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The synthesis of a series of new nucleosides, including ribo-, 2′-deoxyribo- and arabinofuranosides of 5-(*S*-methyl)mercapto-substituted uracil, 4-thiouracil, and cytosine is described. The synthetic methods employed include condensation reactions of the silylated pyrimidine with blocked sugar halides, as well as transformations of both the base and sugar moieties. The separated α and β anomers were identified by nmr spectra as well as by unambiguous synthetic routes or interconversions.

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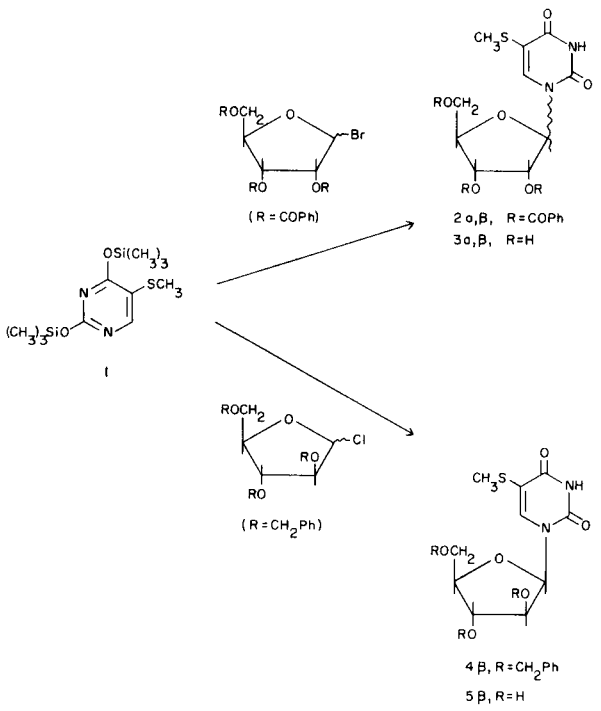
In view of the pronounced antiherpes activity of the previously reported 5-(*S*-methyl)mercapto-2′-deoxyuridine (MeMUdR; **7β**) (2-5), it was of interest to synthesize a series of new 5-(*S*-methyl)mercaptopyrimidine nucleosides as potential chemotherapeutic agents. In the course of this work, several observations and improvements were made relating to some of the standard methods used in nucleoside chemistry.

The synthesis of the parent pyrimidine base, 5-(*S*-methyl)mercaptouracil, and its "silylated" derivative, 2,4-bis-*O*-(trimethylsilyl)-5-(*S*-methyl)mercaptouracil (**1**), have been reported (2); however, in the present work, hexamethyldisilazane was used (instead of trimethylsilyl chloride) for silylation with a resulting much higher yield (93%) of **1**. Condensation of **1** with 1.2 molar equivalent of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (see Scheme I) in dry acetonitrile (6) gave a nearly quantitative yield of the blocked anomeric nucleosides **2** (β + α). After separation and purification, the β-anomer (**2β**) was obtained in a yield of 82%, and the α-anomer (**2α**) in a yield of 9.9% (7). Hydrolysis of the benzoyl blocking groups, either with sodium methoxide in methanol at room temperature or with methanolic ammonia at 4°, gave the corresponding free nucleosides **3β** and **3α**, respectively, in high yields.

Scheme I



The anomeric configurations of **2α** and **2β**, or **3α** and **3β** were tentatively assigned on the basis of the nmr spectra, by comparing the chemical shifts for the anomeric proton which appears, as a doublet, at a higher field in the case of the β than in the case of the corresponding α anomer (8). On the other hand, the magnitude of the coupling constant $J_{1',2'}$ for β-D-ribo (*i.e.*, H-1′/H-2′ *trans*) nucleosides is usually less than 3.5 Hz; however, in the present case, both anomers of either the blocked or the free nucleosides were found to exhibit $J_{1',2'}$ values larger than 3.5 Hz. Unequivocal proof of the assigned anomeric configurations was obtained by the conversion of **3β** to the 2,2′-anhydronucleoside **17** (see below); **3α** could not be converted to an anhydronucleoside under similar conditions.

A previous attempt to prepare the benzoyl-blocked ribonucleosides **2β**, *via* the mercury method, was reported by Carpenter and Shaw (9) to give an 8% yield of the desired compound; however, the elemental analysis reported by these authors was incorrect for **2β**, and the melting point and ultraviolet spectral data given for their compound were quite different from those of our sample which analyzed correctly. Very recently, another preparation of **2β** was reported (10) but without giving yield, melting point, elemental analysis, or any other information except nmr spectra. The anomeric configuration, presumed to be β, was not discussed in either of these reports.

The synthesis of the corresponding 2′-deoxyribosides, **7β** (MeMUdR) and **7α**, *via* the appropriately controlled condensation of **1** with 2-deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-α-D-ribofuranosyl chloride to give a desired ratio of the corresponding blocked nucleosides **6β** and **6α**, respective-

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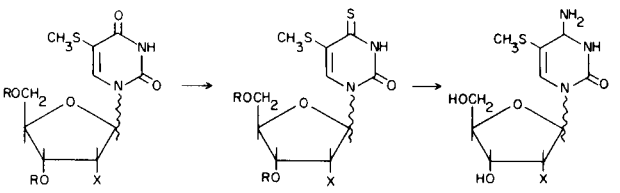
ly, have been described (2). Condensation of **1** with 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (11) by fusion under vacuum gave, after hydrolysis of the 4-trimethylsilyloxy group followed by chromatography of the syrupy residue, an 83% yield of the pure β anomer of the benzyl-blocked arabinoside (**4**β; see Scheme I). The assignement of β configuration was tentatively based on the characteristic coupling constant $J_{1',2'} = 4.5$ Hz of the anomeric proton (at δ 6.30), which indicated *cis*-coupling with the C-2′ proton. This assignment was further confirmed by comparison of the nmr spectrum of **4**β with that of the analogous triacetyl derivative **19**, which had been prepared by a different route leading unequivocally to the β anomer (see Scheme IV, below).

It is interesting that the Hilbert-Johnson type reactions of this benzyl-protected halogenose with **1** as well as with other pyrimidines (12-14) appear to be highly stereoselective, leading only to the formation of β-arabinosides (*i.e.*, "*cis*-nucleosides"), despite the fact that the β-face of the halogenose would seem to be sterically more hindered. In our laboratory, Szekeres (15) was able to separate the commerically available 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinofuranose into the pure α and β anomers, and then by treatment with a saturated solution of hydrogen chloride in methylene chloride both anomers were completely converted to the same halogenose which was identified as the α anomer (11b). It appears that the initially formed β halogenose may isomerize to the thermodynamically more stable α anomer by reaction with excess halide ion. Thus, the stereoselective formation of β-D-arabinonucleosides (which was also observed by other investigators) could be explained by assuming for these coupling reactions the operation of a strict S_N2-mechanism in which the halogenose participates as the pure α anomer, undergoing Walden inversion.

For the conversion of the uracil nucleosides to the corresponding 4-thiouracil and cytosine derivatives, we employed various modifications of Fox's general method (16) which involves thiation of the blocked nucleosides with phosphorous pentasulfide followed by amination with methanolic ammonia. Thus, the blocked ribonucleoside **2**α was heated with 1.5 molequivalent of phosphorous pentasulfide in 1,2-dimethoxyethane at 105° for 1 hour, to give a 76.5% yield of the corresponding blocked 4-thiouracil nucleoside **11**α which, in turn, was converted to the free 5-(*S*-methyl)mercapto-α-cytidine **13**α, in 81.9% yield by treatment with saturated ammonia in methanol at 87° for 20 hours in a steel bomb. The free 4-thiouracil nucleoside **12**α was obtained from **11**α by alkali-catalyzed alcoholysis. (Scheme II) We generally found that the use of dimethoxyethane as a solvent in the thiation of *acyl*-blocked nucleosides is far superior to the hitherto used pyridine or dioxane (17) solvents; it gives higher yields in a

Scheme II



6α,β, X=H R=p-ClC$_6$H$_4$CO
7α,β, X=H R=H
2α,β, X=OCOPh R=COPh
3α,β, X=OH, R=H

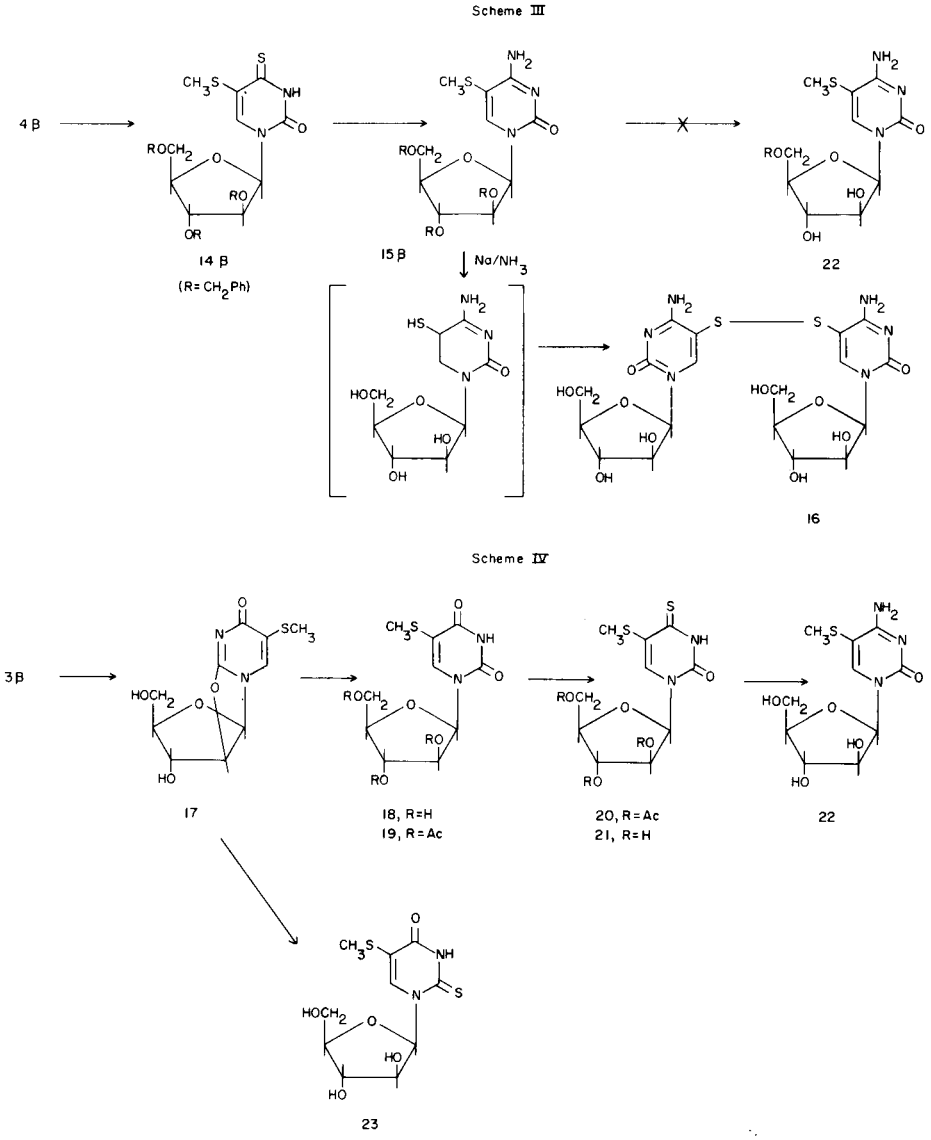
8α,β, X=H R=p-ClC$_6$H$_4$CO
9β, X=H R=H
11α,β, X=OCOPh, R=COPh
12β, X=OH R=H

10α,β, X=H
13α,β, X=OH

relatively short reaction time without necessitating the use of a large excess of the phosphorus pentasulfide reagent and affords a cleaner product. On the other hand, for the thiation of the benzyl-blocked arabinoside **4**β, to give **14**β, pyridine proved to be a relatively good solvent, affording a higher yield than the usually preferred (17) dioxane.

Treatment of **14**β with the methanolic ammonia afforded the corresponding benzyl-blocked *ara*-C derivative **15**β. In order to remove the benzyl groups, **15**β was treated with sodium in liquid ammonia; this, however, resulted not only in the expected reductive cleavage of the benzyl protecting groups but also in the cleavage of the *S*-methyl, to give a moderate yield of 5-mercaptocytosine arabinoside; the latter was isolated in the form of the crude disulfide **16** and identified by ultraviolet and nmr spectra (15) (see Scheme III). All attempts to achieve selective debenzylation failed. Therefore, the synthesis of the arabinoside series was undertaken by an alternative route.

Treatment of the ribonucleoside **3**β with a slight excess of diphenyl carbonate (18) in dimethylformamide afforded a 67.5% yield of analytically pure 2,2′-anhydro-1-β-D-arabinofuranosyl-5-(*S*-methyl)mercaptouracil (**17**). A significant shift of the doublet corresponding to the C-2′-proton in the nmr spectrum of **17**, from δ 3.55 (for **3**β) downfield to δ 5.26, indicated that the cyclization reaction occurred between the C-2′ and C-2 positions. The anhydronucleoside **17** was converted in 94.4% yield to 1-β-D-arabinofuranosyl-5-(*S*-methyl)mercaptouracil (**18**) with 0.1*N* sodium hydroxide. Acetylation of **18** followed by treatment with phosphorus pentasulfide in 1,2-dimethoxyethane gave 93.8% yield of the blocked 4-thio analog **20** which was converted by treatment with saturated methanolic ammonia to the free 5-(*S*-methyl)mercaptocytosine arabinoside **22** in a yield of 84.8% (Scheme IV). Deblocking of **20** by alkali-catalyzed alcoholysis gave the free 4-thio-5-(*S*-methyl)mercaptouracil arabinoside, **21**. In this series, all compounds (**18-22**) necessarily have the β configuration as they were derived from 2,2′-anhydronucleoside **17** by an unambiguous route. In addition, the nmr spectra of these compounds all displayed a doublet



for the anomeric proton with a coupling constant of 4.5 Hz.

Reaction of the anhydronucleoside **17** with hydrogen sulfide in dimethylformamide (19) gave the 2-thio-5-(*S*-methyl)mercaptouracil arabinoside **23**. The nmr spectrum of this compound showed the doublet of the anomeric proton $J_{1',2'}$ = 4.5 Hz) at a significantly lower field (by δ 0.95) than in the case of the 4-thioarabinoside **21**, corresponding to the greater deshielding effect of the 2-thio group in the proximity of the anomeric proton.

EXPERIMENTAL

Melting points were determined on a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer 141 polarimeter. The uv spectra were recorded on a Beckman DBG. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA. Tlc's were performed on microscope slide covered with a layer of silica gel GF_{254} (Merck) and Eastman Chromatogram Sheet, and column chromatography on Merck silica gel type 60 (70-230 mesh).

2,4-Bis-*O*-(trimethylsilyl)-5-(*S*-methylmercaptouracil) (**1**).

A mixture of 5-(*S*-methyl)mercaptouracil (7.91 g., 0.05 mole) and ammonium sulfate (170 mg.) in hexamethyldisilazane (100 ml.) was heated under reflux for 2 hours. Microdistillation of the residue after removal of the solvent yielded 12.57 g. (93%) of **1** as a colorless oil, b.p. 110-111° (0.5 mm), which crystallized on standing, m.p. 36-37° (lit. (2) b.p. 110-111°).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-(*S*-methyl)mercaptouracil (**2β**) and its α Anomer (**2α**).

To a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (20) freshly prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (26.5 g., 53 mmoles) in dry acetonitrile (180 ml.) was added **1** (12 g., 44 mmoles) under anhydrous conditions, and the mixture was stirred for 5 days at room temperature. After removal of the solvent, the residue was dissolved in benzene, filtered and evaporated to dryness. Ethanol (250 ml.) and water (50 ml.) were added to the residue, and the mixture was heated to boiling, then stirred at room temperature overnight. The white precipitate was filtered off, washed with 80% ethanol and dried to give 21.72 g. (82%) of **2β**, m.p. 202-204°. Tlc on silica gel (chloroform-ethyl

acetate, 9:1) showed a single spot. Crystallization from methanol-water (10:1) gave 19.54 g. of pure **2β** with m.p. 202-203°; $[\alpha]_D^{25}$ -137.4° (*c*-1.0, chloroform); nmr (deuteriochloroform): δ 2.17 (s, SCH_3), 4.78 (broad s, H-5′), 5.66-6.00 (m, H-3′,4′), 6.34 (d, H-1′, $J_{1',2'}$ = 5.5 Hz), 7.34-7.60 (m, ArH), 7.87-8.22 (m, C_6-H and ArH), 8.70 (broad s, N_3-H).

Anal. Calcd. for $C_{31}H_{26}N_2O_9S$: C, 61.79; H, 4.35; N, 4.65; S, 5.32. Found: C, 61.78; H, 4.33; N, 4.69; S, 5.39.

The residue after removal of the solvent from the initial mother liquor was chromatographed on a column (4.0 × 40 cm) of silica gel. Elution with chloroform-ethyl acetate (9:1) provided 2.62 g. (9.9%) as a foam. Crystallization from methanol-water (10:1) afforded 2.49 g. of pure **2α** as white needles, m.p. 176-178° $[\alpha]_D^{25}$ +12.5 (*c* 1.0, chloroform); nmr (deuteriochloroform): δ 2.13 (s, SCH_3), 3.03 (broad s, H-5′), 4.91-5.12 (m, H-4′), 5.86-6.24 (m, H-2′,3′), 6.68 (d, H-1′, $J_{1',2'}$ = 4.5 Hz), 7.34-7.56 (m, ArH), 7.76-8.18 (m, C_6-H, and ArH), 9.06 (broad s, N_3-H).

Anal. Calcd. for $C_{31}H_{26}N_2O_9S$: C, 61.79; H, 4.35; N, 4.65; S, 5.32. Found: C, 61.80; H, 4.39; N, 4.65; S, 5.25.

1-(β-D-Ribofuranosyl)-5-(*S*-methyl)mercaptouracil (**3β**).

Method A.

To a solution of sodium methoxide prepared from sodium (0.2 g.) in dry methanol (400 ml.) was added **2β** (4.1 g., 6.8 mmoles) and stirred overnight at room temperature. The solution was neutralized with Dowex 50W-X8 (H^+) resin, filtered and evaporated to dryness. Crystallization from methanol yielded 1.87 g. (94.7%) of **3β** as white crystals, m.p. 188-189.5°; $[\alpha]_D^{25}$ -22.62° (*c* 0.5., water); uv (water): λ max 286 nm (ε 5,300), λ min 268 (4,700); (*p*H 2): λ max 288 (4,000), λ min 270 (2,300); (*p*H 12): λ max 282 (5,000), λ min 264 (4,200); nmr (DMSO-d_6-deuterium oxide): δ 2.27 (s, 3H, SCH_3), 3.44-3.66 (H-5′), overlapping with HDO at 3.58), 3.84-4.13 (m, 3H, H-2′,3′,4′), 5.83 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 7.95 (s, 1H, C_6-H).

Anal. Calcd. for $C_{10}H_{14}N_2O_6S$: C, 41.38; H, 4.86; N, 9.65; S, 11.05. Found: C, 41.25; H, 4.92; N, 9.73; S, 11.01.

Method B.

A solution of **2β** (14 g., 23.2 mmoles) in saturated methanolic ammonia (500 ml.) was stirred overnight at 4°, concentrated to a small volume and triturated with ether. Crystallization from methanol afforded 6.31 g. (93.6%) of pure **3β**.

1-(α-D-Ribofuranosyl)-5-(*S*-methyl)mercaptouracil (**3α**).

Compound **2α** (1.2 g., 1.99 mmoles) was treated as described in Method A for **3β** to give 0.51 g. (88.3%) of **3α** after crystallization from ethanol, m.p. 174-175°; $[\alpha]_D^{25}$ -6.33° (*c* 0.52, water); nmr (DMSO-d_6-deuterium oxide): δ 2.25 (s, SCH_3), 3.83-4.33 (m, H-2′,3′,4′) 6.07 (d, $J_{1',2'}$ = 4.5 Hz), 7.78 (s, C_6-H).

Anal. Calcd. for $C_{10}H_{14}N_2O_6S$: C, 41.38; H, 4.86; N, 9.65; S, 11.05. Found: C, 41.38; H, 4.90; N, 9.73; S, 10.96.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-(*S*-methyl)mercaptouracil (**4β**).

A mixture of **1** (3.5 g., 13 mmoles) and 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (11a,15) which was prepared from 2,3,5-tri-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-D-arabinose (8.4 mmoles), was stirred mechanically under reduced pressure (∿ 0.1 mm) and then heated in an oil-bath (preheated at 115°) for 30 minutes. The vacuum changed from 0.1 mm to ∿ 2.0 mm due to the evolution of the trimethylsilyl chloride that ceased after ∿ 20 minutes. After cooling to room temperature, the solidified mixture was taken up in benzene (60 ml.) and water (2 ml.) was added. The solution was then stirred overnight. The unreacted 5-(*S*-methyl)mercaptouracil was filtered and washed with benzene. The combined filtrate and washings were evaporated to give a syrup which was further dried by coevaporation with ethanol. The residue was dissolved in chloroform (50 ml.) and applied to a column (4 × 15 cm) of silica gel. Elution with chloroform-ethyl acetate (9:1) afforded a syrup that could not be crystallized. Tlc on silica gel in the same solvent system showed a homogenous spot (R_f 0.5). This was further dried over phosphorus pentoxide *in vacuo* leaving 3.91 g. (83%) of **4β**; $[\alpha]_D^{25}$ +19.4° (*c* 2.38, methylene chloride); nmr (deuteriochloroform): δ 2.23 (s, 3H, SCH_3), 4.40,4.54, 4.58 (benzyl-CH_2), 6.30 (d, 1H, H-1′, $J_{1',2'}$ = 4.5 Hz), 7.89 (s, 1H, C_6-H).

Anal. Calcd. for $C_{31}H_{32}N_2O_6S$: C, 66.41; H, 5.75; N, 5.00; S, 5.72. Found: C, 65.97; H, 5.93; N, 4.78; S, 5.64.

1-[2-Deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-β-D-*erythro*-pentofuranosyl]-5-(*S*-methyl)mercaptouracil (**6β**) and its α anomer (**6α**).

These compounds were prepared according to the procedure of Kotick, *et al.* (2). The reaction of **1** (18.73 g., 69 mmoles) and 2-deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-D-*erythro*-pentofuranosyl chloride (33.6 g., 55 mmoles) using the fusion method yielded 13.6 g. (45%) of **6β** as white crystals (from toluene) with m.p. 197-198° (lit. (2) m.p. 196°); nmr (deuteriochloroform): δ 2.24 (s, SCH_3), 2.48-2.99 (m, H-2′), 4.58 (m, H-4′), 4.75 (d, H-5′), 5.64 (broad d, H-3′), 6.38 (apparent q, H-1′, J = 7.5, 6.0 Hz, peak-width = 13.5 Hz), 7.72 (s, C_6-H).

From the mother liquor, **6α** was obtained in a yield of 6.0 g. (19.8%) as white needles with m.p. 186-187° (lit. (2) m.p. 185-186°) after crystallization from toluene; nmr (deuteriochloroform): δ 2.26 (s, SCH_3), 2.61-2.98 (m, H-2′), 4.52 (d, H-5′), 4.86-5.08 (m, H-4′), 5.64 (broad d, H-3′), 6.35 (apparent q, J = 6.5, 2.0 Hz, peak-width = 8.5 Hz), 7.84 (s, C_6-H), 9.48 (broad s, N_3-H).

1-[2-Deoxy-3,5-di-*O*-(*p*-chlorobenzoyl-β-D-*erythro*-pentofuranosyl-5-(*S*-methyl)-mercapto-4-thiouracil (**8β**).

A mixture of **6β** (11.07 g., 0.02 mole) and phosphorus pentasulfide (7.7 g.) in pyridine was heated under reflux for 3 hours at which time an additional portion of phosphorus pentasulfide (4.4 g.) was added and refluxing continued for 1 hour. The mixture was concentrated to ∿ 50 ml., dissolved in hot ethyl acetate, filtered and evaporated leaving a thick gum. This residue was chromatographed on a column (4 × 40 cm) of silica gel. Elution with chloroform-ethyl acetate (9:1) provided 3.5 g. (30.8%) of **8β** as yellow crystals after crystallization from ethanol, m.p. 165-166°; $[\alpha]_D^{25}$ -65.0° (*c* 1.0, chloroform); nmr (deuteriochloroform): δ 2.20 (s, SCH_3), 2.50-3.00 (m, H-2′), 4.56-4.78 (m, H-4′,5′), 6.33 (apparent q, H-1′, J = 7.5, 5.5 Hz, peak-width = 13.0 Hz), 5.63 (d, H-3′), 7.44 (s, C_6-H), 10.35 (s, N_3-H).

Anal. Calcd. for $C_{24}H_{20}N_2O_6S_2Cl_2$: C, 50.80; H, 3.55; N, 4.94; S, 11.30. Found: C, 50.66; H, 3.57; N, 4.87; S, 11.24.

1-[2-Deoxy-3,5-di-*O*-(*p*-chlorobenzoyl)-α-D-*erythro*-pentofuranosyl]-5-(*S*-methyl)mercapto-4-thiouracil (**8α**).

A mixture of **6α** (4.41 g., 8.0 mmoles) and phosphorus pentasulfide (2.67 g.) in 1,2-dimethoxyethane (80 ml.) was refluxed in an oil-bath (preheated at 105°) for 1 hour. Tlc (silica gel, chloroform-ethyl acetate 9:1) showed absence of unreacted starting material. After cooling to ∿ 60°, the mixture was filtered to remove inorganic materials, poured into ice-water (200 ml.) and extracted twice with chloroform (80 ml.). Saturated aqueous sodium chloride was added to break the emulsion formed. The organic phase was twice washed with water (100 ml.), dried (anhydrous sodium sulfate), filtered, and evaporated to afford a yellow solid. This was chromatographed on a column of silica gel (80 g.). Elution with chloroform provided 3.34 g. (73.6%) of **8α** as pale yellow needles (from toluene), m.p. 185-187°; $[\alpha]_D^{25}$ -78.8° (*c* 0.5, methylene chloride); nmr (deuteriochloroform): δ 2.24 (s, SCH_3), 2.69-3.25 (m, H-2′), 4.56 (broad d, H-5′), 4.86-5.02 (m, H-4′), 5.72 (broad d, H-3′), 6.32 (apparent q, H-1′, J = 6.5, 2.0 Hz, peak-width = 8.5 Hz), 7.74 (s, C_6-H).

Anal. Calcd. for $C_{24}H_{20}N_2O_6S_2Cl_2$: C, 50.80; H, 3.55; N, 4.94; S, 11.30. Found: C, 50.91; H, 3.62; N, 4.90; S, 11.12.

1-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-(*S*-methyl)mercapto-4-thiouracil (**9β**).

Treatment of **8β** (0.62 g., 1.1 mmoles) with sodium methoxide (1.3 mmoles) in methanol (65 ml.) as described in Method A for **3β** afforded 0.30 g. (94%) of **9β** after crystallization from ethanol, m.p. 172-173°; $[\alpha]_D^{25}$ +49.6° (*c* 0.5, water); uv (water): λ max 352 nm (ε 11,700), 308 (7,200), 255 (7,100), λ min 277 (4,200), 240 (6,000); (*p*H 2): λ max 353 (11,800), 308 (7,200), 256 (7,300), λ min 278 (4,300), 241 (6,000); (pH 12): λ max 334 (10,800, merged with a peak at 312 nm), 312 (10,300), 253

(8,900), λ min 275 (3,900); nmr (DMSO-d_6-deuterium oxide): δ 2.28 (s, 3H, SCH_3), 2.14-2.33 (overlapped with CH_3, H-2′), 3.65 (d, 2H, H-5′), 3.86 (m, 1H, H-4′), 4.27 (m, 1H, H-3′), 6.18 (apparent t, 1H, H-1′, J = 6.5 Hz, peak-width 13.0 Hz), 7.72 (s, 1H, C_6-H).

Anal. Calcd. for $C_{10}H_{14}N_2O_4S_2$: C, 41.37; H, 4.86; N, 9.65; S, 22.09. Found: C, 41.30; H, 4.89; N, 9.68; S, 22.19.

1-(2-Deoxy-β-*erythro*-pentofuranosyl)-5-(*S*-methyl)mercaptocytosine (**10β**).

A solution of **8β** (1.49 g., 2.6 mmoles) in methanolic ammonia (40 ml.) saturated at 0° was heated at 90° in a sealed steel-bomb for 20 hours. The mixture was then evaporated, and partitioned between ether (80 ml.) and water (40 ml.). The aqueous phase was concentrated to a small volume and chromatographed on a column (1.7 × 21 cm) of Bio-Rad AG-1-X2 (OH-) resin using 30% methanol as eluent. Evaporation of the eluates containing the product, followed by crystallization from methanol and acetone, gave 0.45 g. (63.3%) of a chromatographically homogenous product. Recrystallization from methanol provided an analytical sample of **10β**, m.p. 187-189°; $[\alpha]_D^{25}$ +41.96° (*c* 0.56, water); uv (water): λ max 279 nm (ε 6,500), λ min 261 (5,600); (*p*H 2): λ max 284 (8,800), λ min 249 (4,200); (*p*H 12): λ max 277 (6,400), λ min 259 (5,600); nmr (DMSO-d_6-deuterium oxide): δ 2.11 (H-2′), 2.23 (s, SCH_3), 3.85 (m, H-4′), 4.28 (m, H-3′), 6.13 (apparent t, H-1′, J = 6.5 Hz, peak-width = 13.0 Hz), 8.23 (s, C_6-H).

Anal. Calcd. for $C_{10}H_{15}N_3O_4S$: C, 43.95; H, 5.53; N, 15.37; S, 11.73.Found: C 43.99; H, 5.57; N, 15.44; S, 11.77.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-(*S*-methyl)mercapto-4-thiouracil (**11β**).

To a mixture of phosphorus pentasulfide (5 g.) in boiling pyridine (50 ml.) was added **2β** (6.03 g., 0.01 mole), and refluxing was continued for 6 hours. The mixture was concentrated to 40 ml., poured into warm water (500 ml.) and filtered while hot. The precipitate which formed on standing was chromatographed on a column (3 × 33 cm) of silica gel using chloroform followed by chloroform-ethyl acetate (9:1). Evaporation of the appropriate fractions gave 4.03 g. (65.1%) of a solid with m.p. 190-192°, which was homogenous on tlc (silica gel, chloroform-ethyl acetate, 9:1). Crystallization from toluene afforded pure **11β** as yellow needles, m.p. 195-195.5°; $[\alpha]_D^{25}$ -168.7 (*c* 1.0, chloroform); nmr (deuteriochloroform): δ 2.07 (s, SCH_3), 4.83 (broad s, H-5′), 5.81 (d, H-2′), 5.66-5.99 (m, H-2′,3′,4′), 6.36 (d, H-1′, $J_{1',2'}$ = 5.5 Hz), 7.24-7.54 (m, aromatic), 7.84-8.20 (m, H-6, aromatic), 10.04 (broad s, N_3-H).

Anal. Calcd. for $C_{31}H_{26}N_2O_8S_2$: C, 60.18; H, 4.24; N, 4.53; S, 10.37. Found: C, 60.23; H, 4.25; N, 4.59; S, 10.32.

1-(2,3,5-Tri-*O*-benzoyl-α-D-ribofuranosyl)-5-(*S*-methyl)mercapto-4-thiouracil (**11α**).

Treatment of **2α** (1.36 g., 2.26 mmoles) with phosphorus pentasulfide (0.78 g.) in dimethoxyethane (25 ml.) in a manner analogous to that described above for **8α** afforded 10.7 g. (76.5%) of **11α** after crystallization from ethanol, m.p. 171-173°; $[\alpha]_D^{25}$ -111.73° (*c* 0.5, methylene chloride); nmr (deuteriochloroform): δ 2.15 (s, SCH_3), 4.65-4.79 (broad q, H-5′), 4.94-5.11 (m, H-4′), 5.87-6.27 (m, H-2′,3′), 6.65 (d, H-1′, $J_{1',2'}$ = 5.0 Hz), 7.74 (s, H-6).

Anal. Calcd. for $C_{31}H_{26}N_2O_8S_2$: C, 60.18; H, 4.24; N, 4.53; S, 10.37. Found: C, 60.13; H, 4.28; N, 4.59; S, 10.32.

1-(β-D-Ribofuranosyl)-5-(*S*-methyl)mercapto-4-thiouracil (**12β**).

To a solution of sodium methoxide (5.2 mmoles) in methanol (250 ml.) was added **11β** (2.64 g., 4.27 mmoles). After reaction and work-up (see **3β**), **12β** was obtained in a yield of 1.15 g. (87.9%) as yellow crystals (methanol), m.p. 192-194°; $[\alpha]_D^{25}$ +4.55°; uv: similar to **9β**; nmr (DMSO-d_6-deuterium oxide): δ 2.29 (s, 3H, SCH_3), 3.58-3.75 (H-5′, overlapping with a peak of HDO at 3.63), 3.86-4.19 (m, 3H, H-2′,3′,4′), 5.85 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 7.79 (s, 1H, C_6-H).

Anal. Calcd. for $C_{10}H_{14}N_2O_5S_2$: C, 39.21; H, 4.61; N, 9.14; S, 20.93. Found: C, 39.14; H, 4.64; N, 9.20; S, 20.86.

1-(β-D-Ribofuranosyl)-5-(*S*-methyl)mercaptocytosine (**13β**).

A solution of **11β** (3.0 g., 4.85 mmoles) in saturated methanolic ammonia (150 ml.) at 0°, was heated in a stainless steel-bomb at 90° for 20 hours. Evaporation of the reaction mixture gave a syrup which was triturated with ether, yield 1.21 g. (86.2%) of **13β**. Crystallization from anhydrous methanol provided an analytical sample, m.p. 142-144°; $[\alpha]_D^{25}$ +6.73° (*c* 0.54, water); uv: similar to **10β**; nmr (DMSO-d_6-deuterium oxide): δ 2.23 (s, SCH_3), 3.19 (s, H-5′), 4.69-4.89 (m, H-2′,3′,4′), 5.77 (d, H-1′, $J_{1',2'}$ = 3.0 Hz), 8.32 (s, C_6-H).

Anal. Calcd. for $C_{10}H_{15}N_3O_5S$: C, 41.52; H, 5.23; N, 14.52; S, 11.09. Found: C, 41.43; H, 5.26; N, 14.45; S, 11.02.

1-(α-D Ribofuranosyl)-5-(*S*-methyl)mercaptocytosine (**13α**).

A solution of **11α** (0.62 g., 1.0 mmole) in saturated methanolic ammonia (20 ml.) was heated in a steel-bomb at 90° for 20 hours. Concentration of the mixture to ∼1 ml. and trituration with ether afforded 0.237 g. (81.9%) of **13α**. Crystallization from methanol furnished an anaytical product, m.p. 227-229° dec; $[\alpha]_D^{25}$ -31.07 (*c* 0.75, water); uv (water): λ max 281 nm (ε 6,100), 231 (4,100), λ min 259 (3,200); (*p*H 2): λ max 286 (5,500), λ min 249 (2,300); (*p*H 12), λ max 281 (4,100), 232 (6,000), λ min 260 (3,100); nmr (DMSO-d_6-deuterium oxide): δ 2.23 (s, SCH_3), 6.03 (d, H-1′, $J_{1',2'}$ = 4.0 Hz), 7.83 (s, C_6-H).

Anal. Calcd. for $C_{10}H_{15}N_3O_5S$: C, 41.52; H, 5.23; N, 14.52; S, 11.09. Found: C, 41.51; H, 5.30; N, 14.47; S, 11.05.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-(*S*-methyl)mercapto-4-thiouracil (**14β**).

Method A.

A mixture of **4β** (3.7 g., 6.6 mmoles) and phosphorus pentasulfide (4.5 g.) in dioxane (170 ml.) was heated under reflux for 4 hours. Tlc on silica gel with chloroform-ethyl acetate (9:1) showed that the reaction was incomplete. An additional portion of phosphorus pentasulfide (1 g.) was added and refluxing was continued for 3 hours at which time the reaction was still not complete. After cooling to ∼40°, the mixture was poured into ice-water, extracted with chloroform, dried over magnesium sulfate, filtered and evaporated, leaving a syrup. Chromatography on silica gel using benzene followed by benzene-chloroform (1:1) afforded 1.64 g., (43%) of **14β** as a yellow thick-syrup (dried over phosphorus pentoxide *in vacuo*; $[\alpha]_D^{25}$ +69.92° (*c* 2.3, chloroform); nmr (deuteriochloroform): δ 2.13 (s, 3H, SCH_3), 3.75 (broad d, 2H, H-5′), 4.02-4.34 (m, 3H, H-2′,3′,4′), 4.42, 4.54, 4.57 (s, 2′,3′,5′-benzyl-CH_2), 6.27 (d, 1H, H-1′, $J_{1',2'}$ = 4.5 Hz), 7.63 (s, 1H, C_6-H), 9.88 (broad s, 1H, N_3-H).

Anal. Calcd. for $C_{31}H_{32}N_2O_5S_2$: C, 64.56; H, 5.59; N, 4.86; S, 11.12. Found: C, 64.33; H, 5.67; N, 4.75; S, 11.14.

Method B.

To a mixture of phosphorus pentasulfide (3 g.) in boiling pyridine (80 ml.) was added **4β** (2.6 g., 4.64 mmoles), and the mixture refluxed for 7 hours. Chromatography on a column (4 × 10 cm) of silica gel using benzene followed by benzene-chloroform (1:1) afforded 2.11 g. (78.8%) of **14β**.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-(*S*-methyl)mercaptocytosine (**15β**).

A mixture of **14β** (1.6 g., 2.77 mmoles) in saturated methanolic ammonia (40 ml.) was heated at 95° for 20 hours. Evaporation of the mixture was partitioned between chloroform and water. The chloroform layer was dried and evaporated to dryness. A solution of the residue in anhydrous ethanol was cooled to 0° and dry hydrogen chloride gas (calcium chloride tube) was bubbled for 30 seconds. After addition of ether, the solution was stored at ∼ -20° for 7 days to give 0.85 g. (51.5%) of white needles. From the mother liquor an additional 0.39 g. (23.6%, overall yield 75.1%) was obtained. Recrystallization from ethanol-ether afforded pure **15β** as the hydrochloride salt, m.p. 98-100°; $[\alpha]_D^{25}$ +65.5° (*c* 2.0, ethanol); nmr (DMSO-d_6): δ 2.09 (s, SCH_3), 6.23 (d, H-1′, $J_{1',2'}$ = 4.8 Hz), 8.14 (s, C_6-H).

Anal. Calcd. for $C_{31}H_{34}N_3O_5ClS$: C, 62.46; H, 5.75; N, 7.05; S, 5.38. Found: C, 62.41; H, 5.80; N, 7.00; S, 5.33.

Reaction of **15β** with Sodium-Liquid Ammonia.

To a stirred suspension of **15β** (3.0 g., 5.0 mmoles) in liquid ammonia (100 ml. distilled over lithium) sodium (0.49 g.) was added in small portions. After quenching with ammonium chloride (1.1 g.), the mixture was evaporated to dryness. The residue was partitioned between benzene and water. The aqueous phase was lyophilized and the residue treated with hot ethanol and filtered. Evaporation of the filtrate afforded 1.0 g. of crude **16** as pale yellow solid. The nmr spectrum showed the absence of methyl group. The uv spectra showed a λ max (*p*H 9) at 274 nm which shifted to 334 nm upon addition of dithiothreitol, and a λ max (*p*H 2) at 282 nm, indicating the presence of disulfide bond and an amino group, respectively; yield 37%.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)-5-(*S*-methyl)mercaptouracil (**17**).

A mixture of **3β** (3.02 g., 10.4 mmoles), diphenyl carbonate (2.90 g., 13.5 mmoles) and sodium bicarbonate (0.04 g.) in dimethylformamide (10 ml.) was heated at 155° for 40 minutes. After cooling, the mixture was slowly poured under stirring into ether (350 ml.) and filtered. Crystallization from methanol gave 1.91 g. (67.5%) of **17** as needles, m.p. 174-175°; $[\alpha]_D^{25}$ -138.68 (*c* 0.5, water); uv (water): λ max 291 nm (ε 5,100), 253 (5,700), λ min 272 (4,200), 234 (4,200); (*p*H 2): λ max 289 (3,900), 252 (4,500), λ min 270 (3,100), 232 (2,600); (*p*H 12): λ max 283 (4,500), λ min 264 (3,800); nmr (DMSO-d_6-deuterium oxide): δ 2.29 (s, 3H, SCH_3), 3.28 (d, 2H, H-5′), 4.03-4.27 (broad t, 1H, H-4′), 4.42 (broad s, 1H, H-3′), 526 (d, 1H, H-2′), 6.39 (d, 1H, H-1′, $J_{1',2'}$ = 5.5 Hz), 7.57 (s, 1H, C_6-H).

Anal. Calcd. for $C_{10}H_{12}N_2O_5S$: C, 44.11; H, 4.44; N, 10.29; S, 11.78. Found: C, 43.86; H, 4.53; N, 10.19; S, 11.63.

1-(β-D-Arabinofuranosyl)-5-(*S*-methyl)mercaptouracil (**18**).

A mixture of **17** (1.36 g., 5.0 mmoles) and 0.1*N* sodium hydroxide (53 ml.) was stirred for 6 hours at room temperature. The solution was neutralized with Dowex 50 (H^+), filtered, and lyophilized to give 1.37 g. (94.4%) of a chromatographically homogenous foam. Crystallization from methanol provided anaytically pure **18** as white needles, m.p. 197-198°; $[\alpha]_D^{25}$ +48.2 (*c* 0.5, water); uv: similar to **3β**; nmr (DMSO-d_6-deuterium oxide): δ 2.25 (s, SCH_3), 6.04 (d, H-1′, $J_{1',2'}$ = 4.5 Hz), 7.73 (s, C_6-H).

Anal. Calcd. for $C_{10}H_{14}N_2O_6S$: C, 41.38; H, 4.68; N, 9.65; S, 11.05. Found: C, 41.31; H, 4.87; N, 9.57; S, 11.07.

1-(2,3,5-Tri-*O*-acetyl-1-β-D-arabinofuranosyl)-5-(*S*-methyl)mercaptouracil (**19**).

A mixture of **18** (0.52 g., 1.79 mmoles) in pyridine (2 ml.) and acetic anhydride (3 ml.) was stirred at room temperature for 16 hours. The solution was evaporated by co-evaporation with toluene to dryness. Crystallization from 90% ethanol afforded 0.68 g. (91.2%) of **19** as white needles, m.p. 146-147°; $[\alpha]_D^{25}$ +7.2 (*c* 0.5, methylene chloride); nmr (deuteriochloroform): δ 2.05, 2.16, 2.18 (three $COCH_3$), 2.37 (s, SCH_3), 6.30 (d, H-1′, $J_{1',2'}$ = 4.5 Hz), 7.73 (s, C_6-H).

Anal. Calcd. for $C_{16}H_{20}N_2O_9S$: C, 46.15; H, 4.84; N, 6.73; S, 7.70. Found: C, 46.20; H, 4.85; N, 6.72; S, 7.76.

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-(*S*-methyl)mercapto-4-thiouracil (**20**).

Treatment of **19** (3.75 g., 9.0 mmoles) in 1,2-dimethoxyethane (100 ml.) and phosphorus pentasulfide (3.0 g.) as described above for **8α** afforded, after chromatography on silica gel using chloroform-ethyl acetate (1:1), 3.65 g. (93.8%) of **20**. Recrystallization from ethanol provided 3.42 g. (87.9%) of an analytically pure product, m.p. 164-166°; $[\alpha]_D^{25}$ +58.4 (*c* 0.5, methylene chloride); nmr (deuteriochloroform): δ 2.06 (s, $COCH_3$-2′), 2.18 (s, $COCH_3$-3′5′), 2.40 (s, SCH_3), 6.30 (d, H-1′, $J_{1'2'}$ = 4.0 Hz), 7.51 (s, C_6-H).

Anal. Calcd. for $C_{16}H_{20}N_2O_8S_2$: C, 44.44; H, 4.66; N, 6.48; S, 14.83. Found: C, 44.49; H, 4.66; N, 6.46; S, 14.77.

1-(β-D-Arabinofuranosyl)-5-(*S*-methyl)mercapto-4-thiouracil (**21**).

This material was prepared by treatment of **20** (0.87 g., 2.0 mmoles) with sodium methoxide (2.3 mmole) in methanol (115 ml.) as described for **3β**. Crystallization from methanol gave 0.54 g. (88.1%) of **21** as yellow cystals, m.p. 203-205°; $[\alpha]_D^{25}$ + 84.8 (*c* 0.25, water); uv: similar to **9β**; nmr (DMSO-d_6-deuterium oxide): δ 2.29 (s, 3H, -SCH_3), 3.63 (s, HDO), 3.58-3.75 (broad, overlapping with HDO, H-5′), 3.68-4.19 (m, 3H, H-2′,3′,4′), 5.85 (d, 1H, H-1′, $J_{1',2'}$ = 4.0 Hz), 7.79 (s, 1H, C_6-H).

Anal. Calcd. for $C_{10}H_{14}N_2O_5S_2$: C, 39.21; H, 4.61; N, 9.14; S, 20.93. Found: C, 39.28; H, 4.64; N, 9.16; S, 20.91.

1-(β-D-Arabinofuranosyl)-5-(*S*-methyl)mercaptocytosine (**22**).

A solution of **20** (2.03 g., 4.69 mmoles) in saturated methanolic ammonia (50 ml.) was heated to 85° for 20 hours. The reaction mixture was evaporated to dryness. Recrystallization from methanol gave 1.15 g. (84.8%) of **22**, m.p. 222-224° dec; $[\alpha]_D^{25}$ +86.4 (*c* 0.5, water); uv: similar to **10β**; nmr (DMSO-d_6-deuterium oxide): δ 2.21 (s, SCH_3), 6.02 (d, H-1′, $J_{1',2'}$ = 4.5 Hz), 7.89 (s, C_6-H).

Anal. Calcd. for $C_{10}H_{15}N_3O_5S$: C, 41.52; H, 5.23; N, 14.52; S, 11.09. Found: C, 41.76; H, 5.32; N, 14.47; S, 11.06.

1-(β-D-Arabinofuranosyl)-5-(*S*-methyl)mercapto-2-thiouracil (**23**).

Into a mixture of **17** (0.5 g., 1.84 mmoles) and triethylamine (0.6 ml.) in dimethylformamide (0.8 ml.), hydrogen sulfide (dried over phosphorus pentoxide) was introduced for 1 hour at room temperature. The deep green-blue solution was then heated at 85° for 1 hour and at 120° for an additional 3 hours. After cooling, the mixture was precipitated by trituration with ether to give a gum which was dissolved in hot water, treated with Darco G-60, filtered and evaporated to dryness. The solid was triturated with water (2 ml.) to give 0.27 g. (45.2%) of a chromatographically homogenous product. Recrystallization from water provided an analytical sample of **23** as white needles, m.p. 199-201°; $[\alpha]_D^{25}$ +12.64 (*c* 0.53, water); uv (water): λ max 293 nm (ε 12,400), λ min 252 (3,500); (*p*H 2): λ max 293 (12,500), λ min 253 (3,600), (*p*H 12): λ max 280 (15,200), 249 (14,700), λ min 262 (11,800); nmr (DMSO-d_6-deuterium oxide): δ 2.29 (s, SCH_3), 6.80 (d, H-1′, $J_{1',2'}$ = 4.5 Hz), 7.63 (s, C_6-H).

Anal. Calcd. for $C_{10}H_{14}N_2O_5S_2 \cdot H_2O$: C, 37.03; H, 4.97; N, 8.64; S, 19.77. Found: C, 37.14; H, 4.97; N, 8.67; S, 19.80.

REFERENCES AND NOTES

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