Convenient Synthesis of Substituted 3-Aminothiophene-2-carbonitriles from α-Acetylenic Nitriles and their Conversion to Thieno[3,2-*d*]pyrimidines [1]

Wu-Yun Ren, Kambhampati V. B. Rao and Robert S. Klein*

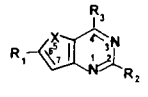
Laboratory of Organic Chemistry, Sloan-Kettering Institute for Cancer Research, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, NY 10021

Received March 31, 1986

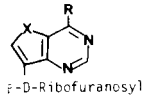
Several novel 2,4,6-trisubstituted thieno[3,2-*d*]pyrimidines were synthesized from the hitherto unknown 3-amino-5-methyl-(or 5-phenyl)thiophene-2-carbonitriles **7** and **8**. *o*-Aminonitriles **7** and **8** were obtained in a single step by conjugate addition of mercaptoacetonitrile (generated *in situ*) to substituted acetylenic nitriles **4** and **5** and annelation of the intermediate vinylic thioethers.

J. Heterocyclic Chem., **23**, 1757 (1986).

The isosteric relationship extant between the purines and members of the 5*H*-pyrrolo[3,2-*d*]pyrimidines ("9-Deazapurines," **1a**) and the thieno[3,2-*d*]pyrimidines **1b** has elicited considerable interest in the synthesis of these purine analogs because of their potential biochemical significance. Noteworthy among recent investigations of the "9-deazapurines" was the study of a series of novel 2,4,6-trisubstituted-5*H*-pyrrolo[3,2-*d*]pyrimidines [2]. Some were found to possess significant growth-inhibitory activity against murine Sarcoma 180 and leukemia L-1210 *in vitro* and *in vivo* and several exhibited antimicrobial activity against *Mycobacterium tuberculosis* H37Rv and *Lactobacillus casei* 7469. Also, as part of a program directed towards the biological evaluation of purine-like *C*-nucleoside analogues, we have synthesized a series of 5*H*-pyrrolo[3,2-*d*]pyrimidines bearing the β-D-ribofuranosyl moiety at C-7 (**2a,b**) [3]. Among these novel 9-deazapurine nucleoside analogues, "9-Deazaadenosine" (**2a**) was



1a: X= NH
b: X= S

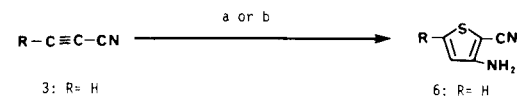


β-D-Ribofuranosyl

2a: X= NH, R= NH_2
b: X= NH, R= OH
c: X= S, R= NH_2
d: X= S, R= OH

found to inhibit the growth of several murine and human tumor cell lines [3b.4] *in vitro* and to possess significant antitumor activity *in vivo* [5]. 9-Deazainosine (**2b**) [3a,c] was also found to have significant antiparasitic activity against several pathogenic hemoflagellates [6]. Concurrent synthetic studies of a series of 7-ribosylated thieno[3,2-*d*] pyrimidine isosteres **2c,d** indicated that the adenosine analog **2c** had significant cytocidal properties similar to **2a** [7] while the inosine analog **2d** [8] had antiparasitic activity similar to that of its pyrrolopyrimidine congener **2b** [6a]. The finding of such parallel biological activities, which undoubtedly reflects the close structural resemblance between the two systems, prompted this synthetic investigation of several trisubstituted thienopyrimidines **1b** similar to the 5*H*-pyrrolo[3,2-*d*]pyrimidines reported by the Russian investigators to have antitumor and antimicrobial activity [2]. The thieno[3,2-*d*]pyrimidines of interest would thus bear alkyl and/or aryl groups at C-2 and/or C-6 and an amino- or thio- group at C-4 but, unlike **2**, would be unsubstituted at C-7. Adaptation of Fiesselmann's well-tried synthesis of 3-amino-2-carboalkoxythiophenes [9,10] to that of the required 5-substituted 3-amino-2-cyanothiophene precursors, *e.g.*, **7,8**, would thus be possible in principle by utilization of appropriately β-substituted α,β-dichloropropionitriles. It was of greater interest, however, to investigate a lesser explored [11d] yet promising approach involving the conjugate addition of α-thiolated acetonitriles directly onto readily available α-acetylenic nitriles [11] such as **4** and **5** (Scheme 1) followed by a modified Thorpe-Ziegler cyclization similar to that implicated in the synthesis of **2**.

Scheme 1



3: R= H
4: R= CH_3
5: R= C_6H_5

6: R= H
7: R= CH_3
8: R= C_6H_5

a= $Na^+\bar{S}$-CH_2CN/ THF, -78°C; b= $AcSCH_2CN$, EtONa/ EtOH, -78°C

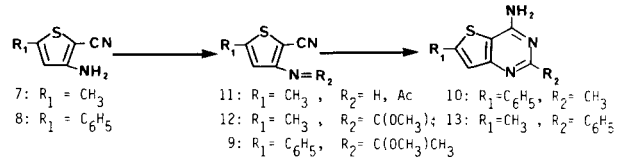
Initial attempts to obtain 5-substituted 3-amino-2-cyanothiophenes by reaction of propiolonitriles **3-5** with the sodium salt of mercaptoacetonitrile [12] under a variety of conditions were met with only limited success. Thus, treatment of **3-5** [13] with this reagent in THF afforded the corresponding *o*-aminonitriles **6-8** in generally poor yields. This could be attributed to the instability of mercaptoacetonitrile which can polymerize and be oxidized to the disulfide under basic conditions [12]. The studies clearly showed, nevertheless, that cyclization of the initially formed adduct occurs immediately after its formation without

the need of additional and/or stronger bases.

An improved method was developed to utilize the *in situ* generation of sodium mercaptoacetonitrile in the presence of the unsaturated nitrile. This involved treatment of *S*-acetyl mercaptoacetonitrile with one equivalent of sodium ethoxide in ethanol at room temperature followed immediately by the addition of one equivalent of β-substituted acetylenic nitriles **4** or **5** and reaction at -78°. Under these conditions, 3-amino-5-methylthiophene-2-carbonitrile (**7**) and 3-amino-5-phenylthiophene-2-carbonitrile (**8**) were obtained in 78% and 70% yields, respectively. These were readily characterized by their elemental microanalyses and by ^{1}H nmr spectroscopy. The spectrum of **7** exhibited a characteristic allylic coupling (J = 1.2 Hz) between H-4 and CH_3 similar to that observed between H-6 and H-1′ in **2d** [8]. Unexpectedly, application of this synthetic procedure to unsubstituted propiolonitrile **3** did not improve appreciably yields of the known thiophene **6** [14].

Synthesis of 2,6-disubstituted-4-aminothieno[3,2-*d*]pyrimidines was originally attempted by treating the 5-substituted 3-aminothiophene-2-carbonitriles with various amidines, a method reportedly useful for obtaining fused 4-aminopyrimidines from *o*-aminonitriles [15] in a single step. Thus, treatment of **7** with benzamidine hydrochloride or of **8** with acetamidine hydrochloride under a variety of conditions only led to recovery of the starting thiophenes with little or no reaction being observed. As an alternative approach, the well-documented and versatile two-step method involving initial conversion of the amino group of *o*-aminonitriles to an iminoether (by treatment with orthoesters) followed by conversion to the *o*-cyanoamidine with ammonia (or other amines) and concurrent (or subsequent) base-catalyzed ring closure appeared promising. While the method had reportedly used mostly orthoformate esters [16], it was of interest to investigate its applicability to the synthesis of 2-substituted pyrimidines with other orthoesters. Thus, treatment of the 5-phenylthiophene derivative **8** with trimethyl orthoacetate and acetic anhydride at 120° afforded acetimidate **9** (Scheme 2) in good yields. Treatment of **9** with methanolic ammonia under a variety of conditions aimed at formation of the acetamide intermediate and ring-closure of the pyrimidine resulted instead in recovery of starting amine **8**. Use of sodium amide in liquid ammonia at 80° in sealed vessel was more successful and afforded, after chromatography, the desired 2,6-disubstituted-4-aminothieno[3,2-*d*]pyrimidine **10** in 57% yield. Treatment of 5-methyl thiophene **7** with trimethyl orthobenzoate and acetic anhydride gave, instead of the expected benzimidate **12**, acetamide **11**. Under these conditions, imidate formation by the less reactive benzoate orthoester apparently competes unfavorably with acetylation of the amino group. Prolonged treatment of **7** with trimethyl orthobenzoate alone at 120° afforded acceptable yields of **12** which readily converted to the desired 2-phenyl-6-methyl-4-amino derivative **13** with sodamide in liquid ammonia.

Scheme 2

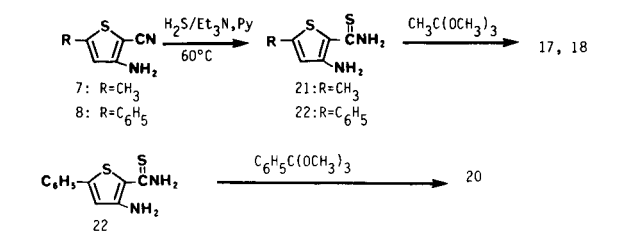


Efforts directed toward the synthesis of 2,6-disubstituted-4-thio-3*H*-thieno[3,2-*d*]pyrimidines included conversion of several *o*-aminocyanothiophenes to their corresponding thioamides which were suitable intermediates for ring-closure to the desired fused pyrimidinethiones. In one study we found that treatment of the *N*-acetyl derivative **11** (Scheme 3) with sodium hydrosulfide in ethanol afforded directly the desired pyrimidinethione product **17**. This convenient one-step conversion was found to be generally applicable to a variety of 3-acylamino-2-cyano derivatives. By this method compounds **11** and **14-16** (Scheme 3) were readily converted to **17-20**, respectively, in generally very good yields. It is noteworthy that the stable *N*-dibenzoyl intermediates **15** and **16** (obtained by benzoylation of **7** and **8**, respectively) were both suitable for direct conversion to thiones **19** and **20** with sodium hydrosulfide in ethanol [17].

Scheme 3

Parallel studies were also conducted for the comparative evaluation of an alternate approach to **17-20** *via* cyclization of *o*-aminothioamides with orthoesters [8] (Scheme 4).

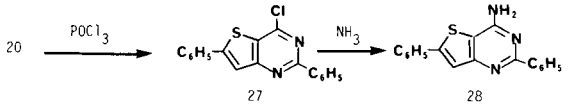
Scheme 4



The *o*-aminonitriles **7** and **8** were converted to their corresponding thioamides **21** and **22**, respectively, in moderate yields with hydrogen sulfide/pyridine/triethylamine. While

treatment of **21** and **22** with triethyl orthoacetate at 90° afforded good yields of the desired fused pyrimidinethiones **17** and **18**, utilization of trimethyl orthobenzoate was less successful. Thus, 2,6-diphenylthieno[3,2-*d*]pyrimidinethione **20** was obtained in poor yields from reaction of thioamide **22** with trimethyl orthobenzoate while treatment of thioamide **21** (Scheme 4) with that reagent failed to produce pyrimidinethione **19** altogether. It is clear that of the methods illustrated in Schemes 3 and 4 for the synthesis of fused pyrimidinethiones such as **17-20**, that involving treatment of *o*-acylaminonitrile derivatives (Scheme 3) is superior in both scope and overall yields obtained. In view of the ready accessibility of variously substituted thieno[3,2-*d*]pyrimidinethiones, *e.g.*, **17-20**, and the desirability for better synthetic approaches to the 4-amino derivatives, *e.g.*, **10** and **13**, it was of interest to investigate the possibility for thione → amine conversion in this heterocyclic system. The standard method of ammonolysis of thioethers, which has been extensively utilized for the preparation of 4-aminopyrimidines [19], when applied to the 4-methylthio derivatives **23-26** (readily obtainable by the *S*-alkylation of thienopyrimidinethiones **17-20** with methyl iodide/aqueous sodium hydroxide) was uniformly unsuccessful under a variety of conditions. By analogy to the well-known conversion of pyrimidine-4-ones to the corresponding chloro derivative [19], treatment of 2,6-diphenyl-4-thio-3*H*-thieno-[3,2-*d*]pyrimidine **20** (Scheme 5) with phosphorus oxychloride in hot *N*,*N*-diethylaniline afforded very good yields of the corresponding crystalline chloro derivative **27**. This could be readily ammonolyzed with saturated methanolic ammonia to the desired 4-amino derivative **28** in good overall yields [20].

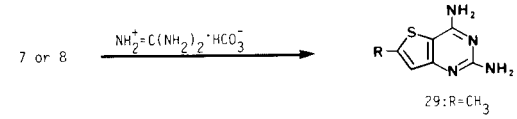
Scheme 5



27 28

In view of the diuretic [21] and antileukemic [22] activity associated with several fused 2,4-diaminopyrimidine systems, a brief investigation of the synthesis of 6-substituted 2,4-diamino derivatives was also of interest. A general procedure for the conversion of *o*-aminonitriles to condensed 2,4-diaminopyrimidines involves the treatment of the former compounds with guanidine. Thus, 2,4-diaminothieno[3,2-*d*]pyrimidines **29** and **30** (Scheme 6) could be obtained directly from *o*-aminonitriles **7** and **8**, respectively, by treatment of **7** with guanidine carbonate and sodium ethoxide in refluxing ethanol or by fusion of **8** with guanidine carbonate.

Scheme 6



29: R = CH_3
30: R = C_6H_5

Results from the preliminary evaluation of several of the thieno[3,2-*d*]pyrimidines reported here as growth inhibitors of two murine leukemic cell lines are found in Table I. The 2,4-diamino derivative **30** was the most active of the thieno[3,2-*d*]pyrimidines tested [23]. Further biological evaluation of the latter in these and other systems will be reported elsewhere.

Table I

Comparison of the *in vitro* Tumor Growth-inhibitory Activity of the 2,4,6-Trisubstituted Thieno[3,2-*d*]pyrimidines

Compound	ID_{50} (μg/ml) L-1210	P-815/0
10	>100	>100
17	53	54
18	>100	>100
19	>100	>100
23	62	--
24	>100	--
25	>100	--
27	>100	--
28	61.3	--
29	>100	--
30	3.6	17.0

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. The ^1H nmr spectra were recorded on a JEOL PFT-100 spectrometer or JEOL FX-90Q spectrometer and chemical shifts are reported as δ values with tetramethylsilane as the internal standard; uv absorption spectra were obtained with a Cary Model 15 and a Unicam Model SP-800A recording spectrophotometer. Microanalyses were performed by M.H.W. Laboratories, Phoenix, AZ. Thin-layer chromatography was performed on 250 μm silica gel GH plates (Analtech, Inc.), and the substances were visualized with a short-wave (254 nm) uv mineral light and/or by spraying with 10% ethanolic sulfuric acid and charring. Preparative tlc was performed on 1000 μm (unless stated otherwise) 20 x 20 cm silica gel plates (Uniplates by Analtech, Inc.), and the products visualized by short-wave uv light. Preparative column chromatography was performed by standard techniques on Merck silica gel 60 (70-230 mesh ASTM) or by flash chromatographic techniques on Merck silica gel 60 (230-400 mesh ASTM). Light petroleum ether (bp 30-60°) was used whenever this solvent was required.

3-Amino-5-phenylthiophene-2-carbonitrile (**8**).

To an ethanolic solution of sodium ethoxide prepared by dissolving sodium metal (0.92 g, 40.0 mg-atom) in 80 ml of absolute ethanol was added *S*-acetylmercaptoacetonitrile (5.00 g, 40.0 mmoles). After being stirred for 1 hour at room temperature, the reaction mixture was cooled to -78° and phenylpropiolonitrile [13a] (5.30 g, 40.0 mmoles) was added in one portion. The mixture was kept at this temperature for 20 minutes and then allowed to reach ambient temperature. The crude product was collected by filtration and recrystallized from ethanol to give **8** as an analytically pure, crystalline (flakes) solid (6.50 g, 78%), mp 174-175°; uv (methanol): λ max 335 nm (ε 7692), 305 (ε 11384) and 285 (ε 16615); ^1H nmr (deuteriochloroform): δ 4.47 (broad s, 2H, NH_2, exch with deuterium oxide), 6.75 (s, 1H, H-4), 7.35-7.59 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{11}H_8N_2S$: C, 65.98; H, 4.02; N, 13.99; S, 16.00. Found: C, 66.09; H, 4.12; N, 14.03; S, 16.29.

3-Amino-5-methylthiophene-2-carbonitrile (**7**).

Following a procedure similar to that described for **8**, methylpropiolonitrile [13b] (5.32 g, 81 mmoles) in ethanol (80 ml) containing sodium ethoxide (81 mmoles) was treated with *S*-acetylmercaptoacetonitrile (9.41 g, 81 mmoles) at -78°. After completion of the reaction, the mixture was evaporated to dryness and the residue partitioned between chloroform and water. The organic layer was washed with water, dried (over sodium sulfate) and evaporated to dryness. The crude product was purified by flash chromatography (chloroform then ethyl acetate as successive eluents) and the residue, after evaporation of the major fractions, was recrystallized from benzene-petroleum ether, (7.90 g, 70%), mp 100-101°; uv (methanol): λ max 300 nm (ε 3332), 257 (ε 3889) and 220 (ε 3556); ^{1}H nmr (deuteriochloroform): δ 2.39 (d, 3H, CH_3, $J_{CH_3, H\text{-}4}$ = 1.2 Hz), 4.40 (broad s, 2H, NH_2, exch with deuterium oxide), 6.25 (q, 1H, H-4).

Anal. Calcd. for $C_6H_6N_2S$: C, 52.15; H, 4.37; N, 18.82; S, 23.20. Found: C, 52.19; H, 4.42; N, 19.12; S, 23.15.

3-Methoxyacetimino-5-phenylthiophene-2-carbonitrile (**9**).

A mixture of **8** (2.0 g, 10 mmoles), acetic anhydride (6 ml) and trimethyl orthoacetate (15 ml) was heated to a gentle reflux for 1 hour while volatile by-products (methanol, acetic acid) were collected by slow distillation until the completion of the reaction. The reaction mixture was evaporated *in vacuo* and the crude product was crystallized from petroleum ether to give analytically pure **9** (2.0 g, 78%), mp 202-204°; ^{1}H nmr (deuteriochloroform): δ 2.02 (s, 3H, OCH_3), 3.84 (s, 3H, CH_3), 6.85 (s, H, H-4), 7.49 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.59; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.81; H, 4.35; N, 10.86; S, 12.60.

4-Amino-2-methyl-6-phenylthieno[3,2-*d*]pyrimidine (**10**).

To a solution of sodium amide in liquid ammonia obtained by dissolving sodium (0.020 g, 0.87 mg-atom) in 50 ml of liquid ammonia was added **9** (0.500 g, 1.95 mmoles). The mixture was heated at 80° for 18 hours in a steel container. After cooling, ammonia was evaporated and the residue was partitioned between chloroform and water. The organic layer was dried (sodium sulfate) and evaporated *in vacuo*. The crude product was purified by flash chromatography (Toluene/ethyl acetate, 10/1) to give **10** as a crystalline solid (270 mg, 57%), mp 179-181°; ^{1}H nmr (deuteriochloroform): δ 3.97 (s, 3H, CH_3), 4.29 (broad s, 2H, NH_2 exch with deuterium oxide), 7.45 (m, 5H, C_6H_5), 7.58 (s, 1H, H-7).

Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.69; H, 4.59; N, 17.41. Found: C, 64.35; H, 4.70; N, 17.23.

5-Methyl-3-methylbenzyliminothiophene-2-carbonitrile (**12**) and 4-Amino-6-methyl-2-phenylthieno[3,2-*d*]pyrimidine (**13**).

A mixture of **7** (0.65 g, 4.7 mmoles), trimethylorthobenzoate (5 ml) and finely ground molecular sieve (Linde, 3 Å) was heated at 120° with vigorous stirring for 4 days. After filtration, the clear solution was subjected to flash chromatography using ethyl acetate/petroleum ether (2:3) as the eluent. Evaporation *in vacuo* of appropriate fractions followed by reduced pressure distillation of some high boiling impurity afforded pure product **12** as a syrup (0.70 g, 58%); ^{1}H nmr (deuteriochloroform): δ 2.39 (d, 3H, CH_3, $J_{CH_3, H\text{-}4}$ = 1 Hz) 3.99 (s, 3H, OCH_3), 6.23 (q, 1H, H-4), 7.34 (narrow m, 5H, C_6H_5). This intermediate was used without further purification in the following step. Methoxybenzyliminothiophene **12** was treated with sodium amide in ammonia (50 mg of Na dissolved in 20 ml of ammonia) in a sealed steel vessel for 5 days at ambient temperature. After evaporation of the ammonia, the residue was subjected to flash chromatography with ethyl acetate/toluene (1:4) as the eluent to give 0.36 g (54%) of desired product **13**. The analytical sample was obtained by crystallization from ethanol, mp 167-168°; ^{1}H nmr (deuteriochloroform): δ 2.69 (d, 3H, CH_3, $J_{CH_3, H\text{-}7}$ = 1 Hz), 5.12 (broad s, 2H, NH_2 exch. with deuterium oxide), 7.15 (q, 1H, H-7), 7.92 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.60; N, 17.42; S, 13.29. Found: C, 65.00; H, 4.78; N, 17.26; S, 13.23.

3-Amino-5-methylthiophene-2-thiocarboxamide (**21**).

Into a solution of **7** (1.0 g, 7.2 mmoles) in pyridine (15 ml) containing triethylamine (3 ml) was bubbled hydrogen sulfide for 5 minutes at ambient temperature. The reaction mixture was stored in a sealed vessel and heated at 60° for 16 hours. After cooling, evaporation *in vacuo* afforded an oily residue which crystallized from ethanol to give **21** (0.86 g, 69%) as a yellow crystalline solid, mp 137-138°; ^{1}H nmr (DMSO-d_6): δ 2.32 (s, 3H, CH_3), 6.38 (s, 1H, H-4), 7.84 (broad s, 2H, NH_2 exch. with D_2O), 7.98 (broad s, 2H, NH_2 exch with deuterium oxide).

Anal. Calcd. for $C_6H_8N_2S_2$: C, 41.84; H, 4.68; N, 16.26. Found: C, 41.88; H, 4.72; N, 16.24.

3-Amino-5-phenylthiophene-2-thiocarboxamide (**22**).

By a procedure identical to that employed for the synthesis of **21**, treatment of **8** (2.0 g, 10 mmoles) in pyridine (20 ml) containing triethylamine (3 ml) with hydrogen sulfide afforded **22** (2.08 g, 89%) as a bright yellow crystalline material, mp 170-174°; ^{1}H nmr (DMSO-d_6): δ 3.33 (s, 3H, CH_3), 7.02 (s, 1H, H-4), 7.41-7.68 (m, 5H, C_6H_5), 7.86 and 8.28 (2 broad s, 2H each, 2 NH_2's exch with deuterium oxide).

Anal. Calcd. for $C_{11}H_{10}N_2S_2 \cdot 1/2\ H_2O$: C, 54.29; H, 4.56; N, 11.51. Found: C, 54.60; H, 4.47; N, 11.55.

3-(Acetylamino)-5-methylthiophene-2-carbonitrile (**11**).

o-Aminonitrile **7** (1.0 g, 7.2 mmoles) in 10 ml of pyridine and 10 ml of acetic anhydride was heated at 80° with stirring for 2 hours. Ethanol was then added to the mixture which was evaporated *in vacuo*. The residue was dissolved in ethanol and evaporated to dryness *in vacuo*. This was repeated once more and the final residue was crystallized from diethyl ether/petroleum ether to give **11** (1.27 g, 98%) as an analytically pure solid, mp 143-145°; ^{1}H nmr (deuteriochloroform): δ 2.22 (s, 3H, $COCH_3$), 2.50 (d, 3H, 5-CH_3, $J_{CH_3, H\text{-}4}$ = 1.2 Hz), 7.66 (q, 1H, H-4), 8.05 (broad s, 1H, NH).

Anal. Calcd. for $C_8H_8N_2OS$: C, 53.31; H, 4.47; N, 15.54; S, 17.79. Found: C, 53.44; H, 4.54; N, 15.53; S, 17.86.

2,6-Dimethyl-4-thio-3*H*-thieno[3,2-*d*]pyrimidine (**17**).

Method A (from **11**).

A solution of *o*-acetylaminonitrile **11** (1.27 g, 7.05 mmoles) in 30 ml of 1.5*N* ethanolic sodium hydrosulfide was heated to reflux for 3 hours. The mixture was concentrated by evaporation *in vacuo* and chloroform was added until precipitation of the crude product **17** occurred. The filtered product was recrystallized from ethanol to give analytically pure **17** (1.20 g, 86%), mp 278-280°; ^{1}H nmr (pyridine-d_5): δ 2.39 (d, 3H, 6-CH_3, $J_{CH_3, H\text{-}7}$ = 0.9 Hz), 2.57 (s, 3H, 2-CH_3), 6.21 (broad s, 1H, NH, exch with deuterium oxide), 7.12 (q, 1H, H-7).

Anal. Calcd. for $C_8H_8N_2S_2$: C, 48.95; H, 4.11; N, 14.27; S, 32.67. Found: C, 49.03; H, 4.22; N, 14.24; S, 32.42.

Method B (from **21**).

A solution of thiophene-2-thiocarboxamide **21** (0.100 g, 0.58 mmole) in 4 ml of trimethyl orthoacetate was heated at 90° for 1.5 hours. Diethyl ether and petroleum ether (3 ml each) were added to the cooled mixture which was then stored at ambient temperature for 18 hours to deposit **17** (0.110 g, 97%) as light brown crystals. The spectroscopic and physical properties of this product were identical with those of the material obtained by method A.

3-(Acetylamino)-5-phenylthiophene-2-carbonitrile (**14**).

To a solution of *o*-aminonitrile **8** (0.50 g, 2.5 mmoles) in pyridine (5 ml) was added acetic anhydride (5 ml) and the mixture was heated at 80° for 18 hours. Evaporation *in vacuo* afforded a residue containing both the monoacetyl derivative **14** and the *N,N*-diacetylated product. To a solution of the residue in chloroform (20 ml) and methanol (2 ml) was added 150 μl of triethyl amine and the mixture was stirred at ambient temperature for 1 hour until tlc indicated the presence of **14** only. Evaporation to dryness and crystallization of the crude product from chloroform/ether afforded pure **14** (0.513 g, 85%), mp 138-139°; ^{1}H nmr

(deuteriochloroform); δ 2.27 (s, 3H, CH_3), 7.47 (m, 5H, C_6H_5), 8.04 (broad s, 1H, NH exch with deuterium oxide), 8.19 (s, 1H, H-4).

Anal. Calcd. for $C_{13}H_{10}N_2SO$: C, 64.44; H, 4.16; N, 11.56; S, 13.23. Found: C, 64.36; H, 4.30; N, 11.82; S, 12.96.

2-Methyl-6-phenyl-4-thio-3*H*-thieno[3,2-*d*]pyrimidine (**18**).

Method A (from **14**).

A solution of *o*-acetaminonitrile **14** (0.936 g, 3.85 mmoles) in 25 ml of 1.5 *N* ethanolic sodium hydrosulfide was heated to reflux for 2 hours. The mixture was concentrated by evaporation *in vacuo* and product **18** was collected by filtration to give 0.90 g (91%) as an analytically pure crystalline material, mp >300°; uv (methanol): λ max 370 nm (ε 14136), 325 (ε 12631), 310 (ε 17894), 266 (ε 24736). ^{1}H nmr (deuteriochloroform): δ 2.56 (s, 3H, CH_3), 7.52 (s, 1H, H-7), 7.61 (m, 5H, C_6H_5), 13.57 (broad s, 1H, NH exch with deuterium oxide).

Anal. Calcd. for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.84; S, 24.82. Found: C, 60.31; H, 3.97; N, 10.65; S, 24.78.

Method B (from **22**).

By a method similar to that used for the synthesis of **17** from **21**, treatment of thiocarboxamide derivative **22** (0.055 g, 0.23 mmole) with trimethyl orthoacetate (2 ml) at 90° for 18 hours afforded **18** (0.040 g, 67%) identical in all respects with the product obtained from **14**.

3-(Dibenzoylamino)-5-methylthiophene-2-carbonitrile (**15**).

A mixture of *o*-aminonitrile **7** (1.00 g, 15.2 mmoles) pyridine (5 ml) and benzoyl chloride (5 ml) was stirred at ambient temperature for 1/2 hour. The mixture was poured over crushed ice and thoroughly stirred to destroy excess reagent, then extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and evaporated to dryness. The crude product was crystallized from ether/petroleum ether to give **15** (1.70 g, 68%), mp 189-190°, ^{1}H nmr (deuteriochloroform): δ 2.46 (d, 3H, CH_3, $J_{CH_3,\ H\text{-}4}$ = 1.2 Hz), 6.65 (q, 1H, H-4), 7.33-7.78 (m, 10H, $2C_6H_5$).

Anal. Calcd. for $C_{20}H_{14}N_2SO_2$: C, 69.34; H, 4.07; N, 8.08; S, 9.25. Found: C, 69.16; H, 4.12; N, 7.95; S, 9.57.

6-Methyl-2-phenyl-4-thio-3*H*-thieno[3,2-*d*]pyrimidine (**19**).

A solution of *N,N*-dibenzoylamino **15** (0.500 g, 1.44 mmoles) in 1.5*N* ethanolic sodium hydrosulfide (15 ml) was heated to reflux for 30 minutes. The reaction mixture was concentrated by evaporation *in vacuo* and the residue was dissolved in chloroform and washed with water (twice). After drying over sodium sulfate, the chloroform layer was evaporated to dryness. Crystallization from ethanol afforded pure **18** (0.203 g, 54%), mp 258-260°; uv (methanol): λ max 254 nm (ε 9677), 295 (ε 12903), 248 (ε 30645): ^{1}H nmr (deuteriochloroform): δ 2.65 (s, 3H, CH_3), 7.13 (s, 1H, H-7), 7.54-8.06 (m, 5H, C_6H_5), 10.75 (broad s, 1H, NH exch with deuterium oxide).

Anal. Calcd. for $C_{13}H_{10}N_2S_2$: C, 60.43; H, 3.90; N, 10.84; S, 24.82. Found: C, 60.59; H, 3.86; N, 10.75; S, 24.75.

3-Dibenzoylamino-5-phenylthiophene-2-carbonitrile (**16**).

A mixture of *o*-aminonitrile **8** (10.0 g, 49.9 mmoles) and benzoyl chloride (60.5 g, 430 mmoles) in dry pyridine (70 ml) was stirred magnetically for 3 hours at ambient temperature. The solution was then poured over crushed ice, stirred thoroughly and extracted with dichloromethane. The organic layer was washed with 1*N* hydrochloric acid until washings were acidic, then with water, dried (sodium sulfate) and evaporated *in vacuo*. The residue was crystallized from ethyl acetate to give pure **16** (18.7 g, 94%), mp 169-170°; ^{1}H nmr (deuteriochloroform): δ 7.12 (s, 1H, H-4), 7.82 (m, 15H, $3C_6H_5$).

Anal. Calcd. for $C_{25}H_{26}N_2O_2S$: C, 75.74; H, 4.07; N, 7.06; S, 8.09. Found: C, 75.35; H, 4.28; N, 6.84; S, 7.76.

2,6-Diphenyl-4-thio-3*H*-thieno[3,2-*d*]pyrimidine (**20**).

A solution of *N,N*-dibenzoylamine **16** (12.0 g, 30.3 mmoles) in 240 ml of 1.5*N* ethanolic sodium hydrosulfide was heated to reflux for 1.5 hours. The mixture was evaporated *in vacuo* and the residue was partitioned between water and chloroform. The organic layer was washed with brine, dried (sodium sulfate) and evaporated to dryness *in vacuo*. The residue was triturated with cold ethanol, filtered and dried to give thione **20** (6.94 g, 71%). An analytical sample was obtained by recrystallization from hot ethanol, mp 247-248°; ^{1}H nmr (deuteriochloroform): δ 7.56 (m, 6H, *m* and *p* to 2, 6-C_6H_5) 7.80 (m, 3H, H-7 and 2-H's *o* to 6-C_6H_5), 8.31 (s, 1H, NH exch with deuterium oxide), 8.66 (m, 2H, *o* to 2-C_6H_5).

Anal. Calcd. for $C_{18}H_{12}N_2S_2$: C, 67.47; H, 3.78; N, 8.74; S, 20.01. Found: C, 67.19; H, 3.81; N, 8.61; S, 19.86.

2,6-Dimethyl-4-(methylthio)thieno[3,2-*d*]pyrimidine (**23**).

To a solution of thione **17** (0.200 g, 1.02 mmoles) in 1*N* sodium hydroxide (5 ml) was added methyl iodide (2.28 g, 16.1 mmoles) and the mixture was stirred magnetically for 2 hours at ambient temperature. The unreacted excess of methyl iodide was remove *in vacuo* and the reaction mixture was extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and evaporated to dryness. The residue was recrystallized from ether to give **23** as an analytically pure crystalline (flakes) material (0.205 g, 96%), mp 106-108°; ^{1}H nmr (deuteriochloroform): δ 2.65 (d, 3H, 6-CH_3, $J_{CH_3,\ H\text{-}7}$ = 1.2 Hz), 2.72 and 2.74 (2s, 3H each, SCH_3 and 2-CH_3), 7.05 (q, 1H, H-7).

Anal. Calcd. for $C_9H_{10}N_2S_2$: C, 51.40; H, 4.79; N, 13.32; S, 30.49. Found: C, 51.27; H, 4.83; N, 13.40; S, 30.47.

2-Methyl-4-(methylthio)-6-phenylthieno[3,2-*d*]pyrimidine (**24**).

By a procedure identical to that used for conversion of **17** to **23**, treatment of thione **18** (0.125 g, 0.480 mmole) in 1*N* sodium hydroxide (6 ml) with methyl iodide (2.28 g, 16.1 mmoles) afforded crystalline 4-methylthio derivative **24** (0.122 mg, 93%) as needles, mp 141-142°, from ether; ^{1}H nmr (deuteriochloroform): δ 2.75 and 2.77 (2s, 3H each, 2-CH_3 and 4-SCH_3), 7.58 (s, 1H, H-7), 7.64 (m, 5H, C_6H_5).

Anal. Calcd. for $C_{14}H_{12}N_2S_2$: C, 61.73; H, 4.44; N, 10.28; S, 23.54. Found: C, 61.48; H, 4.49; N, 10.18; S, 23.82.

6-Methyl-4-(methylthio)-2-phenylthieno[3,2-*d*]pyrimidine (**25**).

Treatment of thione **19** (0.100 g, 0.38 mmole) in 1*N* sodium hydroxide (6 ml) with methyl iodide (2.28 g, 16.1 mmoles) at ambient temperature with vigorous stirring for 20 minutes afforded **25**, which precipitated directly from the reaction mixture. The light-yellow crystalline product was collected by filtration and washed with small amounts of ether and water. Recrystallization from ethanol gave analytically pure **25** (0.090 g, 71%), mp 141-142°; ^{1}H nmr (deuteriochloroform): δ 2.65 (d, 3H, 6-CH_3, $J_{CH_3,\ H\text{-}7}$ = 1.2 Hz), 2.85 (s, 3H, SCH_3), 7.19 (q, 1H, H-7), 7.47 and 8.53 (2m, 5H, C_6H_5).

Anal. Calcd. for $C_{14}H_{12}N_2S_2$: C, 61.73; H, 4.44; N, 10.28; S, 23.54. Found: C, 61.48; H, 4.49; N, 10.18; S, 23.82.

2,6-Diphenyl-4-(methylthio)thieno[3,2-*d*]pyrimidine (**26**).

Methyl iodide (4.56 g, 32.1 mmoles) was added to a solution of thione **20** (0.200 g, 0.600 mmole) in 1*N* aqueous sodium hydroxide (12 ml) and the mixture was stirred for 4 hours at 25°. Excess methyl iodide was removed by evaporation *in vacuo* and the suspension was diluted with water. The precipitate formed was filtered, washed with water, dried and recrystallized from methylene chloride-hexanes to give **26** (0.165 g, 79%), mp 171-172°; ^{1}H nmr (deuteriochloroform): δ 2.87 (s, 3H, CH_3), 7.42-7.53 (m, 6H, *m* and *p* to C_6H_5), 7.70-7.82 (m, 3H, H-7 and 2H's *o* to 6-C_6H_5), 8.50-8.61 (m, 2H, *o* to 2-C_6H_5).

Anal. Calcd. for $C_{19}H_{14}N_2S_2$: C, 68.23; H, 4.22; N, 8.37; S, 19.17. Found: C, 68.21; H, 4.30; N, 8.39; S, 19.29.

2,6-Diphenyl-4-chlorothieno[3,2-*d*]pyrimidine (**27**).

A mixture of thione **20** (4.32 g, 13.5 mmoles), phosphorous oxychloride (30 ml) and *N,N*-diethylaniline (12.4 g, 12.4 mmoles) was heated to reflux for 15 minutes. After slow cooling to ambient temperature, the solution was poured over crushed ice and the mixture was stirred for 1/2 hour. It was then twice extracted with chloroform and the pooled organic extracts

were washed successively with 1*N* hydrochloric acid (twice), 10% aqueous sodium bicarbonate (twice) and saturated aqueous sodium chloride (twice). After drying over sodium sulfate, the chloroform solution was evaporated *in vacuo* and the residue was crystallized from methylene chloride to give the desired chloro derivative **27** (3.87 g, 89%), mp 174-175°; ^{1}H nmr (deuteriochloroform): δ 7.44-7.53 (m, 6H, *m* and *p* and to 2,6-C_6H_5), 7.72-7.81 (m, 3H, H-7 and 2H's *o* to 6-C_6H_5), 8.47-8.56 (m, 2H, *o* to 2-C_6H_5).

Anal. Calcd. for $C_{18}H_{11}ClN_2S$: C, 66.97; H, 3.43; Cl, 10.98; N, 4.34; S, 9.93. Found: C, 66.82; H, 3.41; Cl, 11.07; N, 4.65; S, 10.03.

4-Amino-2,6-diphenylthieno[3,2-*d*]pyrimidine (**28**).

To a saturated solution of methanolic ammonia (120 ml) was added chloro derivative **27** (0.50 g, 1.5 mmoles). The mixture was placed in a sealed steel container and heated at 110° for 24 hours. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in chloroform. The solution was washed with water (twice) then dried (sodium sulfate) and evaporated to dryness. The crude product was subjected to preparative tlc (benzene-ethyl acetate, 9:1, developed twice) to give **28** as a white solid (0.30 g, 64%), mp 174-175°; ^{1}H nmr (deuteriochloroform): δ 5.29 (broad s, 2H, NH_2 exch in deuterium oxide), 7.25-7.49 (m, 6H, *m* and *p* to C_6H_5), 7.65-7.73 (m, 3H, H-7 and 2H's *o* to 6-C_6H_5), 8.37-8.47 (m, 2H, *o* to 2-C_6H_5).

Anal. Calcd. for $C_{18}H_{13}N_3S$: C, 71.27; H, 4.32; N, 13.85; S, 10.57. Found: C, 71.03; H, 4.45; N, 13.81; S, 10.52.

2,4-Diamino-6-methylthieno[3,2-*d*]pyrimidine (**29**).

A mixture of *o*-aminonitrile **7** (1.0 g, 7.2 mmoles) and guanidine carbonate (6.0 g, 35 mmoles) was added to an ethanolic solution of sodium ethoxide (prepared by dissolving 0.80 g of sodium metal in 60 ml of ethanol). After heating at reflux for 60 hours, the suspension was filtered while hot and the clear filtrate was cooled to 0°. A first crop of the product was collected by filtration. The mother liquor, after further concentration, afforded a second crop. The combined crops were dissolved in chloroform and insoluble inorganic material was removed by filtration. The clear filtrate was evaporated to dryness and the residue was recrystallized from hot ethanol to give **29** as white needles (0.710 g, 55%), mp 231-232°; ^{1}H nmr (DMSO-d_6): δ 2.50 (d, 3H, 6-CH_3, $J_{CH_3, H\text{-}7}$ = 0.9 Hz), 5.65 (broad s, 2H, NH_2 exch with deuterium oxide), 6.69 (q, 1H, H-7), 7.02 (broad s, NH_2 exch with deuterium oxide).

Anal. Calcd. for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09; S, 17.79. Found: C, 46.31; H, 4.59; N, 31.39; S, 17.47.

2,4-Diamino-6-phenylthieno[3,2-*d*]pyrimidine (**30**).

An intimate mixture of *o*-aminonitrile **8** (0.200 g, 1.0 mmole) and guanidine carbonate (0.40 g, 3.3 mmoles) was heated to a melt (>200° for ~5 minutes) with liberation of ammonia. After cooling, the solid was crushed in hot water to give a light yellow suspension. The crude product was collected by filtration, washed with water and recrystallized from hot ethanol to give the desired compound **30** (0.232 g, 96%), mp 228-230°; ^{1}H nmr (DMSO-d_6): δ 5.82 and 6.88 (broad s, 2H each, 2 NH_2 exch with deuterium oxide), 7.39 (s, 1H, H-7), 7.39-7.81 (m, 5H, C_6H_5),

Anal. Calcd. for $C_{12}H_{10}N_4S \cdot 1/2\ C_2H_5OH$: C, 58.85; H, 4.93; N, 21.11; S, 12.03. Found: C, 59.16; H, 4.81; N, 21.67; S, 12.22.

Acknowledgement.

We are indebted to Dr. Jack J. Fox for his continued interest and to Dr. J. H. Burchenal for the preliminary communication of growth-inhibitory activity data. We also thank Mr. Marvin Olsen for recording the nmr spectra.

REFERENCES AND NOTES

[1] This investigation was supported by PHS funds from the National Cancer Institute, Department of Health and Human Services (PHS Grants CA-24634 and CA-08748).

[2] A. I. Kravchenko, V. A. Chernov, L. I. Shcherbakova, L. N. Filitis, G. N. Pershin, and V. N. Sokolova, *Farmakol. Toksikol.* (Moscow), **42**, 659 (1979) and references therein; *Chem. Abstr.*, **92**, 69323 (1980).

[3a] M.-I. Lim, R. S. Klein, and J. J. Fox, *Tetrahedron Letters*, **21**, 1013 (1980); [b] M.-I. Lim and R. S. Klein, *Tetrahedron Letters*, **22**, 25 (1981); [c] M.-I. Lim, W.-Y. Ren, B. A. Otter, and R. S. Klein, *J. Org. Chem.*, **48**, 780 (1983).

[4] R. I. Glazer, K. D. Hartman, and M. C. Knode, *Pharmacol.*, **24**, 309 (1983).

[5] M. Y. Chu, L. B. Zuckerman, S. Sato, G. W. Crabtree, A. E. Bogden, M.-I. Lim, and R. S. Klein, *Biochem. Pharmacol.*, **33**, 1229 (1984).

[6a] J. J. Marr, R. L. Berens, N. K. Cohn, D. J. Nelson, and R. S. Klein, *Antimicrobial Agents Chemother.*, **25**, 292 (1984); [b] W. A. Fish, J. J. Marr, R. L. Berens, D. L. Looker, D. J. Nelson, S. W. LaFon, and A. E. Balker, *ibid.*, **27**, 33 (1985).

[7] T. P. Zimmerman, R. D. Deeprose, G. Solberg, C. R. Stopford, G. S. Duncan, W. H. Miller, R. L. Miller, M.-I. Lim, W.-Y. Ren, and R. S. Klein, *Biochem. Pharmacol.*, **32**, 1211 (1983).

[8] W.-Y. Ren, M.-I. Lim, B. A. Otter, and R. S. Klein, *J. Org. Chem.*, **47**, 4633 (1982).

[9] H. Fiesselmann, *Angew Chem.*, **71**, 377 (1959); German Patent 1,005,007; *Chem. Abstr.*, **55**, P6497*c* (1961); British Patent 837,086, Farbwerke Hoechst Akt.-Ges. vorm Meister Lucius and Bruning; *Chem. Abstr.*, **54**, P24798e (1960).

[10] The synthesis of various thieno[3,2-*d*]pyrimidines from their most common precursors, the 3-amino-2-carbalkoxythiophenes is described in the following: [a] M. Robba, J.-M. Lecomte, M. Cugnon de Sevricourt, *Bull. Soc. Chim. France*, 3630 (1970); [b] *ibid.*, *Tetrahedron*, **27**, 487 (1971); [c] *C. R. Acad. Sci., Ser. C*, **267**, 697, (1968); [d] W. Ried and R. Giesse, *Angew. Chem., Int. Ed. Engl.*, **7**, 136 (1968); [e] *Ann. Chem.*, **713**, 143 (1968); [f] W. Ried and E. Kahr, *ibid.*, **716**, 219 (1968); [g] S. Gronowitz, J. Fortea-Laguna, S. Ross, B. Sjoberget, and N. E. Stjernstrom, *Acta. Pharm. Suec.*, **5**, 563 (1968).

[11a] The reaction of acetylenes with nucleophiles has been reviewed: J. I. Dickstein and S. I. Miller, in "Chemistry of the Carbon-Carbon Triple Bond", Vol **2**, S. Patai, ed, John Wiley and Sons, Chichester, England, 1978. For specific examples of nucleophilic addition of Selenols and Thiols, see: [b] I. N. Azerbaev, L. A. Tsoi, A. B. Asmanova, and A. K. Patsaev, *USSR Tr. Inst. Khim. Nauk., Akad. Nauk Kaz. SSR*, **46**, 147 (1977); [c] M. N. Basyouni, M. T. Omar, and E. A. Ghali, *Bull. Chem. Soc. Japan*, **53**, 1739 (1980); [d] Cyclization of adducts obtained from α-mercaptoacetates and α-mercaptoketones with acetylenecarboxylic esters to give 3-OH substituted thiophenes has been reported: F. Bohlman and E. Bresinsky, *Chem. Ber.*, **97**, 2109 (1964).

[12] E. Mathias, M. Shimanski, *J. Chem. Soc., Chem. Commun.*, 569 (1981).

[13] Acetylenic nitriles **3-5** [13a-13c] were obtained by ammonolysis of the commercially available corresponding acetylenic ethyl esters to the corresponding amides and dehydration to the nitriles with phosphorus oxychloride by slight modifications to the procedure reported in reference [13c]; [a] F. Texier and R. Carrie, *Bull. Soc. Chim. France*, 2381 (1972); [b] R. A. van der Welle and L. Brandsma, *Rec. Trav. Chim.*, **92**, 667 (1973); [c] C. Moureu and J. C. Bongrand, *Ann. Chim.*, **14**, 45 (1920).

[14] S. Gronowitz, C. Westerlund, and A. B. Hornfeldt, *Acta Chem. Scand.*, **B29**, 224 (1975).

[15] Conditions required for the amidine exchange implicated in such reactions are generally strenuous and the use of amidines other than formamidine have been studied relatively little [15a-c]. Benzamidine has been condensed with 2,4-diamino-5-cyano-6-dimethylaminopyridine to give a 7-phenylpyrimido[4,5-*d*]pyrimidine [15a] and acetamidine similarly reacts with 3-amino-4-cyano-5-methylpyrazole to give 4-amino-3,6-dimethylpyrazolo[3,4-*d*]pyrimidine [15b]; [a] J. Weinstock and V. D. Wichelhaus, French Patent 1,335,354 (August 6, 1963): *Chem. Abstr.*, **60**, 2975 (1964); [b] M. Ochiai and K. Morita, *Tetrahedron Letters*, **25**, 2349 (1967); for other examples, see [c] A. Albert, *J. Chem. Soc., Perkin Trans*

I, 345 (1975) and references therein.

[16] For a review, see E. C. Taylor, J. Chan, and A. McKillop, *Adv. Org. Chem.*, **7**, 219 (1970).

[17] This method is akin to an early report of the formation of 2-alkyl-4-thionoquinazoline by the treatment of anthranilonitrile with an acid anhydride and sodium sulfide. That method involved *in situ* acylation of the amino group, conversion of the nitrile to the thioamide and condensation to the thioquinazoline as a one-pot conversion: M. T. Bogert, H. C. Breneman, and W. F. Hand, *J. Am. Chem. Soc.*, **25**, 372 (1903).

[18] Conversion of aromatic *o*-aminothioamides to the corresponding pyrimidinethione derivatives with triethylorthoformate (either alone [18a,3c] or in the presence of acetic anhydride [18b]) has been reported: [a] E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron*, **23**, 885 (1977); (b) H. G. Mautner, *J. Org. Chem.*, **23**, 1450 (1958) and references therein.

[19] D. J. Brown, in "The Pyrimidines", Wiley-Interscience, New York, 1962, "The Pyrimidines", Supplement I, 1st Ed, *ibid.*, 1970.

[20] This method (which has received little, if any, attention to date) appears to be an attractive alternative to the conventional set of conversions hydroxy → chloro → amino in 4-substituted pyrimidines [19] whenever the corresponding thione is readily accessible. The scope of this approach to amino derivatives from this and other fused pyrimidinethione systems is under investigation.

[21a] E. C. Taylor, R. J. Knopf, and A. L. Borror, *J. Am. Chem. Soc.*, **82**, 3152 (1960); [b] H. Graboyes, G. E. Jaffe, I. J. Pachter, J. P. Rosenbloom, A. J. Villani, J. W. Wilson, and J. Weinstock, *J. Med. Chem.*, **11**, 568 (1968).

[22a] L. F. Larionov, "Cancer Chemotherapy", Pergamon Press, Oxford, 1965; [b] "Experimental Chemotherapy", Vol IV, Part I, R. J. Schnitzer and F. Hawkins, eds, Academic Press, New York, 1966; [c] F. M. Sirotnak, D. M. Dorick, and D. M. Moccio, *Cancer Treatment Rep.*, **60**, 547 (1976).

[23] Private communication from Dr. Joseph H. Burchenal.