New Syntheses of 7-Substituted-2-aminothieno- and Furo[3,2-*d*]pyrimidines

Philip E. Morris, Jr.,* Arthur J. Elliott and John A. Montgomery

BioCryst Pharmaceuticals, Inc., 2190 Parkway Lake Drive, Birmingham, AL 35244

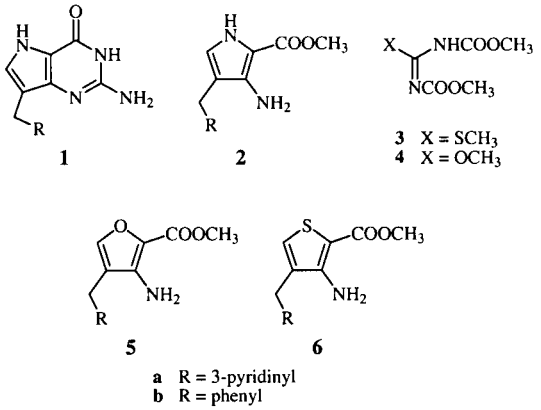
Received April 30, 1998

In a recent publication, we have the described the synthesis of 7-substituted-2-amino-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-ones which are potent inhibitors of the enzyme Purine Nucleoside Phosphorylase from the corresponding 3-aminopyrrole-2-carboxylate esters. A key step in the synthesis is condensation of the amino group with the highly reactive guanylating reagents **3** or **4** followed by annulation. The furo[3,2-*d*]pyrimidin-4-one and thieno[3,2-*d*]pyridin-4-one are closely related rings systems. However, these rings have not been reported in the literature with a 2-amino, substituent which would arise from such guanylation reactions. In this report, the syntheses of the novel furans **5** are described based on our improved pyrrole synthesis (Scheme 1). The syntheses of the novel thiophenes **6** are described. The guanylation of **5** and **6** were studied and compared to **2**. The 3-amino group of **5** and **6** failed to react with **3** or **4** under mild acid catalysis; conditions under which **2** easily condensed. Guanylation was finally achieved by generating the carbodiimide intermediate of **3** under mercury catalysis affording the guanylated adducts which were converted to the novel 2-aminothieno- and furo[3,2-*d*]pyrimidin-4-ones **16**.

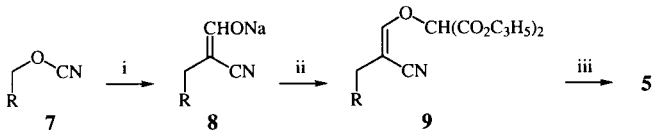
J. Heterocyclic Chem., **36**, 423 (1999).

Introduction.

As part of our efforts aimed at the synthesis of inhibitors of the enzyme Purine Nucleoside Phosphorylase [1], we have recently described an efficient synthesis of 7-substituted-2-amino-1,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-ones **1** which utilizes 3-aminopyrrole-2-carboxylate esters **2** as key intermediates [2]. The amino group in **2** is surprisingly unreactive towards the usual guanylating reagents such as amidine derivatives, cyanamide, and *S*-methylthiouronium salts and it required the more reactive 1,3 dicarbomethoxy-2-methyl-2-thiopseudourea (**3**) [3] or its methoxy analog (**4**) [4] to effect the annulation of the 2-aminopyrimidine ring. This lack of reactivity of the amino group is presumably due to the fact that it is in conjugation with the ester moiety and we were interested to determine if the corresponding aminofurans **5** and aminothiophenes **6** would behave similarly towards guanylating agents. Derivatives of both the furo[3,2-*d*]pyrimidine [5,6] and the thieno[3,2-*d*]pyrimidine [7,8] ring systems have been described but there have been no reports of such compounds containing a 2-amino group which would result from such guanylation reactions.



Scheme 1



(i) NaH, $HCOOC_2H_5$; (ii) $ClCH(CO_2H_5)_2$; (iii) 1,5-diazabicyclo[4.3.0]non-5-ene

Results and Discussion.

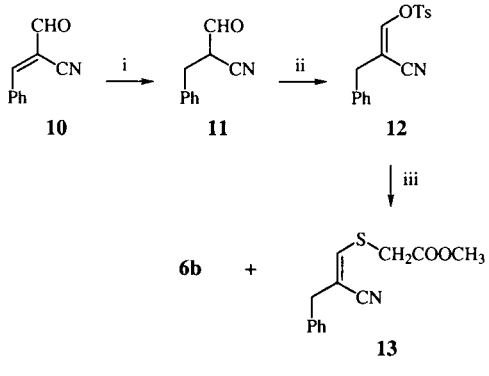
Synthesis of the Furans and Thiophenes.

For our comparison study, we decided to prepare the furans **5** and thiophenes **6** since we had considerable experience with these substituents in the pyrrole series. For the furans we adapted our improved pyrrole synthesis [2,9] as shown in Scheme I. Formylation of **7a** [1] with sodium hydride/ethyl formate gave the sodium enolate **8a**, which proved remarkably stable, there being no decomposition of a sample stored at room temperature for more than a year. Reaction of **8a** with diethyl chloromalonate gave the key malonate ester intermediate **9a**. We have shown [2,9] that the use of malonate in place of acetate [5,6] allows for an efficient and facile cyclization reaction under mild conditions. In this case, treatment of **9a** with 1,5-diazabicyclo-[4.3.0]non-5-ene/methanol at room temperature resulted in cyclization and ester exchange giving **5a** in 73% yield.

Similarly, formylation of hydrocinnamonitrile (**7b**) with sodium hydride/ethyl formate followed by alkylation of the sodium enolate **8b** with diethyl chloromalonate gave the key malonate ester intermediate **9b**. Cyclization with 1,5-diazabicyclo[4.3.0]non-5-ene/methanol gave **5b** in 71% yield.

Since the corresponding malonate ester derivatives were not readily available for the synthesis of the thiophene analogs **6**, we relied on an adaptation of a literature procedure [8]. Our route to **6b** is shown in Scheme 2. Catalytic reduction of 2-cyano-3-phenylpropenal **10** [2] gave **11** which was treated directly with 1,5-diazabicyclo[4.3.0]-non-5-ene and tosyl chloride to give the tosylate **12**. Displacement of the tosyl group with the anion of methyl thioglycolate (generated *in situ* from 1 equivalent of methyl mercaptoacetate and 2 equivalents of sodium methoxide) in refluxing methanol gave a mixture of **6b** (30%) and sulfide **13** (12%).

Scheme 2



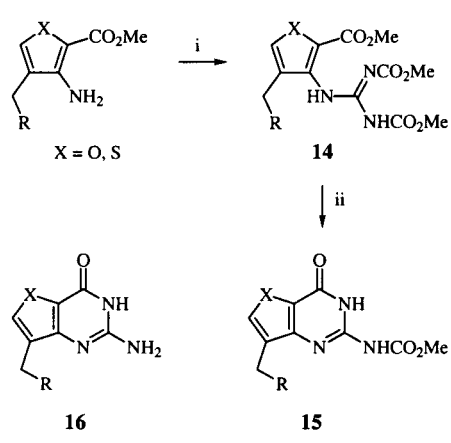
(i) H_2/Pd; (ii) TsCl, 1,5-diazabicyclo[4.3.0]non-5-ene; (iii) $HSCH_2COOCH_3$, $NaOCH_3$

Similarly, the reaction of the mesylate obtained from the condensation of **8a** with mesyl chloride with the anion of methyl thioglycolate gave the thiophene **6a**, albeit in poor yield (15%), as the only isolable product.

Annulation of the Pyrimidine Ring.

We had shown earlier that the pyrroles **2** readily condensed with both **3** and **4** under mild acid catalysis. [2]. However, the amino groups in both the furans **5** and the thiophenes **6** were found to be less reactive and failed to condense with either reagent under these conditions. Condensation was achieved using **3** and mercury(II) catalysis presumably *via* the highly reactive carbodiimide intermediate [10] (Scheme 3). The phenyl substituted compounds **5b** and **6b** reacted at room temperature while the pyridinyl derivatives **5a** and **6a** required an excess of **3** and heating to complete the condensation. While the guanidine adducts **14** could be isolated, it was found to be more convenient to add an excess of sodium methoxide, whereupon cyclization occurred with concomitant loss of a carbamate group to give **15**. The remaining carbamate group was removed by treatment with warm aqueous sodium hydroxide. The overall yields from the respective furan/thiophene were **16a,** (X = O) 20%, **16b,** (X = O) 36%,**16a,** (X = S) 36% and **16b,** (X = S), 28%.

Scheme 3



(i) $HgCl_2$, **3**, NEt_3, dimethylformamide; (ii) NaOMe; (iii) NaOH

In summary, we have reported an improved synthesis of the 3-aminofuran-2-carboxylic esters **5** and the preparation of aminothiophenes **6**. These compounds are less reactive than the corresponding aminopyrroles towards guanylating reagents and, among these compounds, the 3-pyridinyl substituted compounds are the least reactive. Mercury(II) catalyzed guanylation using **3** afforded the adducts **14** which were smoothly converted in base to the novel thieno- and furo[3,2-*d*]pyrimidines **16**.

EXPERIMENTAL

Thin layer chromatography was performed on Kieselgel aluminum backed silica gel 60 F_{254} plates (0.2 mm) obtained from E. Merck unless otherwise noted and were visualized using an ultraviolet light (254 nm) and iodine. Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. All ^1H nmr spectra were recorded at 360 MHz with a Bruker AM 360 spectrometer and resonances are reported downfield from internal tetramethylsilane. Infrared spectra were recorded at on a Bio-Rad FTS-7 spectrophotometer and mass spectra were recorded using a Fisions VG Trio 2000 mass spectrometer operating in the positive electrospray mode. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

2-Cyano-3-(3-pyridinyl)propionaldehyde Sodium Enolate (**8a**).

Compound **7a** [1] (77.5 g, 0.59 mole) was added to a mechanically stirred suspension of 60% sodium hydride (35 g, 1.45 moles) in dry tetrahydrofuran (1 l) under nitrogen. Ethyl formate (15 ml) was added to initiate the reaction and vigorous gas evolution was observed after 10 minutes. The mixture was cooled in an ice-bath and additional ethyl formate (100 ml, 1.77 moles) was added over 6 hours to control gas evolution. The mixture was allowed to warm to ambient temperature and stirred overnight. During the second day, additional 60% sodium hydride (35 g, 1.45 moles) was added in three equal portions at 3 hours intervals while additional ethyl formate (175 ml) as added over 8 hours. The mixture was allowed to stir overnight at ambient temperature. Hexane (600 ml) was added and the precipitated **8a** was collected by vacuum filtration,

washed with hexane and air-dried to give 106.8 g as an off-white powder. The salt was characterized as the aldehyde as follows. A sample was dissolved in water and the *p*H adjusted to **6** (*p*H paper) with acetic acid. The neutralized solution was extracted with an equal volume of ethyl acetate, the organic layer separated, dried (magnesium sulfate) and the filtrate concentrated to give the aldehyde as an off-white solid which was recrystallized from ethyl acetate/hexane as a cream-colored powder, mp 156-158°; ir (potassium bromide) 2203 (CN) and 1649 (CO) cm^{-1}; ms: 161.2 (100%, MH^+); ^{1}H-nmr (360 MHz, dimethyl-d_6 sulfoxide): 11.30 (s, 1H), 8.5-7.1 (m, 5H) and 3.45 (s, 2H).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.48. Found C, 67.27; H, 5.13; N, 17.39.

Methyl 3-Amino-4-(3-pyridinylmethyl)furan-2-carboxylate (**5a**).

Compound **8a** (6.84 g, 92.5 mmoles) was suspended in dimethylformamide (75 ml) and diethyl chloromalonate (18 g, 92.5 mmoles) was added in one-portion. The mixture was allowed to stir for 2 hours, concentrated *in vacuo* and the dark oil passed through silica gel (100 g, 5% methanol-chloroform) to give **9a** as an orange syrup with an assumed quantitative yield. A portion (3.18 g, 10 mmoles) was dissolved in methanol (50 ml) to which 1,5-diazabicyclo[4.3.0]-non-5-ene (1.23 ml, 10 mmoles) was added and the mixture was allowed to stir overnight. The solution was concentrated and the residue passed through a small pad of silica gel to remove baseline material. Crystallization from methanol gave 1.7 g (73%) of **5a** as a pale-yellow powder, mp 137-139°; ir (potassium bromide): 3420 (NH) and 1667 (CO) cm^{-1}; ms: 233.2 (MH^+, 100%), 201 (-methanol, 25%); ^{1}H-nmr (360 MHz, dimethyl-d_6 sulfoxide): δ 8.50 (d, J = 1.8 Hz, 1H), 8.40 (dd, J = 1.5 and 4.8 Hz, 1H) 7.62 (d, J = 6.4 Hz, 1H), 7.38 (s, 1H), 7.30 (dd, J = 4.8 and 7.9 Hz, 1H), 5.59 (bs, deuterium oxide exchangeable, 2H), 3.72 (s, 2H), 3.70 (s, 3H).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found C, 62.02; H, 5.22; N, 12.08.

Methyl 3-Amino-4-(phenylmethyl)furan-2-carboxylate (**5b**).

Hydrocinnamonitrile (**7b**) (36.2 g, 0.2 mole) was formylated as described for **7a** to give **8b** in quantitative yield. The salt was dissolved in dry dimethylformamide (150 ml) and diethyl chloromalonate (32.3 ml, 0.2 mole) was added in one-portion. The mixture was stirred for 2 hours at ambient temperature, filtered and the filtrate concentrated *in vacuo*. The resulting cyanoether **9b** was dissolved in methanol (200 ml), 1,5-diazabicyclo[4.3.0]non-5-ene (24.8 g, 0.2 mole) was added and the mixture was stirred overnight. The mixture was concentrated *in vacuo* to give a dark residue which was passed through a short silica gel pad (chloroform) to give 32.7 g (0.14 mole, 71%) of the aminofuran **5b** as a dark oil which was homogenous on thin layer chromatography and which was suitable for direct use. An analytical sample was prepared by silica gel chromatography (chloroform) as a pale-yellow solid, mp 69-72°; ir (potassium bromide) 3500 (NH), 3380 (NH), and 1671 (CO) cm^{-1}; ms: 232.0 (MH^+, 100%); ^{1}H-nmr (360 MHz, dimethyl-d_6 sulfoxide): δ 7.1-7.4 (m, 5H), 5.52 (bs, deuterium oxide exchangeable, 2H), 3.70 (s, 3H), 3.68 (s, 2H), 3.67 (s, 1H).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found C, 67.30; H, 5.66; N, 6.00.

Methyl 3-Amino-4-(3-pyridinylmethyl)thiophene-2-carboxylate (**6a**).

Compound **8a** (18.2 g, 0.1 mole) was dissolved in dry dimethylformamide (50 ml) and methanesulfonyl chloride (11.45 g, 0.1 mole) was added in one-portion. The mixture was stirred overnight at ambient temperature and the filtrate concentrated *in vacuo*. The residue was partitioned between ethyl acetate (200 ml) and water (100 ml), the organic layer was separated, dried (magnesium sulfate) and concentrated *in vacuo* to give the intermediate mesylate (10.2 g, 0.043 mole, 43%) which was used directly. The mesylate (4.76 g, 20.0 mmoles) was dissolved in methanol (75 ml) and added to a mixture of methyl thioglycolate (1.88 ml, 21.0 mmoles) and sodium methoxide (25% solution, 4.75 g, 22.0 mmoles). The mixture was refluxed for 1 hour, and then concentrated to give a dark residue, which was triturated with cold methanol. The solid was filtered off and recrystallized from methanol to give **6a** (0.74 g, 2.98 mmoles, 15%) as an off-white powder, mp 150-152°, ir (potassium bromide): 3419 (NH), 1677 (CO) cm^{-1}; ms: 249.0 (100%, MH^+); ^{1}H-nmr (360 MHz, dimethyl-d_6 sulfoxide): δ 8.50 (d, J = 1.8 Hz, 1H), 8.41 (dd, J = 1.2 and 4.5 Hz, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.30 (dd, J = 7.9 and 7.6 Hz, 1H), 7.24 (s, 1H), 6.45 (bs, deuterium oxide exchangeable, 2H), 3.82 (s, 2H), 3.69 (s, 3H).

Anal. Calcd. for $C_{12}H_{12}N_2O_2S$: C, 58.05; H, 4.87; N, 11.28. Found C, 57.95; H, 4.88; N, 11.28.

2-Benzyl-3-(*p*-toluenesulfonyl)acrylonitrile (**12**).

Compound **10** (6.28 g, 40 mmoles), 10% Pd/C (0.2 g) and methanol (150 ml) were shaken together under *ca* 50 psig hydrogen pressure for 1 hour. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residue was dissolved in dichloromethane (200 ml) containing 1,5-diazabicyclo-[4.3.0]non-5-ene (6.9 g, 5.6 mmoles) and the solution was cooled to 10° during the addition of a solution of *p*-toluenesulfonyl chloride (8.0 g, 42 mmoles) in dichloromethane (50 ml). The mixture was then stirred at room temperature overnight. The organic solution was washed with water (400 ml), dried (magnesium sulfate) and evaporated *in vacuo*. The residue was crystallized from toluene as colorless needles, mp 98-100° (8.3 g, 66%); ir (potassium bromide): 2220 (CN) cm^{-1}; ms: 288.2 (100%, MH^+-CN); ^{1}H nmr (deuteriochloroform): δ 7.81 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 7.27 (s, 1H), 7.20-7.23 (m, 3H), 7.0 (m, 2H), 3.35 (s, 2H), 2.50 (s, 3H).

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.83; N, 4.47. Found C, 65.26; H, 4.82; N, 4.51.

Methyl 3-Amino-4-(3-phenylmethyl)thiophene-2-carboxylate (**6b**).

Methyl thioglycolate (3.4 g, 31.5 mmoles) was added to a solution of sodium methoxide (3.56 g, 66.0 mmoles) in methanol (100 ml) at 10° and the mixture was stirred for 15 minutes. The tosylate (12) (9.39 g, 30.0 mmoles) was added and the mixture was boiled under reflux for 2 hours. Most of the methanol was evaporated *in vacuo* and the residue was treated with water (400 ml). The red oil was extracted into ether (400 ml), the ether dried (sodium sulfate) and evaporated *in vacuo*. The residue was chromatographed on silica gel (120 g) using toluene to give the product, which was recrystallized from cyclohexane as colorless prisms, mp 101-102° (2.2 g, 30%); ir (potassium bromide) 3485 (NH) and 1685 (CO) cm^{-1}; ms: 248.3 (100%, MH^+); ^{1}H nmr (deuteriochloroform): δ 7.18-7.34 (m, 5H), 6.95 (s, 1H), 5.30 (bs, deuterium oxide exchangeable, NH_2), 3.81 (s, 3H), 3.80 (s, 2H).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found C, 63.38; H, 5.37; N, 5.61.

Later fractions yielded the uncyclized 2-benzyl-3-(methoxycarbonylmethylthio)-acrylonitrile (**13**) (0.9 g, 12%) which crystallized from cyclohexaneane as yellow needles, mp 46-48°; ir

(potassium bromide) 2205 (CN) 1638 (CO) cm^{-1}; ms: 248.2 (100%, MH^+); ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.1-7.4 (m, 6H), 3.79 (s, 3H), 3.55 (s, 4H).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.00; H, 5.34; N, 5.69.

2-Amino-1,5-dihydro-7-(3-pyridinylmethyl)-4*H*-furo[3,2-d']-pyrimidin-4-one (**16a**, X = O).

Compound **5a** (2.32 g, 10 mmoles) was dissolved in dimethylformamide (25 ml) containing **3** (2.06 g, 10 mmoles) and triethylamine (4.2 ml, 30 mmoles) and mercury (II) chloride (2.72 g, 10 mmoles) was added. The mixture was stirred overnight after which time thin layer chromatography analysis (ethyl acetate) indicated *ca* 60% conversion to **14a** (X = O). Additional mercury(II) chloride (2.72 g, 10 moles) and **3** (2.06 g, 10 mmoles) were added and the mixture was stirred overnight. Thin layer chromatography analysis now indicated *ca* 80% conversion. The mixture was then heated at 50° overnight during which time the reaction went to completion. The dark solution was filtered to remove inorganic salts and the dark filtrate concentrated *in vacuo* to give **14a** (X = O) as a dark brown residue. The product was dissolved in methanol (50 ml) and 25% sodium methoxide (2.16 g, 10 mmoles) was added in one-portion. The mixture was allowed to stir for 6 hours and then carefully neutralized with acetic acid. The resulting precipitate was collected by vacuum filtration, washed thoroughly with water and air-dried to give 1.45 g (4.83 mmoles, 48%) of **15a** (X = O). A portion (1.3 g, 4 mmoles) was suspended in 1 *N* sodium hydroxide (10 ml, 10 mmoles) and the mixture was stirred overnight at room temperature. The mixture was then heated at 50° for 2.5 hours during which time the mixture became homogenous. The solution was cooled and neutralized with acetic acid to give an off-white solid which was recrystallized from water-ethanol (8:2) to give **16a**, (X = O) as an off-white powder, mp >250°; ir (potassium bromide) 3464 (NH) and 1694 (CO) cm^{-1}; ms: 243.1 (MH^+, 100%); ^1H-nmr (360 MHz, dimethyl-d_6 sulfoxide): δ 10.85 (bs, deuterium oxide exchangeable, 1H), 8.51 (d, J = 1.4 Hz, 1H) 8.40 (d, J = 3.8 Hz, 1H), 7.80 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 3.0 and 7.8 Hz, 1H), 6.28 (bs, 2H), 3.81 (s, 2H).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found C, 59.27; H, 4.27; N, 23.04.

2-Amino-1,5-dihydro-7-(phenylmethyl)-4*H*-furo[3,2-*d*]pyrimidin-4-one (**16b**, X = O).

Compound **5b** (2.89 g, 12.5 mmoles) was dissolved in dry dimethylformamide containing triethylamine (5.2 ml, 37.5 mmoles) and **3** (2.58 g, 12.5 mmoles). Mercury(II) chloride (3.4 g, 12.5 mmoles) was added in one-portion and the mixture was stirred overnight. The mixture was diluted with dichloroform filtered through Celite to remove inorganic salts and the solvent was removed to give **14b** (X = O). This was taken in methanol (75 ml), sodium methoxide solution (25%, 8.1 g, 37.5 mmoles) was added and the mixture was stirred for 3 hours. Neutralization with acetic acid gave **15b** (X = O) as a brown solid (2.0 g, 56%) which was used in the next step with no further purification. The product was dissolved in 1 *N* sodium hydroxide (21 ml, 21 mmoles) and the solution was heated at 55° for 3 hours. Neutralization of the mixture with acetic acid gave the product as an off-white solid. Chromatography on silica gel (30 g, chloroform-methanol-ammonium hydroxide 80:18:2) gave **16b** (X = O) (36%) as a tan powder, mp >250°; ir (potassium bromide): 3443 (NH), 1700 (CO) cm^{-1}; ms: 242.0 (MH^+, 100%); ^1H-nmr (360 MHz, dimethyl-d_6 sulfoxide): δ 10.84 (bs, deuterium oxide exchangeable, 1H), 7.74 (s, 1H), 7.3-7.0 (m, 6H), 6.28 (bs, deuterium oxide exchangeable, 2H), 3.78 (s, 2H).

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.59; N, 17.41. Found C, 64.56; H, 4.73; N, 17.17.

2-Amino-1,5-dihydro-7-(3-pyridinylmethyl)-4*H*-thieno[3,2-*d*]-pyrimidin-4-one (**16a**, X = S).

Compound **6a** (4.26 g, 17.2 mmoles) was dissolved in dry dimethylformamide (30 ml) containing triethylamine (7.2 ml, 51.6 mmoles) and **3** (3.54 g, 17.2 mmoles). Mercury(II) chloride (4.67 g, 17.2 mmoles) was added in one-portion and the mixture was stirred overnight. Thin layer chromatography (silica gel, 5% methanol-chloroform) indicated incomplete reaction. Additional **3** (1.77 g), mercury(II) chloride (2.34 g) and triethylamine (3.6 ml) was added and the mixture was heated at 50° for 18 hours. The mixture was cooled, diluted with ethyl acetate, filtered through Celite to remove inorganic salts and the filtrate concentrated to give **14a** (X = S). The product was taken in methanol (75 ml), sodium methoxide solution (25%, 3.7 g, 17.2 mmoles) was added and the mixture was stirred for 3 hours. Neutralization of the solution with acetic acid gave the cyclized **15a** (X = S) (3.1 g, 9.98 mmoles, 58%) as an off-white solid. A portion (1.24 g, 3.9 mmoles) was dissolved in 1 *N* sodium hydroxide (12.0 ml, 12.0 mmoles) and the mixture was heated at 55° for 3 hours. Neutralization with acetic acid gave the product as an off-white solid which was purified on silica gel (25 g, chloroform-methanol-ammonium hydroxide 80:18:2) to give **16a** (X = S) (0.64 g, 63%) as a white powder, mp 280-282°; ir (potassium bromide): 1673 (CO) cm^{-1}; ms: 259.0 (MH^+, 75%); ^1H-nmr (360 MHz, dimethyl-d_6 sulfoxide): δ 10.93 (bs, deuterium oxide exchangeable, 1H), 7.51 (s, 1H), 7.3-7.1 (m, 4H), 6.38 (bs, deuterium oxide exchangeable, 2H), 3.93 (s, 2H).

Anal. Calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found C, 55.67; H, 4.00; N, 21.49.

2-Amino-1,5-dihydro-7-(phenylmethyl)-4*H*-thieno[3,2-*d*]-pyrimidin-4-one (**16b**, X = S).

Compound **6b** (3.09 g, 12.5 mmoles) was dissolved in dry dimethylformamide (25 ml) containing triethylamine (5.2 ml, 37.5 mmoles) and **3** (2.58 g, 12.5 mmoles). Mercury(II) chloride (3.4 g, 12.5 mmoles) was added in one-portion and the mixture was stirred overnight. The mixture was diluted with ethyl acetate, filtered through Celite to remove inorganic salts and the filtrate was concentrated to give **14b** (X = S). The product was taken in methanol (75 ml), sodium methoxide solution (25% Aldrich, 8.1 g, 37.5 mmoles) was added and the mixture stirred for 12 hours. Neutralization of the solution with acetic acid gave initially a gray-colored precipitate which was removed by filtration and the filtrate was chilled in ice-water. The chilled filtrate gave **15b** (X = S) (1.4 g, 36%) as an off-white solid. A portion (1.3 g, 4.1 mmoles) was dissolved in 1 *N* sodium hydroxide (12.4 ml, 12.4 mmoles) and the mixture was heated at 55° for 2 hours. Neutralization with acetic acid gave the product as an off-white solid (0.83 g, 78%). An analytical sample was obtained by silica gel chromatography (chloroform-methanol-ammonium hydroxide 80:18:2) to give **16b** (X = S) as an off-white, mp > 250°; ir (potassium bromide) 1677 (CO) cm^{-1}; ms 258.0 (100%, MH^+); ^1H-nmr (360 MHz, dimethyl-d_6 sulfoxide): δ 10.93 (bs, deuterium oxide exchangeable, 1H), 7.51 (s, 1H), 7.3-7.1 (m, 5H), 6.38 (bs, deuterium oxide exchangeable, 2H), 3.93 (s, 2H).

Anal. Calcd. for $C_{13}H_{11}N_3OS \cdot 0.2H_2O$: C, 59.85; H, 4.40; N, 16.10. Found C, 60.16; H, 4.45; N, 15.77.

Acknowledgment.

We thank the BioCryst Analytical Chemistry Department for the spectral data.

REFERENCES AND NOTES

[1] J. A. Montgomery, S. Niwas, J. D. Rose, J. A. Secrist, III, Y. S. Babu, C. E. Bugg, M. D. Erion, W. C. Guida, and S. E. Ealick, *J. Med. Chem.*, **36**, 55 (1993).

[2] A. J. Elliott, P. E. Morris, Jr., S. L. Petty, and C. H. Williams, *J. Org. Chem.* **62**, 8071 (1997).

[3] A. Skibinski, Z. Stec, M. Januchowski, and L. Parys, *J. Appl. Chem.*, **37**, 291 (1993).

[4] N. Viswananthan, Indian Patent 168,784; *Chem. Abstr.*, **118**, 22237 (19??).

[5] B. K. Bhattacharya, B. A. Otter, R. L. Berens, and R. S. Klein, *S. Nucleosides Nucleotides,* **9**,1021 (1990).

[6] B. K. Bhattacharya, M-I. Lim, B. A. Otter, and R. S. Klein, *Tetrahedron Letters,* **27**, 815 (1986).

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

[8] F. Jourdan, D. Ladure'e, and M. Robba, *J. Heterocyclic Chem.*, **31**, 305 (1994).

[9] A. J. Elliott, J. A. Montgomery, and D. A. Walsh, *Tetrahedron Letters,* **37**, 4339 (1996).

[10] K. S. Kim and L. Qian, *Tetrahedron Letters,* **34**, 7677 (1993).