A Convenient Synthesis of 5-Substituted-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidines Structurally Related to the Antibiotics Toyocamycin and Sangivamycin

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4-Amino-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**6a**), prepared from 2-ethoxymethyleneamino-5-bromopyrrole-3,4-dicarbonitrile (**4**), was debenzylated with boron trichloride to give *ara*-toyocamycin (**6b**). Further functional group transformation of **6b** provided a route to 4-amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (*ara*-thiosangivamycin, **7a**), and the corresponding 5-carboxamidoxime **8a** and 5-carboxamidine **8b** derivatives. Phosphorylation of unprotected **7a** with phosphorus oxychloride gave *ara*-thiosangivamycin 5'-monophosphate (**7b**). 2'-*O*-Acetyl-*ara*-thiosangivamycin (**10b**) was prepared as a prodrug by acetylation of **9a**, followed by deprotection of the *t*-butyldimethylsilyl groups under acidic conditions without acyl migration.

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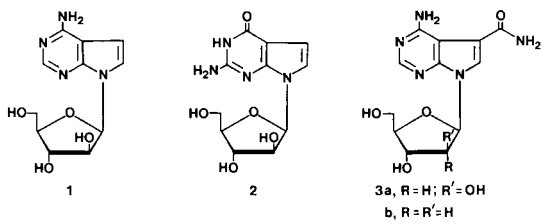
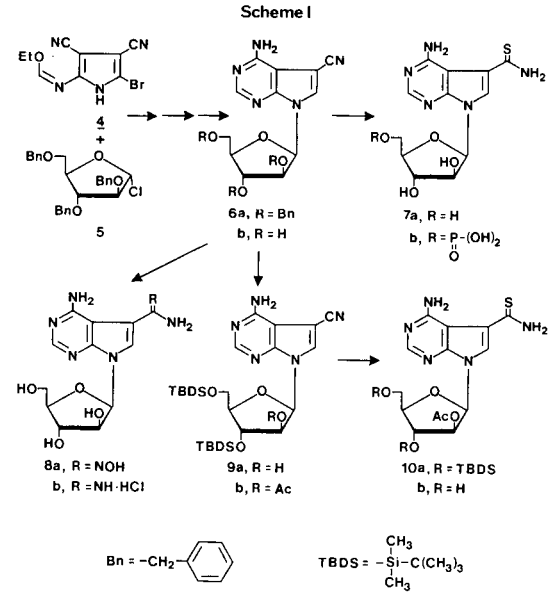
Introduction.

Various arabinofuranosyl nucleosides, such as *ara*-A [1], *ara*-G [2], *ara*-tubercidin [3,4] (**1**) and 7-deaza-*ara*-G [5] (**2**) have been synthesized and their biological properties have been studied [6,7]. *Ara*-tubercidin is resistant to deactivation by deaminases and exhibits antiviral activity, and so does 7-deaza-*ara*-G. Of particular interest is *ara*-sangivamycin (**3a**), since **3a** and 2'-deoxysangivamycin (**3b**) were found to be highly active *in vitro* against human cytomegalovirus [8]. Compounds **3a** and **3b** have also been reported to be active against other DNA viruses such as herpes simplex types 1 and 2 and vaccinia [8-10], and various RNA viruses [10,11]. *Ara*-sangivamycin (**3a**) was shown to be very active *in vitro* against vaccinia virus with a specificity index of 200 in PRK cells [10]. Therefore, it was of interest to prepare the 5-substituted-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidines (**7-10**) to study structure-antiviral activity relationships.



The synthesis of *ara*-tubercidin (**1**), *ara*-toyocamycin (**6b**) and *ara*-sangivamycin (**3a**) have been reported [12] in low to moderate yield, employing a four-step oxidation-reduction procedure, from their corresponding preformed β-D-ribonucleosides. In our study the precursor **6a** was prepared [13] by the stereospecific glycosylation of the sodium salt of readily available 2-ethoxymethyleneamino-5-bromopyrrole-3,4-dicarbonitrile (**4**) [13] with 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**5**) [14], and is

Scheme I



therefore totally free of contamination with the ribonucleoside antibiotics, toyocamycin or sangivamycin. Since sangivamycin is about 100-fold more active on a molar basis than **3a** as an antiviral agent [10,11], trace amount of sangivamycin in preparations of **3a** by the sugar-modified procedure [12] could contribute to misleading virus-inhibiting results. Synthesis of these analogs by the described procedure is readily accomplished in sufficient quantities for *in vivo* evaluation.

4-Amino-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**6a**) was readily prepared (Scheme I) by our regio- and stereospecific sodium salt glycosylation procedure [15] from 2-ethoxymethyleneamino-5-bromopyrrole-3,4-dicarbonitrile (**4**) followed by ring closure and dehydrobromination [16]. Debenzylation of **6a** with boron trichloride in dichloro-

methane at -78° furnished *ara*-toyocamycin (**6b**) in 72% yield. Compound **6b** revealed a sharp absorption band at 2220 cm^{-1} in the infrared spectrum, indicating the nitrile function.

It is of particular interest that thiosangivamycin (4-amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide), prepared and reported from our laboratory [17], exhibits a T/C of 175 against L1210 leukemia [18]. Thiosangivamycin also showed considerable activity against MX-1 human mammary-carcinoma xenograft [18]. 4-Amino-7-β-D-ribofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxamidoxime [17] at 3.12 mg/kg/day on 1 x 9 daily dosage treatment schedule exhibits a T/C of 204 against L1210 leukemia [18]. This carboxamidoxime has also shown activity against colon 26 and colon 38 carcinoma. In view of these observations, we have now prepared the corresponding arabinosyl derivatives. Treatment of **6b** with hydrogen sulfide in pyridine at room temperature gave *ara*-thiosangivamycin (**7a**) in 83% yield. However, **7a** was found to be quite insoluble in water. In an effort to prepare more water soluble form of **7a**, the preparation of the 5'-monophosphate **7b** was considered. Phosphorylation of unprotected **7a** with phosphorus oxychloride in trimethyl phosphate gave the desired *ara*-thiosangivamycin 5'-monophosphate (**7b**). When **6b** was allowed to react with free hydroxylamine in ethanol at reflux temperature 4-amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxamidoxime (**8a**) was formed, which was isolated in excellent yield. Our attempt to convert **6b** directly to **8b** with liquid ammonia/ammonium chloride was not successful. However, hydrogenation of **8a** with Raney nickel in the presence of ammonium chloride at 50 psi provided 4-amino-7-β-D-arabinofuranosylpyrrolo-[2,3-*d*]pyrimidine-5-carboxamidine (**8b**), isolated as the hydrochloride salt.

The preparation of the 2'-*O*-acetyl derivative of *ara*-thiosangivamycin **10b** is of special interest, since **10b** is a prodrug of **7a**. Compound **10a** may provide increased water solubility, liphophilicity and hence, enhance the potential for membrane transport than that of **7a**. The synthetic approach to prepare **10b** involved the selective protection of 3',5'-OH groups, acetylation of the 2'-OH and subsequent deprotection of 3',5'-OH without affecting the labile 2'-ester function. We elected to use the *t*-butyldimethylsilyl group as the selective protecting group which had been used for the derivatization of arabinonucleosides [19]. Thus, treatment of **6b** with *t*-butylchlorodimethylsilane in an inert atmosphere gave 3',5'-di-*O*-(*t*-butyldimethylsilyl)derivative **9a**. Acetylation of **9a** with acetic anhydride in pyridine at 0-5° afforded 2'-*O*-acetyl-3',5'-di-*O*-(*t*-butyldimethylsilyl) derivative **9b**. Reaction of **9b** with hydrogen sulfide in pyridine at ambient temperature provided the thiocarboxamide **10a**, which on deprotection with excess tetra-*n*-butylammonium fluoride in glacial acetic acid furnished 2'-*O*-acetyl-*ara*-thiosangivamycin (**10b**). Acetic acid was used in order to prevent 2' → 5' *O*-acyl migration. A similar procedure has recently been used for the synthesis of 2'-*O*-acyl derivatives of *ara*-A [20]. In the ^1H nmr spectrum of **10b**, the H-2' was shifted downfield by 0.2 ppm from that observed for the H-2' of **7a**, (due to the deshielding effect of the 2'-*O*-acetyl group) which is characteristic of 2'-*O*-acyl derivatives [20].

Details on the anti-DNA and visna viral evaluation of the compounds synthesized during this study (**7**, **8** and **10b**) will be reported elsewhere [21].

EXPERIMENTAL

Melting points (uncorrected) were determined in a Thomas-Hoover capillary melting-point apparatus. Elemental analyses were performed by Robertson Laboratory, Madison, NJ. Thin-layer chromatography (tlc) was performed on plates of silica gel 60F-254 (EM Reagents). Silica gel (E. Merck; 230-400 mesh) was used for flash column chromatography. All solvents used were reagent grade. Detection of nucleoside components in tlc was by uv light, and with 10% sulfuric acid in methanol spray followed by heating. Evaporations were conducted under diminished pressure with the bath temperature below 30°. Infrared (ir) spectra were recorded in potassium bromide with a Perkin-Elmer 1420-spectrophotometer and ultraviolet (uv) spectra with a Beckman DU-50 spectrophotometer (sh = shoulder). Nuclear magnetic resonance (^1H nmr) spectra were recorded at 300 MHz with an IBM NR/300 spectrometer. The chemical-shift values were expressed in δ values (parts per million) relative to tetramethylsilane as the internal standard. The signals are described as s (singlet), d (doublet) and m (multiplet). The presence of water as indicated by elemental analysis was verified by ^1H nmr spectroscopy. Preparative hplc was performed utilizing the Waters Delta prep 3000 system.

4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (*ara*-Toyocamycin, *6b*).

To a cold (-78°) stirred solution of 4-amino-7-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**6a**, 2.7 g, 4.82 mmoles) [13] in dry dichloromethane (100 ml) was added 1*M* boron trichloride in dichloromethane (80 ml, 80 mmoles) and the mixture was stirred at -78° for 2 hours, then at -20° for 2 hours. Methanol/dichloromethane (1:1, 50 ml) was added and the mixture stirred at ambient temperature for 30 minutes. The reaction mixture was diluted with more methanol (50 ml), cooled to 0° and neutralized with concentrated ammonium hydroxide solution. The precipitated solid was collected by filtration and the filtrate evaporated to dryness. The combined residue and the precipitate were dissolved in water and purified by hplc on a C-18 reverse phase column using 10% aqueous methanol as the eluent. The homogeneous fractions were pooled and evaporated to dryness. The residue on crystallization from ethanol gave 1.0 g (72%) of **6b**, mp 260-262° (Lit [12] 259-260°); ir: ν max 2220 (C≡N), 3300-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 234 nm (ε 14,700), 272 (10,700); (*p*H 7): 230 nm (ε 9,200), 276 (13,100); (*p*H 11): 230 nm (ε 8,900), 277 (13,000); ^1H nmr (DMSO-d_6): δ 6.43 (d, 1, $J_{1',2'}$ = 4.98 Hz, $C_1'H$), 6.84 (br s, 2, NH_2), 8.21 and 8.24 (2s, 2, C_2H and C_6H).

Anal. Calcd. for $C_{12}H_{13}N_5O_4$: C, 49.49; H, 4.49; N, 24.03. Found: C, 49.21; H, 4.48; N, 23.89.

4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (*ara*-Thiosangivamycin, **7a**).

A solution of **6b** (0.29 g, 1 mmole) in dry pyridine (35 ml) containing triethylamine (5 ml) was saturated with hydrogen sulfide gas at room temperature. The reaction mixture was stirred at ambient temperature for 24 hours, before it was purged with nitrogen for 1 hour. The solution was evaporated to dryness and the residue was triturated with methanol/dichloromethane (3:7, 10 ml). The solid that separated was collected and

crystallized from aqueous methanol to yield 0.27 g (83%) of **7a** as yellow needles, mp 260-262°; ir: ν max 1250 (C=S), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 241 nm (ε 15,800), 291 (11,800); (*p*H 7): 280 nm (ε 12,200), 310 (sh) (9,100); (*p*H 11): 279 nm (ε 12,500), 305 (sh) (7,800); ^1H nmr (DMSO-d_6): δ 6.45 (d, 1, $J_{1',2'}$ = 4.68 Hz, $C_1'H$), 7.85 and 8.10 (2s, 2, C_2H and C_6H), 7.94 (br s, 2, NH_2), 9.41 and 9.55 (2s, 2, $CSNH_2$).

Anal. Calcd. for $C_{12}H_{15}N_5O_4S$: C, 44.31; H, 4.65; N, 21.52; S, 9.84. Found: C, 44.45; H, 4.56; N, 21.43; S, 9.66.

4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide 5'-Monophosphate (**7b**).

To a cold (0°), stirred suspension of **7a** (1.8 g, 5.54 mmoles) in freshly distilled trimethyl phosphate (50 ml) was added phosphorus oxychloride (0.67 ml, 7.2 mmoles). The mixture was stirred at 0-5° for 10 hours (the reaction mixture became homogeneous after 2 hours) and at -5 to -15° for 20 hours. The solution was poured over crushed ice (200 g) and stirred vigorously. The precipitated solid was collected by filtration, washed with cold water (3 x 10 ml) and air dried. The solid was dissolved in concentrated ammonium hydroxide/water mixture (5:10 ml) and the solution was evaporated to dryness. The residue was redissolved in water (10 ml) and loaded onto a DEAE cellulose (HCO_3^- form) column (3 x 40 cm). The column was eluted with water (1 l) and then a gradient of water → 0.4 *M* ammonium bicarbonate. The fractions containing the homogeneous product were pooled and evaporated to dryness. The residue was dissolved in water (50 ml) and lyophilized to give 1.7 g (73%) of the title compound; mp > 220° dec; ir: ν max 1250 (C=S), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 242 nm (ε 15,800), 293 (11,600); (*p*H 7): 257 nm (ε 11,300), 283 (12,200), 309 (9,700); (*p*H 11): 261 nm (ε 1,200), 281 (12,300), 310 (9,300); ^1H nmr (DMSO-d_6): δ 6.51 (d, 1, $J_{1',2'}$ = 5.40 Hz, $C_1'H$), 7.26 (br s, 2, NH_2), 8.06 and 8.11 (2s, 2, C_2H and C_6H), 9.41 and 10.13 (2s, 2, $CSNH_2$).

Anal. Calcd. for $C_{12}H_{19}N_6O_7PS$: C, 34.13; H, 4.54; N, 19.89; S, 7.58. Found: C, 33.87; H, 4.43; N, 19.59; S, 7.79.

4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxamidoxime (**8a**).

A solution of **6b** (0.20 g, 1 mmole) and free hydroxylamine (0.30 g) in absolute ethanol (25 ml) was heated under reflux for 3 hours and cooled to 0°. The precipitated solid was collected by filtration and crystallized from 95% aqueous ethanol to give 0.20 g (89%) of **8a**, mp 253-255°; ir: ν max 3300-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 224 nm (ε 20,300), 274 (13,900); (*p*H 7): 276 nm (ε 17,100); (*p*H 11): 275 nm (ε 16,900); ^1H nmr (DMSO-d_6): δ 5.95 (s, 2, NH_2), 6.43 (d, 1, $J_{1',2'}$ = 4.50 Hz, $C_1'H$), 7.15 and 9.27 (2br s, 2, NH_2), 7.75 and 8.01 (2s, 2, C_2H and C_6H) and 9.60 (s, 1, NO*H*).

Anal. Calcd. for $C_{12}H_{16}N_6O_5$: C, 44.45; H, 4.97; N, 25.91. Found: C, 44.19; H, 4.92; N, 25.64.

4-Amino-7-β-D-arabinofuranosylpyrrolo[2,3-*d*]pyrimidine-5-carboxamidine Hydrochloride (**8b**).

A solution of **8a** (1.0 g, 3.1 mmoles) and ammonium chloride (0.18 g, 3 mmoles) in water/ethanol (100:25 ml) was hydrogenated at 50 psi on a parr apparatus in the presence of Raney nickel (1.0 g, wet weight) at room temperature for 12 hours. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was triturated with hot ethanol (10 ml) to give a colorless solid, which was collected and dried over phosphorus pentoxide. The solid was crystallized from ethanol to yield 0.8 g (75%) of **8b**, mp 250-253°; ir: ν max 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 275 nm (ε 18,300); (*p*H 7): 251 nm (sh) (ε 12,800), 277 (20,700); (*p*H 11): 278 nm (ε 20,400); ^1H nmr (DMSO-d_6): δ 6.46 (d, 1, $J_{1',2'}$ = 4.35 Hz, $C_1'H$), 6.88 (s, 2, NH_2), 8.12 and 8.22 (2s, 2, C_2H and C_6H), 8.95-9.09 (m, 4, amidine hydrochloride).

Anal. Calcd. for $C_{12}H_{17}ClN_6O_4 \cdot 1/2\ H_2O$: C, 40.74; H, 5.13; N, 23.74; Cl, 10.03. Found: C, 40.77; H, 4.95; N, 23.56; Cl, 10.21.

4-Amino-7-[3,5-di-*O*-(*t*-butyldimethylsilyl)-β-D-arabinofuranosyl]pyrrolo-[2,3-*d*]pyrimidine-5-carbonitrile (**9a**).

To a stirred suspension of **6b** (1.0 g, 3.44 mmoles) in dry *N,N*-dimethylformamide (50 ml) was added triethylamine (2.4 ml, 17.2 mmoles), followed by *t*-butylchlorodimethysilane (1.29 g, 8.6 mmoles). The mixture was stirred under argon atmosphere at room temperature for 36 hours, and evaporated to dryness. The residue was suspended in water (30 ml) and extracted with ethyl acetate (2 x 75 ml). The combined ethyl acetate extracts were washed with saturated brine solution (30 ml), dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane → acetone gradient. The fractions containing the homogeneous product were pooled and evaporated to give 1.2 g (67%) of **9a**, mp 167-170°; ir λ max 2220 (C≡N), 3400 (NH_2) cm^{-1}; uv (methanol): λ max 278 nm (ε 17,600); ^1H nmr (DMSO-d_6): δ 0.11-0.15 (m, 12, 2 $Si(CH_3)_2$), 0.91 (m, 18, 2 *t*-Bu), 6.44 (d, 1, $J_{1',2'}$ = 5.28 Hz, $C_1'H$), 6.86 (br s, 2, NH_2), 8.10 and 8.22 (2s, 2, C_2H and C_6H).

Anal. Calcd. for $C_{24}H_{41}N_5O_4Si_2$: C, 55.46; H, 7.95; N, 13.47. Found: C, 55.23; H, 7.92; N, 13.24.

4-Amino-7-[2-*O*-acetyl-3,5-di-*O*-(*t*-butyldimethylsilyl)-β-D-arabinofuranosyl]pyrrolo[2,3-*d*]pyrimidine-5-carbonitrile (**9b**).

To a cold (0-5°) solution of **9a** (1.0 g, 1.9 mmoles) in dry pyridine (50 ml) was added acetic anhydride (0.29 g, 2.89 mmoles) and the mixture was stirred under nitrogen atmosphere for 48 hours. Water (3 ml) was added to the reaction mixture and evaporated to dryness. The residue was purified by flash chromatography using dichloromethane/ethyl acetate (7:3) as the eluent to give 1.0 g (93%) of **9b** as an amorphous solid; ir: λ max 2220 (C≡N), 3300-3400 (NH_2) cm^{-1}; uv (methanol): λ max 278 nm (ε 30,700); ^1H nmr (DMSO-d_6): δ 0.10 (m, 12, 2 $Si(CH_3)_2$), 0.90 (m, 18, 2 *t*-Bu), 1.69 (s, 3, $COCH_3$), 6.60 (d, 1, $J_{1',2'}$ = 6.0 Hz, $C_1'H$), 6.92 (br s, 2, NH_2), 8.19 and 8.21 (2s, 2 C_2H and C_6H).

Anal. Calcd. for $C_{26}H_{43}N_5O_5Si_2$: C, 55.58; H, 7.72; N, 12.46. Found: C, 55.60; H, 7.61; N, 12.38.

4-Amino-7-[2-*O*-acetyl-3,5-di-*O*-(*t*-butyldimethylsilyl)-β-D-arabinofuranosyl]pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (**10a**).

A solution of **9b** (1.2 g, 2.14 mmoles) in dry pyridine (50 ml) containing triethylamine (5 ml) was saturated with hydrogen sulfide gas at room temperature. The reaction mixture was stirred at ambient temperature for 12 hours, before it was purged with nitrogen for 1 hour. The solution was evaporated to dryness. The residue was adsorbed onto silica gel (5 g) and placed on top of a flash column (3 x 30 cm) packed in dichloromethane. The column was eluted with dichloromethane/acetone (7:3) and the homogeneous fractions were pooled. Evaporation of the solvent gave 0.90 g (71%) of the title compound as a foam; ir: ν max 1260 (C=S), 3300-3400 (NH_2) cm^{-1}; uv (*p*H 1): λ max 239 nm (ε 18,100), 286 (13,900); (*p*H 7): 248 nm (sh) (ε 14,800), 286 (15,500), 324 (sh) (11,900); (*p*H 11): 282 nm (ε 15,500), 320 (sh) (10,100); ^1H nmr (DMSO-d_6): δ 0.12 (m, 12, 2 $Si(CH_3)_2$), 0.89 (m, 18, 2 *t*-Bu), 1.75 (s, 3, $COCH_3$), 6.65 (d, 1, $J_{1',2'}$ = 5.50 Hz, $C_1'H$), 7.68 and 8.11 (2s, 2, C_2H and C_6H), 7.90 (s, 2, NH_2), 9.52 and 9.69 (2s, 2, $CSNH_2$).

Anal. Calcd. for $C_{26}H_{45}N_5O_5SSi_2$: C, 52,41; H, 7.61; N, 11.75; S, 5.37. Found: C, 52.61; H, 7.72; N, 11.61; S, 5.38.

4-Amino-7-(2-*O*-acetyl-β-D-arabinofuranosyl)pyrrolo[2,3-*d*]pyrimidine-5-thiocarboxamide (**10b**).

To a stirred solution of **10a** (0.9 g, 1.51 mmoles) in dry tetrahydrofuran (30 ml) was added acetic acid (0.22 ml, 3.76 mmoles), followed by tetra-*n*-butylammonium fluoride (1*M*, 12 ml, 12 mmoles). The mixture was stirred at ambient temperature for 5 hours before the solution was filtered through a bed of silica gel (10 g). The silica gel was washed with tetrahydrofuran (2 x 50 ml) and the combined filtrates evaporated to dryness. The residue was purified by flash chromatography using dichloromethane/methanol (9:1) as the eluent. The homogeneous product after crystallization from acetone gave 0.4 g (72%) of **10b**, mp 218-220°; ir: ν max 1250 (C=S), 3200-3400 (NH_2, OH) cm^{-1}; uv (*p*H 1): λ max 274 nm (ε 12,000), 292 (sh) (10,800); (*p*H 7): 274 nm (ε 12,600), 296 (12,100); (*p*H 11): 222 nm (sh) (ε 18,100), 309 (14,600); ^1H nmr (DMSO-d_6): δ 1.70 (s,

3, $COCH_3$), 6.60 (d, 1, $J_{1',2'}$ = 5.43 Hz, $C_1'H$), 7.89 and 8.09 (2s, 2, C_2H and C_6H), 7.96 (s, 2, NH_2), 9.45 and 9.64 (2s, 2, $CSNH_2$).

Anal. Calcd. for $C_{14}H_7N_5O_5S$: C, 45.78; H, 4.66; N, 19.06; S, 8.71. Found: C, 45.49; H, 4.59; N, 19.00; S, 8.57.

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