o*-aminoesters **8** afforded a mixture of isomeric 2-aminothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **10** and **11**. The reaction presumably proceeds through a non-isolable guanidine intermediate **9** [11] (Scheme I).

Scheme I



8 **7** **9**

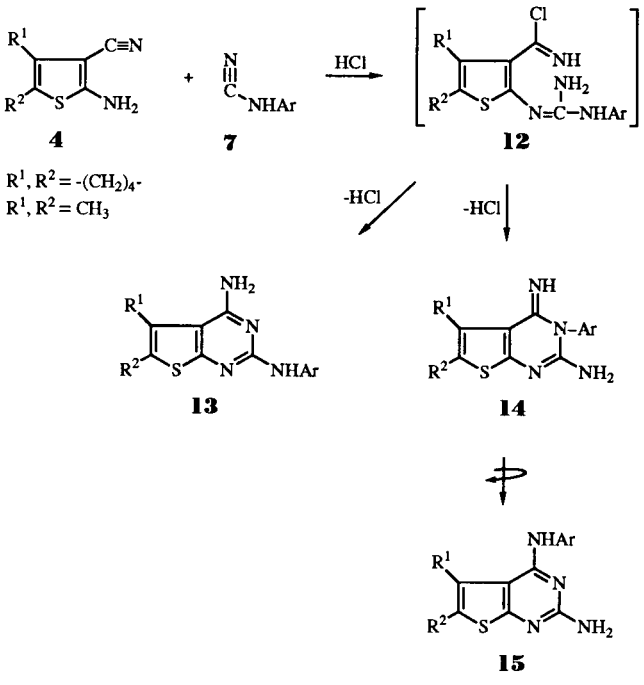
$R^1, R^2 = -(CH_2)_4-$
$R^1, R^2 = CH_3$

10 **11**

Analogously, the reaction of thiophene *o*-aminonitriles **4** with an arylcyanamide **7** can be presumed to proceed through nonisolable guanidine intermediate **12**. Through alternate modes of cyclization the guanidine **12** should afford not only the target compound **13** but also lead to another isomeric diaminothieno[2,3-*d*]pyrimidine **14**. At the same time, the formation of the third isomer **15** *via* a Dimroth rearrangement involving the ring opening and recyclization of **14** should not be overlooked (Scheme II).

Thus, when thiophene *o*-aminonitrile **4** was reacted with **7** in the presence of dry hydrogen chloride gas the workup of the reaction mixture yielded a mixture of two products which could be separated over neutral alumina by column chromatography. However, the major product was not the expected 4-amino-2-arylaminothieno[2,3-*d*]pyrimidine **13**. It was characterized as 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidine **14** on the basis of its microanalysis and spectral data as well as its comparison (ir, mixed mp, tlc) with an authentic sample of **14** prepared through unequivocal route [5]. The minor component of the mixture of products

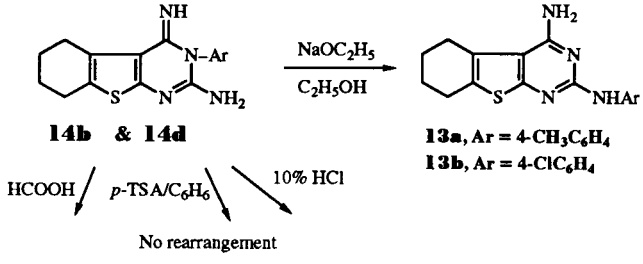
Scheme II



was surprisingly found to match with none of the three expected isomeric diaminothieno[2,3-*d*]pyrimidines **13-15**. It could be instead characterized as 2-amino-3-arylthieno-[2,3-*d*]pyrimidin-4(3*H*)-one **16** (Scheme III). This structural assignment was based not only on its elemental analysis and spectral data but also on its comparison (mixed mp, tlc, ir) with an authentic sample prepared by an unequivocal route involving the reduction of the corresponding 2-azido-3-arylthieno[2,3-*d*]pyrimidin-4-one [12].

Iminopyrimidines are known to undergo Dimroth rearrangement under basic and acidic conditions [13-15]. In order to study the chemical properties of the 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidines, Dimroth rearrangement of **14b** and **14d** was attempted under basic as well as acidic conditions. While in the presence of catalytic amounts of sodium ethoxide in ethanol at 40-50° **14b** and **14d** undergo isomerisation to an extent of about 50%, no isomerization occurred under acid catalysis (10% hydrochloric acid, *p*-toluenesulfonic acid in benzene and formic acid). The rearranged product obtained under basic conditions was separated from the starting material on a neutral alumina column and was characterized as 4-amino-2-arylaminothieno[2,3-*d*]pyrimidine. The rearranged products **13a** and **13b** were found identical with the authentic samples of the corresponding 2,4-diaminothieno[2,3-*d*]pyrimidines, namely, 4-amino-2-(4-methylphenyl)amino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine and 4-amino-2-(4-chlorophenyl)amino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine [5] (Scheme IV).

Scheme IV

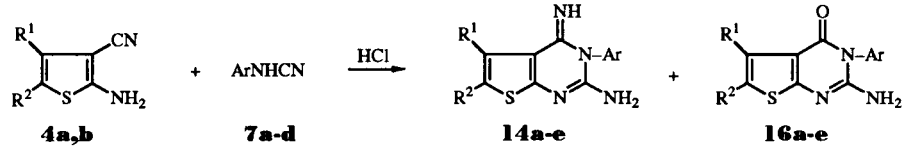


The formation of 4-amino-2-arylaminothieno[2,3-*d*]pyrimidine **13a** and **13b** may be explained by the reaction pathway depicted in Scheme V, involving the cleavage of C_4-N_3 bond of **14** followed by a free rotation around the C_2-N_1 bond of the resultant guanidine intermediate and its recyclization to the 4-aminothienopyrimidine **13**.

While the 4-iminopyrimidine **14** was found stable in dilute hydrochloric acid, it did hyrolyse under more drastic conditions, *viz.*, when refluxed with 6*M* hydrochloric acid and nitrous acid. Under these conditions, **14b** yielded the corresponding 4-oxo compound **16b** in two different sets of experiments (Scheme VI).

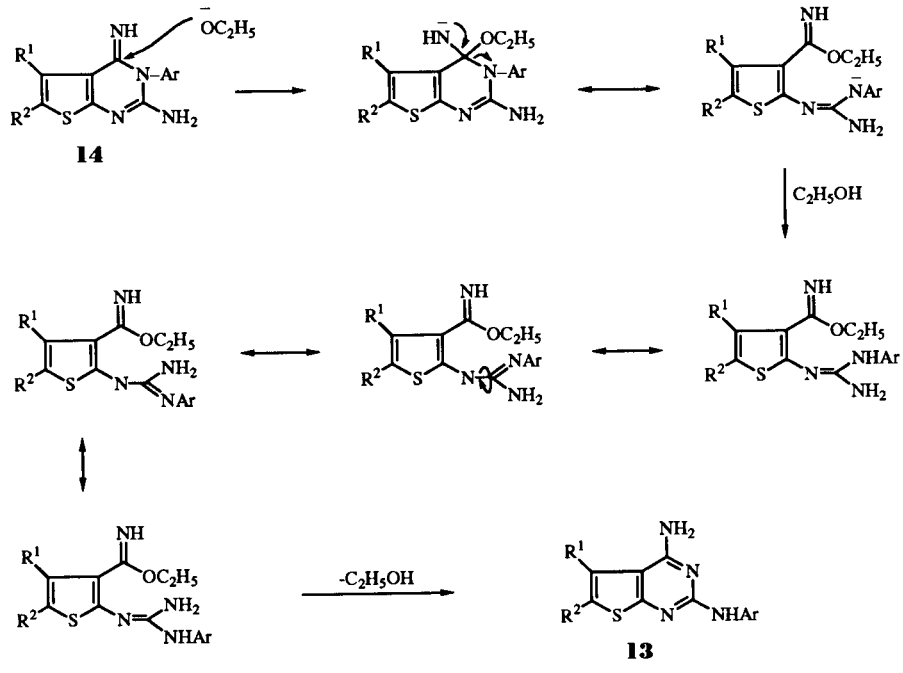
The formation of the minor product 2-amino-3-arylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **16** cannot be viewed as an artifact in the reaction. Its formation can be rationalized as proceeding through the protonated guanidine intermediate **12** which undergoes hydrolysis through a Ritter-type reaction, followed by cyclization during the workup (Scheme VII).

Scheme III

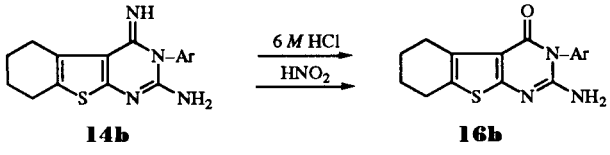


14a,16a, $R^1, R^2 = -(CH_2)_4-$, Ar = C_6H_5
14b,16b, $R^1, R^2 = -(CH_2)_4-$, Ar = 4-$CH_3C_6H_4$
14c,16c, $R^1, R^2 = -(CH_2)_4-$, Ar = 4-$CH_3OC_6H_4$
14d,16d, $R^1, R^2 = -(CH_2)_4-$, Ar = 4-ClC_6H_4
14e,16e, $R^1 = R^2 = CH_3$, Ar = 4-ClC_6H_4

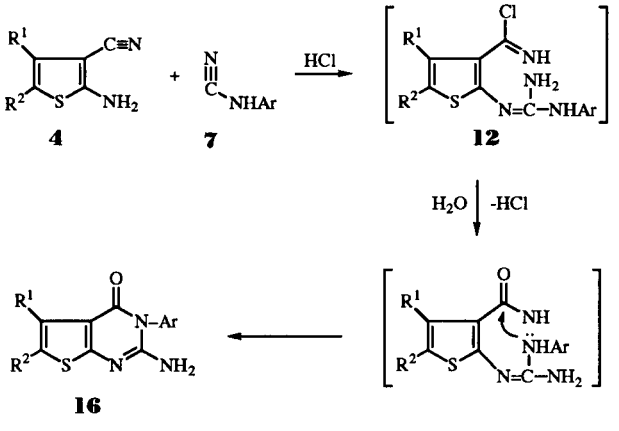
Scheme V



Scheme VI



Scheme VII



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. Ultraviolet spectra were recorded on a Beckman Model 25 spectrophotometer using methanol as the solvent. 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 direct insertion probe.

The *N*-arylcyanamides **7a-d** [16] and thiophene *o*-aminonitriles **4a,b** [17] were prepared by methods described in the literature.

I. Reaction of Thiophene *o*-Aminonitriles **4a** and **4b** with *N*-Arylcyanamides **7a-d** in the Presence of Dry Hydrogen Chloride Gas.

General Procedure.

A stream of dry hydrogen chloride gas was bubbled through an ice-cold mixture of the appropriate thiophene *o*-aminonitrile **4** (0.01 mole) and *N*-arylcyanamide **7** (0.01 mole) in dry dioxane [18] (30 ml) for 12-14 hours. After allowing to stand overnight at room temperature, the reaction mixture was poured into ice-water mixture and basified with dilute ammonium hydroxide solution (*p*H 8). The solid separated was filtered, washed with water, and dried. The dried product was extracted with hot benzene (30 ml) and the benzene extract was concentrated (10 ml) and chromatographed on a neutral alumina column. The elution was first carried out with benzene. The appropriate benzene fractions were combined and evaporated to dryness to afford a yellow coloured residue, which on recrystallization from benzene yielded the pure compound, characterized as 2-amino-3-arylthieno[2,3-*d*]pyrimidin-4-(3*H*)-one **16**.

Continued elution with a benzene:chloroform (1:1) mixture afforded a solid, which on recrystallization from benzene or benzene-hexane mixture yielded the pure compound characterized as 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidine **14**.

2-Amino-4-imino-3-phenyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**14a**).

This compound obtained through the reaction of **4a** and **7a** was a light yellow crystalline solid (benzene-*n*-hexane), mp 198-200°, yield 41%; ir (Nujol): 3420, 3350, 3300 (NH), 1640 cm^{-1}; uv (methanol): λ max 325, 271; ms: (m/z) 296 (M$^+$), 295, 268,

267, 219.

Anal. Calcd. for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44. Found: C, 64.51; H, 5.13.

2-Amino-3-phenyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**16a**).

This compound obtained as the minor component in the reaction of **4a** and **7a** was a colorless crystalline solid (benzene), mp 230-232° (lit [12] mp 227-229°); yield 17%; ir (potassium bromide): 3360, 3200 (NH), 1710 (CO) cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08. Found: C, 64.30; H, 5.01.

2-Amino-4-imino-3-(4-methylphenyl)-5,6,7,8-tetrahydrobenzo[*b*]-thieno[2,3-*d*]pyrimidine (**14b**).

This compound obtained as the major product of the reaction between **4a** and **7b** was a colorless crystalline solid (benzene), mp 195-196°, yield 44%; ir (potassium bromide): 3480, 3360, 3320 3240 (NH), 1660 cm^{-1}; uv (methanol): λ max 330, 276; ^1H nmr (deuteriochloroform): δ 1.7-1.9 (m, 4H, CH_2 at 6 and 7), 2.4 (s, 3H, Ar-CH_3), 2.6-2.9 (m, 4H, CH_2 at 5 and 8), 4.9 (s, 3H, NH_2 at 2 and N*H* at 4, deuterium oxide-exchangeable), 7.1-7.6 (m, 4H, phenyl protons).

Anal. Calcd. for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.84; N, 18.05. Found: C, 65.75; H, 6.00; N, 17.93.

2-Amino-3-(4-methylphenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidin-4(3*H*)-one (**16b**).

The compound obtained as the minor product of the reaction between **4a** and **7b** was a colorless crystalline solid (benzene), mp 250-252° (lit [11] mp 243-245°), yield 16%; ir (potassium bromide): 3360, 3200 (NH); 2920; 1600 (CO) cm^{-1}; uv (methanol): λ max 315, 265; ^1H nmr (deuteriochloroform + dimethyl sulfoxide-d_6): δ 1.7-2.0 (m, 4H, CH_2 at 5 and 8), 5.7 (s, 2H, NH_2, deuterium oxide-exchangeable, 7.1-7.5 (m, 4H, phenyl protons).

Anal. Calcd. for $C_{17}H_{17}N_3OS$: C, 65.57; H, 5.50. Found: C, 65.98; H, 5.37.

2-Amino-4-imino-3-(4-methoxyphenyl)-5,6,7,8-tetrahydrobenzo-[*b*]thieno[2,3-*d*]pyrimidine (**14c**).

This compound representing the major component in the reaction of **4a** and **7c** was obtained as colorless crystals (benzene), mp 200-202°, yield 38%; ir (nujol): 3460, 3300, 3180 (NH), 1650 cm^{-1}; uv (methanol): λ max 332, 279; ms: (m/z) 326 (M^+), 325, 311, 298, 297, 295, 284, 283, 219, 217.

Anal. Calcd. for $C_{17}H_{18}N_4OS$: C, 62.55; H, 5.56. Found: C, 62.63; H, 5.70.

2-Amino-3-(4-methoxyphenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidin-4(3*H*)-one (**16c**).

This compound obtained as the minor component in the reaction of **4a** and **7c** was a light yellow crystalline compound (benzene), mp 248-251° (lit [19] mp 252-253°), yield 18%; ir (potassium bromide): 3460, 3380 (NH), 1680 (CO) cm^{-1}; uv (methanol): λ max 320, 272; ms: (m/z) 327 (M^+), 326, 312, 311, 285, 284.

Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.35; H, 5.24. Found: C, 62.65; H, 5.57.

2-Amino-3-(4-chlorophenyl)-4-imino-5,6,7,8-tetrahydrobenzo[*b*]-thieno[2,3-*d*]pyrimidine (**14d**).

This compound obtained as the major product in the reaction of **4a** with **7d** formed colorless crystals (benzene) mp 185-188° (lit [5] mp 185-188°), yield 42%; ir (Nujol): 3480, 3350, 3300 (NH), 1640 cm^{-1}; uv (methanol): λ max 332, 280; ^1H nmr (deuteriochloroform): δ 1.7-1.8 (m, 4H, CH_2 at 6 and 7), 2.6-2.8 (m, 4H, CH_2 at 5 and 8), 5.1 (s, 3H, NH_2 at 2 and N*H* at 4, deuterium oxide exchangeable), 7.2-7.77 (m, 4H, phenyl protons); ms: (m/z) 332 (M + 2), 330 (M^+), 329, 302, 301, 295, 294, 267, 260.

Anal. Calcd. for $C_{16}H_{15}ClN_4S$: C, 58.09; H, 4.57; N, 16.98. Found: C, 58.45; H, 4.51; N, 16.47.

2-Amino-3-(4-chlorophenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (**16d**).

This compound was obtained as the minor product of the reaction between **4a** and **7d** as pale yellow crystals (benzene) mp 260-262° (lit [19] mp 260-262°) yield 20%, ir (potassium bromide): 3340, 3200 (NH), 1660 (CO) cm^{-1}; uv (methanol): λ max 322, 270; ^1H nmr (deuteriochloroform): δ 1.7-1.9 (m, 4H, CH_2 at 6 and 7), 2.5-3.0 (m, 4H, CH_2 at 5 and 8), 5.4 (s, 2H, NH_2 deuterium oxide exchangeable), 7.3-7.6 (m, 4H, phenyl protons); ms: (m/z) 333 (M + 2), 331 (M^+), 330, 315, 303, 296, 289, 220, 179.

Anal. Calcd. for $C_{16}H_{14}ClN_3OS$: C, 57.91; H, 4.26. Found: C, 58.07; H, 4.47.

2-Amino-3-(4-chlorophenyl)-4-imino-5,6-dimethylthieno[2,3-*d*]-pyrimidine (**14e**).

This compound obtained as the major product of the reaction between **4b** and **7d** formed shiny colorless crystals (benzene-*n*-hexane), mp 186-188°, yield 46%; ir (Nujol): 3460, 3360, 3320 (NH), 1650 cm^{-1}; uv (methanol): λ max 331, 278; ms: (m/z) 306 (M + 2), 304 (M^+), 303, 193.

Anal. Calcd. for $C_{14}H_{13}ClN_4S$: C, 55.17; H, 4.30. Found: C, 54.87; H, 4.42.

2-Amino-3-(4-chlorophenyl)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (**16e**).

This compound obtained as the minor product of the reaction between **4b** and **7d** was a colorless crystalline solid (benzene), mp 215-220°, yield 15%; ir (Nujol): 3500, 3320 (NH), 1670 (CO) cm^{-1}; uv (methanol): λ max 322, 271; ms: (m/z) 307 (M + 2), 305 (M^+), 304, 290, 277, 270, 269, 194, 153.

Anal. Calcd. for $C_{14}H_{12}ClN_3OS$: C, 54.99; H, 3.96. Found: C, 54.92; H, 3.78.

II Unequivocal Synthesis of 2-Amino-3-phenyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one **16a**.

To a well stirred solution of 2-azido-3-phenyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one [12] (3.23 g, 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 removal of benzene under reduced pressure recrystallized to yield colorless crystals (ethanol) mp 230-232°, yield 61%, identical (mixed mp, tlc, ir) with **16a**; ir (potassium bromide): 3360, 3200 (NH), 1710 (CO) cm^{-1}; ms: (m/z) 297 (M^+), 282, 281, 270, 269, 268, 255, 220, 179.

Anal. Calcd. for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08. Found: C, 63.32; H, 4.91.

III Base Catalyzed Isomerization of 2-Amino-3-aryl-4-imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidines **14b** and **14d** to 4-Amino-2-arylaminothieno[2,3-*d*]pyrimidines **13a** and **13b** in the Presence of Sodium Ethoxide in Absolute Ethanol.

General Procedure.

A mixture of 2-amino-3-aryl-4-iminothieno[2,3-*d*]pyrimidine (**14**) (0.01 mole) and absolute ethanol (30 ml) containing sodium ethoxide (10-15 mg) was warmed on a water bath (40-50°) for 2 hours and allowed to stand at room temperature for 12 hours. The solid obtained was filtered, dried and dissolved in benzene (10-15 ml). The benzene solution was chromatographed on a neutral alumina column using benzene for elution. Appropriate benzene fractions were combined and concentrated (under reduced pressure) to give a colorless solid, which on recrystallization from benzene-*n*-hexane afforded the pure crystalline material, characterized as 4-amino-2-arylaminothieno[2,3-*d*]pyrimidine (**13**).

4-Amino-2-(4-methylphenyl)amino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**13a**).

This compound was obtained through the base catalyzed isomerization of **14b** and formed colorless crystals (benzene-*n*-hexane), mp 220-222° (lit [5] mp 220-222°), yield 55%; ir (potassium bromide): 3360, 3320, 3180 (NH), 1650 cm^{-1}; uv (methanol): λ max 325, 263; ^1H nmr (deuteriochloroform): δ 1.8-2.0 (m, 4H, CH_2 at 6 and 7), 2.3 (s, 3H, Ar-CH_3), 2.6-2.8 (m, 4H, CH_2 at 5 and 8), 5.1 (s, 2H, NH_2 at 4, deuterium oxide exchangeable), 6.8 (s, 1H, Ar-N*H* at 2, deuterium oxide-exchangeable), 7.0-7.6 (m, 4H, phenyl proton) ms: (m/z) 310 (M^+), 309, 295, 294, 282, 281, 268, 267, 178.

Anal. Calcd. for $C_{17}H_{18}N_4S$: C, 65.78; H, 5.85; N, 18.04. Found: C, 65.94; H, 6.35; N, 17.63.

4-Amino-2-(4-chlorophenyl)amino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**13b**).

This compound obtained through the base catalyzed isomerization of **14d** was a colorless crystalline solid (benzene-*n*-hexane), mp 214-215° (lit [5] mp 213-215°), yield 56%; ir (potassium bromide): 3500, 3420, 3300, 3180 (NH), 1640 cm^{-1}; uv (methanol): λ max 330, 265; ^1H nmr (deuteriochloroform): δ 1.8-2.0 (m, 4H, CH_2 at 6 and 7), 2.7-3.0 (m, 4H, CH_2 at 5 and 8), 5.2 (s, 2H, NH_2 at 4, deuterium oxide exchangeable), 6.9 (s, 1H, Ar-N*H* at 2, deuterium oxide exchangeable), 7.2-7.7 (m, 4H, phenyl protons); ms: (m/z) 332 (M+2), 330 (M^+), 329, 302, 301 295, 288, 287, 260, 219, 204, 178, 177.

Anal. Calcd. for $C_{16}H_{15}ClN_4S$: C, 58.09; H, 4.57; N, 16.88. Found: C, 57.62; H, 4.12; N, 16.93.

IV Attempted Acid Catalyzed Isomerization of 2-Amino-3-(4-chlorophenyl)-4-imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-pyrimidine (**14d**) using *p*-Toluenesulfonic Acid in Benzene.

A mixture of **14d** (3.30 g, 0.01 mole) and *p*-toluenesulfonic acid (1.72 g, 0.01 mole) in benzene (30 ml) was refluxed for 6 hours. The reaction mixture was cooled and filtered, the filtrate concentrated and the solid obtained was recrystallized from benzene to yield 2.9 g of colorless crystals, mp 185-188°, identical (mixed mp, tlc) with the starting material.

V Attempted Acid Catalyzed Isomerization of 2-Amino-3-(4-chlorophenyl)-4-imino-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]-pyrimidine (**14d**) using Formic Acid.

A solution of **14d** (3.30 g, 0.01 mole) in formic acid (20 ml) was refluxed for 3 hours. The reaction mixture was cooled to room temperature and poured into ice-water mixture. The solid obtained was filtered, washed with water and dried. Recrystallization from benzene yielded 3.0 g of colorless crystals, mp 185-187°, identical (mixed mp, tlc) with the starting material.

VI Attempted Acid Catalyzed Isomerization of **14d** using Dilute Hydrochloric Acid (10%).

A solution of **14d** (3.30 g, 0.01 mole) in 10% hydrochloric acid (30 ml) was stirred at 40-50° for 3 hours and allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water mixture and basified with dilute ammonium hydroxide (*p*H 8). The solid separated was filtered immediately, washed with water, dried and recrystallized from benzene to yield 3.0 g of colorless crystalline solid, mp 185-187°, identical (mixed mp, tlc) with the starting material.

VII Hydrolysis of 2-Amino-4-imino-3-(4-methylphenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**14b**) in 6*M* Hydrochloric Acid.

The imino compound **14b** (3.10 g, 0.01 mole) was boiled in 6*M* hydrochloric acid (100 ml) for 18 hours. The reaction mixture was cooled to room temperature, poured into ice-water mixture and basified with concentrated aqueous ammonium hydroxide (*p*H 8). The solid separated was filtered, washed with water, dried and recrystallized from benzene to yield a colorless crystalline product, mp 249-251°, yield 41%, identical (mixed mp, tlc, ir) with the authentic sample of **16b** [11,19]; ir (potassium bromide): 3360, 3200 (NH), 2920, 1660 (CO) cm^{-1}.

Besides the above product, 0.6 g of an impure tarry material was also obtained, which could not be purified.

VIII Nitrous Acid Deamination of 2-Amino-4-imino-3-(4-methylphenyl)-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**14b**).

To a solution of **14b** (3.10 g, 0.01 mole) in boiling 0.5*M* sulfuric acid (10 ml) was added over a period of 10 minutes, a solution of sodium nitrite (0.1 g) in water (5 ml). This reaction mixture was boiled for a further 5 minutes, cooled and made alkaline with aqueous sodium hydroxide (2*M*). The solid separated was collected, washed with water and dried. Recrystallization of this solid from benzene afforded shining colorless crystals, mp 250-252°, yield 64%, identical (mixed mp, tlc, ir) with the authentic sample of **16b** [11,19]; ir (potassium bromide): 3360, 3200 (NH), 2920, 1660 (CO) cm^{-1}.

Acknowledgements.

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

REFERENCES AND NOTES

[1] E. F. Elslager, C. Hess, J. Johnson, D. Ortwine, V. Chien and L. M. Werbel, *J. Med. Chem.*, **24**, 127 (1981).

[2] E. F. Elslager, P. Jacob and L. M. Werbel, *J. Heterocyclic Chem.*, **9**, 775 (1972).

[3] F. H. S. Curd, J. K. Lindquist and F. Rose, *J. Chem. Soc.*, 775 (1947).

[4] C. J. Shishoo, M. B. Devani, K. S. Jain, V. S. Bhadti, S. M. Shishoo, U. S. Pathak, S. Ananthan and I. S. Rathod, *Indian J. Chem.*, **22B**, 42 (1989).

[5] C. J. Shishoo and K. S. Jain, *J. Heterocyclic Chem.*, **29**, 883 (1992).

[6] D. R. Shah, M. Pharm. Dissertation, Gujarat University, Ahmedabad, India, April 1984.

[7] K. G. Dave, C. J. Shishoo, M. B. Devani, R. Kalyanaraman, S. Ananthan, G. V. Ullas and V. S. Bhadti, *J. Heterocyclic Chem.*, **17**, 1497 (1980).

[8] C. J. Shishoo, M. B. Devani, V. S. Bhadti, K. S. Jain and S. Ananthan, *J. Heterocyclic Chem.*, **27**, 119 (1990).

[9] P. Molina, A. Arques and H. Hernandez, *J. Heterocyclic Chem.*, **21**, 685 (1984).

[10] K. Eger, J. G. Pfahl, G. Folkers and H. J. Roth, *J. Heterocyclic Chem.*, **24**, 425 (1987).

[11] C. J. Shishoo, M. B. Devani, U. S. Pathak, S. Ananthan, V. S. Bhadti, G. V. Ullas, K. S. Jain, I. S. Rathod, D. S. Talati and N. H. Doshi, *J. Heterocyclic Chem.*, **21**, 375 (1984).

[12] U. S. Pathak, N. V. Gandhi, S. Singh, R. P. Warde and K. S. Jain, *Indian J. Chem.*, **31B**, 223 (1992).

[13] D. J. Brown and M. S. Paddon-Row, *J. Chem. Soc. (C).* 903 (1967).

[14] E. C. Taylor and A. McKillop, Advances in Organic Chemistry: Methods and Results, The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles, Vol **7**, E. C. Taylor, ed, Interscience Publishers, 1970, p 240.

[15a] S. Robev, *Dokl. Bolg. Akad. Nauk.*, **30**, 719 (1977); *Chem. Abstr.*, **87**, 167970 (1977); [b] S. Robev, *Dokl. Bolg. Akad. Nauk.*, **32**, 1235 (1979); *Chem. Abstr.*, **93**, 8129 (1980); [c] S. Robev, *Dokl. Bolg. Akad. Nauk*, **34**, 1677 (1981); *Chem. Abstr.*, **97**, 127597 (1982).

[16] K. Sahasrabudhe, *J. Indian Chem. Soc.*, **19**, 345 (1942).

[17] K. Gewald, E. Schinke and M. Bottcher, *Chem. Ber.*, **99**, 94 (1966).

[18] Weygund/Hilgetag Preparative Organic Chemistry, G. Hilgetag and A. Martini, eds, John Wiley and Sons, New York, 1973, p 1100.

[19] K. S. Jain, M. Pharm. Dissertation, Gujarat University, Ahmedabad, India, 1982.