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5-Benzylthio-1,2-dihydro-2-oxypyrazine (**8**) was prepared from 2-amino-5-bromopyrazine by sequential treatment with sodium thiobenzylate and diazotization. Condensation of the silyl derivative of **8** with a protected 2-deoxyribofuranosyl chloride gave  $\alpha$  and  $\beta$  anomers of 5-benzylthiopyrazine nucleosides. Reaction of 2,5-dichloropyrazine 4-oxide with sodium thiobenzylate followed by hydrolysis gave 5-benzylthio-1,2-dihydro-2-oxypyrazine 4-oxide (**16**).

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### Introduction.

Pyrazine analogs of uridine [1], 2'-deoxyuridine [2], and inosine [3] have been synthesized and it has been shown that some of these compounds have pronounced antibacterial activity but are essentially inactive against leukemia L1210 cells. In contrast, a pyrazine analog of cytidine [4] showed moderate activity as a cytostatic (L1210) agent while that of thymidine [5] demonstrated the reverse selectivity, being weakly active against bacterial cells but significantly active against leukemia L1210 *in vitro* and *in vivo*. Because of the significant antitumor activity of the pyrazine analog of thymidine and the fact that 5-mercapto-2'-deoxyuridine, as an analog, was found to be a potent inhibitor of the bacterial [6] and tumor [7] cells growth, it was of interest to synthesize 5-thio-substituted pyrazines as potential analogs of thymidine.

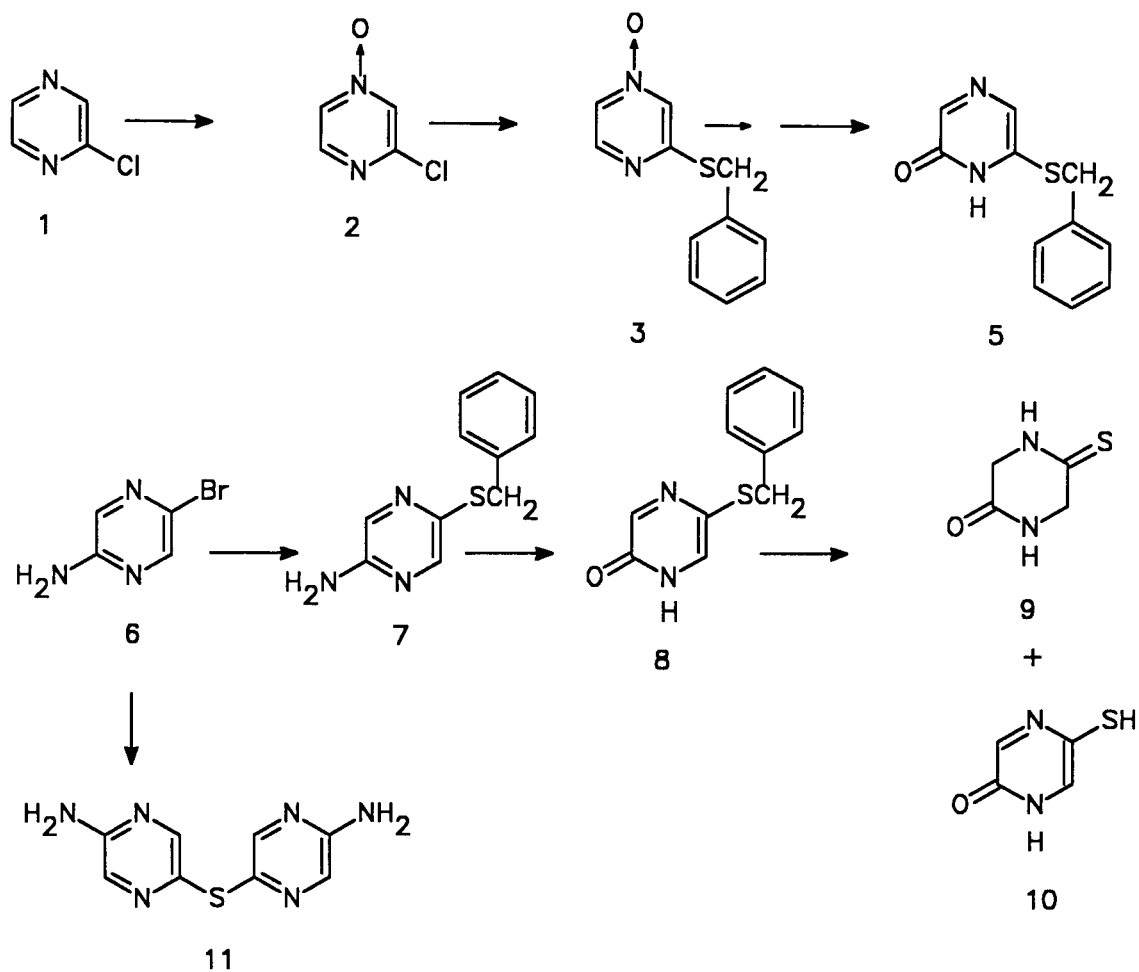
### Chemistry.

For the synthesis of protected 5-thio derivatives of 1,2-dihydro-2-oxypyrazines, we elected displacement of halogens in appropriately substituted halogenopyrazines with sodium benzylthiolate to introduce the thio substituent into the pyrazine ring (Scheme 1). Oxidation of 2-chloropyrazine (**1**) with *m*-chloroperbenzoic acid in 1,2-dichloroethane gave 2-chloropyrazine 4-oxide (**2**). Nucleophilic displacement of chlorine in **2** has been shown to proceed readily with various nucleophiles [8]. Thus, treatment of **2** with benzylthiolate gave 2-benzylthiopyrazine 4-oxide (**3**). Rearrangement of pyrazine *N*-oxides with acetic anhydride followed by hydrolysis of the intermediate acetoxy derivatives has been a useful method for the synthesis of hydroxypyrazines [9,10]. This method can lead to isomeric hydroxypyrazines [11]. However, treatment of **3** with boiling acetic anhydride followed by hydrolysis with aqueous sodium hydroxide gave a single product. The pmr spectrum of this product, which indicated the presence of a

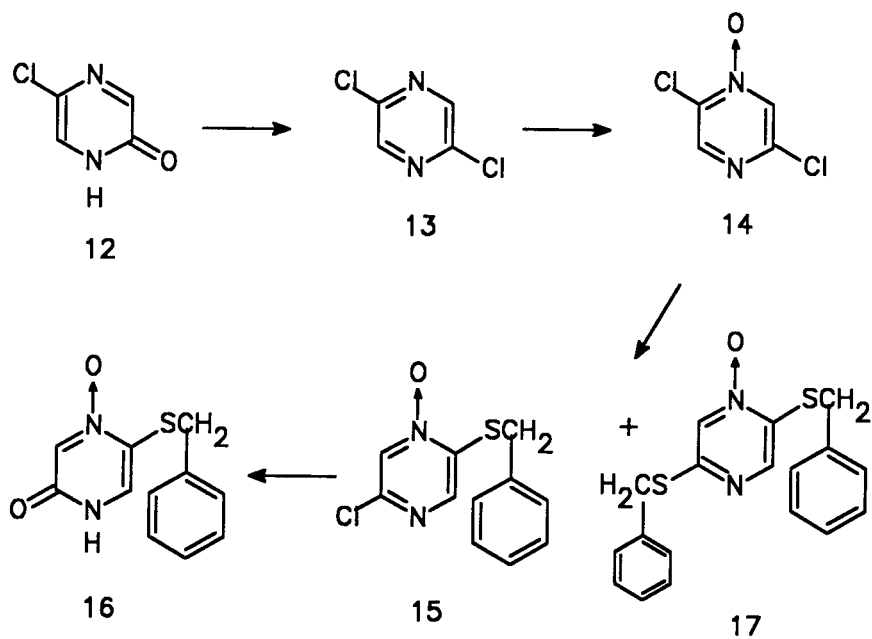
benzyl group and two additional aromatic protons appearing as singlets, was consistent with two isomeric structures **5** and **8**. Its structure was confirmed as **5** by an unambiguous synthesis of the isomeric 5-benzylthio-1,2-dihydro-2-oxypyrazine (**8**) as shown in Scheme 1. Thus, replacement of bromine in 2-amino-5-bromopyrazine (**6**) with benzylthiolate gave 2-amino-5-benzylthiopyrazine (**7**), and diazotization of **7** yielded 5-benzylthio-1,2-dihydro-2-oxypyrazine (**8**). The pmr spectrum of **8**, which showed the presence of a benzyl group and two aromatic protons appearing as singlets differed from that of **5** in the chemical shifts of the signals. The ir spectrum of **8** showed an absorption at  $1650\text{ cm}^{-1}$  (amide C=O) while that of **5** showed a broad peak at  $1750\text{ cm}^{-1}$ . Silylation of **8** (Scheme 3) gave 2-(trimethylsilyloxy)-5-benzylthiopyrazine (**18**), in 94% yield, which was purified by vacuum distillation. Condensation of **18** with 2-deoxy-3,5-di-*O*-*p*-chlorobenzoyl- $\alpha$ -D-ribofuranosyl chloride furnished an anomeric mixture of blocked nucleosides **19a** and **20a** which were separated by fractional crystallization. Deblocking of **19a** and **20a** with methanolic ammonia gave 5-benzylthio-1-(2-deoxy- $\beta$ -D-ribofuranosyl)-1,2-dihydro-2-oxypyrazine (**19b**) and the corresponding  $\alpha$ -anomer **20b**, respectively. The anomeric configurations of **19b** and **20b** were assigned on the basis of the patterns [12] of the pmr signals for the anomeric protons. Thus, the signal for H-1' appeared as a quartet for the  $\alpha$ -anomer while that for the  $\beta$ -anomer appeared as a triplet.

Removal of the benzyl group from **20b** was attempted by treatment with sodium in liquid ammonia at  $-78^\circ$ . However, the pmr spectrum of the product did not show the presence of aromatic protons, indicating that reduction of the pyrazine ring had also occurred. As a potential method for removal of benzyl groups from benzylthiopyrazines, the treatment with sodium in liquid ammonia was studied in some detail with compound **8** (Scheme 1) which lacks

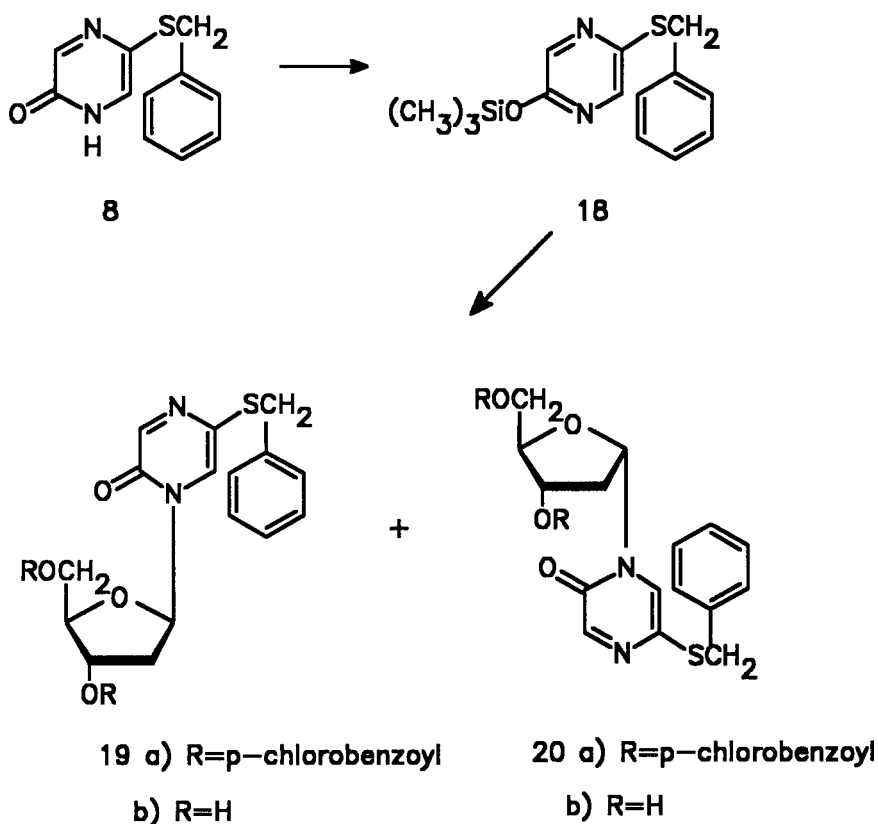
Scheme 1



Scheme 2



Scheme 3



the complexity of **20b**. At  $-78^{\circ}$  and with 1:5 mole-equivalent ratio between **8** and sodium, the only product isolated was 2-oxo-1,2,4,5-tetrahydro-5-thiopyrazine (**9**). Reduction of **8** using ratio of 1:3 gave a mixture of the starting material **8** and a more polar product, as indicated by tlc on silica gel. The uv spectrum of this product showed maxima at 238 and 325 nm and the ir spectrum showed peaks at 3300 (br, NH) and  $1650\text{ cm}^{-1}$  (amide C=O), which was consistent with the debenzylated product **10** (Scheme 1). However, the extremely low yield did not permit further characterization of this product. Further lowering the ratio of sodium to **8** to 2:1 gave similar results and the method was, therefore, abandoned. To avoid the reduction of the pyrazine ring, an alternative procedure for the synthesis of **10**, using sodium hydrosulfide for the displacement of bromine in **6**, was attempted. Treatment of **6** with two equivalents of sodium hydrosulfide in dimethylformamide at room temperature for 16 hours or at  $100^{\circ}$  for 50 hours failed to give a displacement product. Reaction of **6** with two equivalents of sodium hydrosulfide in dimethylformamide at the reflux temperature for 24 hours gave a mixture of the starting material and bis-(2-aminopyrazine) 5-sulfide (**11**). Treatment of **6** with sodium thioacetate in dimethylformamide at room temperature or at the reflux temperature led only to recovery of the starting material.

Synthesis of the corresponding *N*-oxide derivatives was carried out as outlined in Scheme 2. Refluxing 5-chloro-1,2-dihydro-2-oxypyrazine with excess phosphoryl chloride gave 2,5-dichloropyrazine (**13**) in 9% yield, as reported [13]. However, a much improved yield of **13** (69%) was obtained when the reaction was carried out in a sealed tube at  $130^{\circ}$ . Oxidation of **13** with *m*-chloroperbenzoic acid or hydrogen peroxide in acetic acid gave 2,5-dichloropyrazine 1-oxide (**14**) in very low yield, presumably as a result of deactivation of the pyrazine nitrogen by two chloro substituents. But a stronger oxidation reagent, hydrogen peroxide in trifluoroacetic acid, reacted with **13** to afford compound **14** in 72% yield. The *N*-oxide function has been shown to facilitate selective displacement reactions [14,15] of the pyrazine ring at the position adjacent to the *N*-oxide. Treatment of compound **14** with sodium benzylthioate gave 2-benzylthio-5-chloropyrazine 1-oxide in 75% yield. A trace amount of 2,5-dibenzylthiopyrazine 1-oxide (**17**) was isolated by chromatography. Hydrolysis of **15** with aqueous sodium hydroxide afforded 5-benzylthio-1,2-dihydro-2-oxypyrazine 4-oxide (**16**) in 65% yield. Attempts at the removal of the benzyl group in **16** using 10 *N* hydrochloric acid, hydrogen bromide-trifluoroacetic acid, or mercuric chloride-2 *N* hydrochloric acid were not successful.

## EXPERIMENTAL

All melting points, taken in open capillary tubes in a Mel-Temp apparatus, and boiling points are uncorrected. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer using potassium bromide pellets. The nmr spectra were recorded on a Varian A-60 spectrometer and are reported in ppm downfield from TMS internal standard. The uv spectra were recorded on a Beckman DBG. Optical rotations were measured in a 10 cm tube with a Perkin-Elmer 141 polarimeter at 589 nm. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

## 2-Chloropyrazine 4-Oxide (2).

2-Chloropyrazine (1) (5.73 g, 0.05 mole) was dissolved in dry 1,2-dichloroethane (138 ml). To this solution, 85% *m*-chloroperbenzoic acid (13.8 g, 0.06 mole) was added in small portions with stirring. The reaction mixture was sequentially heated at 60° for 24 hours, cooled to room temperature, and cooled in an ice bath to precipitate *m*-chlorobenzoic acid which was filtered and washed with methylene chloride (2 x 15 ml). The combined filtrate was evaporated to dryness. The residue was suspended in methylene chloride (50 ml), filtered, and washed with methylene chloride (15 ml). The filtrate was washed with saturated sodium bicarbonate solution (2 x 75 ml) and with water (75 ml). The sodium bicarbonate solution and the water wash were each extracted with chloroform (6 x 60 ml). The combined methylene chloride filtrate and the chloroform extracts were dried (sodium sulfate) and evaporated *in vacuo* to give 6.43 g (99%) of crude 2 which was crystallized from ethanol (50 ml) to give 4.2 g of pure product. The mother liquor was evaporated to dryness. The slightly yellow residue was subjected to dry column chromatography on 200 g of silica gel using chloroform (200 ml) as eluent. The band corresponding to the product was extracted with dichloromethane-methanol (150 ml, 1:1). Removal of the solvent gave an additional 1.6 g of pure 2. The total yield was 5.8 g (89%), mp 93.0-94.5°; <sup>1</sup>H nmr (deuteriochloroform): δ 7.97 (q, J = 1.5 and 4.0 Hz, 1H), 8.07-8.28 (overlapping, m, 2H).

## 2-Benzylthiopyrazine 4-Oxide (3).

Sodium (2.92 g, 0.13 g-atom) was dissolved in absolute ethanol (150 ml) and the clear solution was evaporated to dryness. The residue was dissolved in dry DMF (450 ml) and the solution was stirred for 10 minutes. Benzylmercaptan (14.1 ml, 0.12 mole) was added to this mixture followed by 2 (15.5 g, 0.12 mole) which was added in small portions with stirring. The yellow suspension was stirred at room temperature for 48 hours and evaporated *in vacuo* to dryness. The yellow residue was suspended in chloroform (250 ml), filtered and washed with chloroform (50 ml). Removal of the solvent gave a yellow residue which was crystallized from absolute methanol to yield 22.4 g (86%) of light yellow crystals. A portion of the crystals was recrystallized twice from ethanol to give pure 3, mp 114-115°; uv (methanol): λ max (log ε), 262 nm (4.11), 338 nm (3.39); ir (potassium bromide): ν max 1270, 840 cm<sup>-1</sup> (N - O); <sup>1</sup>H nmr (deuteriochloroform): δ 4.42 (s, 2H), 7.30 (s, 5H), 7.75 (q, J = 1.0 and 4.0 Hz, 1H), 7.93 (d, J = 1 Hz, 1H), 8.20 (d, J = 4.0 Hz, 1H).

*Anal.* Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>SO: C, 60.53; H, 4.62; N, 12.83; S, 14.69; O, 7.33. Found: C, 60.46; H, 4.61; N, 12.75; S, 14.78.

## 6-Benzylthio-1,2-dihydro-2-oxopyrazine (5).

A mixture of 2-benzylthiopyrazine 4-oxide (3) (10.4 g, 0.048 mole) and acetic anhydride (100 ml) was refluxed for 1 hour. The reaction mixture was cooled to room temperature and evaporated *in vacuo* to give a brown syrup. A portion (0.225 g) of this syrup was chromatographed on preparative tlc plates (silica gel, 20 x 20 cm), developed twice with methylene chloride. The band corresponding to 2-*O*-acetyl-6-benzylthiopyrazine was extracted with dichloromethane-methanol (100 ml, 1:1). After removal of the solvent by evaporation, the brown syrup was taken up into chloroform, filtered and evaporated to afford 0.09 g of 2-*O*-acetyl-6-benzylthiopyrazine; <sup>1</sup>H nmr (deuteriochloroform): δ 2.32 (s, 3H), 4.33 (s, 2H), 7.23 (s, 5H), 8.00 (s, 1H). Aqueous sodium hydroxide (2*N*, 50 ml) was added to the remaining brown syrup and the mixture was refluxed for 1 hour. The brown solution was cooled to room temperature and neutralized with concentrated hydrochloric acid. The yellow precipitate was filtered and crystallized from 25% aqueous ethanol to yield 5 (5.5 g, 52%) as pale yellow crystals, mp 161-162°; uv (methanol): λ max (log ε), 330 nm (3.94), 245 nm (3.76); ir (potassium bromide): ν max 1750 cm<sup>-1</sup> (amide, C=O); <sup>1</sup>H nmr (DMSO-*d*<sub>6</sub>): δ 4.37 (s, 2H), 7.28 (s, 5H), 7.72 (s, 1H), 7.85 (s, 1H), 11.70 (broad, 1H).

The analytical sample was obtained by recrystallization of 5 from water.

*Anal.* Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>SO: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.51; H, 4.66; N, 12.88; S, 14.76.

## 2-Amino-5-benzylthiopyrazine (7).

Sodium metal (1.77 g, 0.08 g-atom) was dissolved in absolute ethanol (100 ml) and the solution was evaporated to a white residue which was dissolved in dry DMF (300 ml). Benzylmercaptan (6.44 ml, 0.08 mole) was added to this solution and after stirring for 5 minutes, 2-amino-5-bromopyrazine [16] (6) (10.0 g, 0.06 mole) was added and the mixture was stirred at room temperature for 48 hours. It was evaporated to dryness and the residue was extracted with chloroform. Upon removal of chloroform, a brown residue was obtained which was separated by dry column chromatography on silica gel using 30:1 chloroform-ethyl acetate as the eluent. The band corresponding to the product was extracted with 1:1 methylene chloride-methanol to give, after removal of the solvent, 11.0 g (93%) of a brown solid. This solid was crystallized from 1:1 benzenecyclohexane to yield 10.3 g of crystals, mp 66-69°; uv (methanol): λ max (log ε), 261 nm (4.09), 347 nm (3.64); ir (potassium bromide): ν max 3320 cm<sup>-1</sup> (broad, NH<sub>2</sub>); <sup>1</sup>H nmr (deuteriochloroform): δ 4.20 (s, 2H), 4.50 (broad, 2H), 7.20 (s, 5H), 7.83 (s, 2H).

The analytical sample (mp 72-74°) was obtained by recrystallization of the product (mp 66-69°) from ethanol.

*Anal.* Calcd. for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>S: C, 60.80; H, 5.10; N, 19.34. Found: C, 60.74; H, 5.14; N, 19.25.

## 5-Benzylthio-1,2-dihydro-2-oxopyrazine (8).

To a suspension of 2-amino-5-benzylthiopyrazine (7) (6.0 g, 0.03 mole) in cold (5°) 50% aqueous acetic acid (60 ml) was added dioxane to obtain a clear solution to which a cold (5°) solution of sodium nitrite (2.4 g, 0.03 mole) in 50% aqueous acetic acid (60 ml) was added dropwise with stirring. After stirring for 10 minutes, the mixture was neutralized with 4*N* sodium hydroxide. The precipitate was filtered and crystallized from water to give 8 (2.8 g, 46%) as slightly yellow needles, mp 125-126°; uv (methanol): λ max (log ε), 243 (3.91), 260 (3.99), 342 (3.53); ir (potassium

bromide):  $\nu$  max 1650  $\text{cm}^{-1}$  (amide, C=O);  $^1\text{H}$  nmr (DMSO- $d_6$  + deuterium oxide):  $\delta$  4.12 (s, 2H), 7.19 (s, 5H), 7.42 (s, 1H), 7.93 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{SO}$ : C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.42; H, 4.65; N, 12.84; S, 14.77.

5-Benzylthio-1-(3,5-di-*O-p*-chlorobenzoyl-2-deoxy- $\beta$ -D-ribofuranosyl)-1,2-dihydro-2-oxypyrazine (**19a**) and 5-Benzylthio-1-(3,5-di-*O-p*-chlorobenzoyl-2-deoxy- $\alpha$ -D-ribofuranosyl)-1,2-dihydro-2-oxypyrazine (**20a**).

5-Benzylthio-1,2-dihydro-2-oxypyrazine (**8**) (2.7 g, 0.012 mole) was refluxed in hexamethyldisilazane (30 ml) with a catalytic amount of ammonium sulfate for 1.5 hours. The resulting clear solution was evaporated to give a thick liquid which was distilled at 143°/0.05 mm Hg to give 3.36 g (93%) of 5-benzylthio-2-(trimethylsilyloxy)pyrazine (**18**);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  0.35 (s, 9H), 4.27 (s, 2H), 7.20 (s, 5H), 7.81 (d, J = 1 Hz, 1H), 7.95 (d, J = 1 Hz, 1H). The silyl derivative **18** (3.3 g, 0.011 mole) was condensed with 2-deoxy-3,5-di-*O-p*-chlorobenzoyl- $\alpha$ -D-ribofuranosyl chloride (2.52 g, 0.006 mole) at 95-110°/0.05 mm Hg for 20 minutes. The initial bubbling stopped after about 5 minutes. The resulting brown syrup was dissolved in benzene-methanol (40:4) and the solvent was evaporated. The syrupy residue, which solidified upon cooling, was chromatographed on a dry column of silica gel (350 g) using chloroform-ethyl acetate (30:1, 350 ml) as the eluent. The band corresponding to the product was extracted with dichloromethane-methanol (1:1). The solvent was removed and the residue was dissolved in chloroform. The solution was filtered and evaporated *in vacuo* to give 2.5 g (70%) of a slightly yellow solid. This product, which was a mixture of anomers and showed only one spot on tlc using several solvent systems, was separated by crystallization from methanol-acetone (1:1, 150 ml) to give 0.78 g of 5-benzylthio-1-(3,5-di-*O-p*-chlorobenzoyl-2-deoxy- $\alpha$ -D-ribofuranosyl)-1,2-dihydro-2-oxypyrazine (**20a**). The mother liquor was evaporated; the residue was dissolved in hot acetone (25 ml) and treated with methanol (125 ml) until the solution was turbid. The mixture was kept in the refrigerator overnight. Additional **20a** (0.82 g) separated and was collected. The total yield of the  $\alpha$ -anomer (**20a**) was 1.52 g. Yellow crystals, which formed in the filtrate during filtration, were collected and dried to give 0.43 g of 5-benzylthio-1-(3,5-di-*O-p*-chlorobenzoyl-2-deoxy- $\beta$ -D-ribofuranosyl)-1,2-dihydro-2-oxypyrazine (**19a**). A portion (0.82 g) of the  $\alpha$ -anomer **20a** was recrystallized twice from methanol-acetone (1:1) to give 0.60 g of slightly yellow crystals, mp 157-158.5°; uv (chloroform):  $\lambda$  max (log  $\epsilon$ ), 253 nm (4.59), 356 nm (3.47);  $[\alpha]_D^{25} = -99.8^\circ$  (c 0.53, chloroform); ir (potassium bromide):  $\nu$  max 1720 (ester, C=O), 1640  $\text{cm}^{-1}$  (amide, C=O);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  6.22 (pseudoquartet, J = 6.0 and 1.0 Hz,  $\text{W}_{\text{HI}'} = 13.0$  Hz,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{30}\text{H}_{24}\text{N}_2\text{SCl}_2\text{O}_6$ : C, 58.93; H, 3.96; N, 4.58; S, 5.24; Cl, 11.60. Found: C, 58.81; H, 3.98; N, 4.57; S, 5.31; Cl, 11.66.

A portion (0.35 g) of the  $\beta$ -anomer **19a** was crystallized twice from methanol-acetone (25:4) to yield 0.29 g of yellow needles, mp 127-128°; uv (chloroform):  $\lambda$  max (log  $\epsilon$ ), 253 nm (4.53), 355 nm (3.38);  $[\alpha]_D^{25} = +22.1^\circ$  (c 0.70, chloroform); ir (potassium bromide):  $\nu$  max 1720 (ester, C=O), 1650  $\text{cm}^{-1}$  (amide, C=O);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  6.25 (t, J = 6.5 Hz,  $\text{W}_{\text{HI}'} = 18.0$  Hz,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{30}\text{H}_{24}\text{N}_2\text{SCl}_2\text{O}_6$ : C, 58.93; H, 3.96; N, 4.58; S,

5.24; Cl, 11.60. Found: C, 58.90; H, 3.97; N, 4.56; S, 5.31; Cl, 11.71.

5-Benzylthio-1-(2-deoxy- $\alpha$ -D-ribofuranosyl)-1,2-dihydro-2-oxypyrazine (**20b**).

The blocked nucleoside **20a** (0.5 g, 0.0008 mole) in dry methanol (50 ml), presaturated with ammonia at 0°, was stirred at 5° for 28 hours. The clear solution was evaporated to a slightly yellow residue which was separated by preparative tlc on alumina. The chromatograms were developed with ethyl acetate and subsequently with ethyl acetate-methanol (40:7). The bands were extracted with methanol and the residue obtained after removal of methanol was extracted with ether (50 ml). The ether extract was filtered and kept in the refrigerator overnight. Compound **20b** separated as white crystals (0.166 g, 61%), mp 90-92°; uv (methanol):  $\lambda$  max (log  $\epsilon$ ), 260 nm (4.04), 357 nm (3.34);  $[\alpha]_D^{25} = -114.3^\circ$  (c 0.28, methanol); ir (potassium bromide):  $\nu$  max 3380 (broad, OH), 1650  $\text{cm}^{-1}$  (amide, C=O);  $^1\text{H}$  nmr (DMSO- $d_6$  + deuterium oxide):  $\delta$  6.05 (pseudoquartet, J = 6.0 and 1.0 Hz,  $\text{W}_{\text{HI}'} = 13.0$  Hz,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{SO}_4$ : C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.50; H, 5.42; N, 8.32; S, 9.60.

5-Benzylthio-1-(2-deoxy- $\beta$ -D-ribofuranosyl)-1,2-dihydro-2-oxypyrazine (**19b**).

Starting with the blocked nucleoside **19a** (0.25 g, 0.0004 mole) and following the procedure for the preparation of the  $\alpha$ -anomer **20b**, free nucleoside **19b** was obtained as a thick syrup (0.119 g, 87%); ir (neat, sodium chloride):  $\nu$  max 3400 (broad, OH), 1640  $\text{cm}^{-1}$  (amide, C=O);  $^1\text{H}$  nmr (DMSO- $d_6$  + deuterium oxide):  $\delta$  6.12 (t, J = 6.5 Hz,  $\text{W}_{\text{HI}'} = 18.0$  Hz,  $\text{H}_1$ ).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{18}\text{N}_2\text{SO}_4$ : C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.65; H, 5.50; N, 8.24; S, 9.42.

Debenzylation of 5-Benzylthio-1,2-dihydro-2-oxypyrazine (**8**) by Sodium-Liquid Ammonia Reduction.

5-Benzylthio-1,2-dihydro-2-oxypyrazine (**8**) (0.0048 mole) 1.0 g, was suspended in 30 ml of liquid ammonia at -76° and sodium (0.06 g, 0.026 g-atom) was added in small pieces with vigorous stirring. Stirring was continued for 1 hour, ammonium chloride (0.15 g) was added and ammonia was allowed to evaporate at room temperature. The residue was dissolved in water (5 ml), neutralized with 2N hydrochloric acid and evaporated. The ethanolic extract of the residue was evaporated to give 0.5 g of a yellow residue which was separated by preparative tlc on silica gel using ethyl acetate-methanol (4:1) as the developing solvent. Only one band was visible under uv light. The band was extracted with dichloromethane-methanol (1:1). Removal of the solvent gave 0.38 g of 1,2,4,5-tetrahydro-2-oxo-5-thiopyrazine (**9**), mp 262-264°; uv (methanol):  $\lambda$  max (log  $\epsilon$ ), 279 nm (4.09); ir (potassium bromide):  $\nu$  max 3220 (broad, NH), 1650  $\text{cm}^{-1}$  (amide, C=O);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  3.78 (s, 2H), 4.13 (s, 2H), 8.20 (broad, 1H), 10.54 (broad, 1H).

*Anal.* Calcd. for  $\text{C}_6\text{H}_6\text{N}_2\text{SO}$ : C, 36.91; H, 4.65; N, 21.52; S, 24.63. Found: C, 36.79; H, 4.70; N, 21.37; S, 24.63.

The reaction was repeated, however, a smaller quantity of sodium was used. When the mole-equivalent ratio of **8** to sodium was 1:3, tlc of the ethanolic extract obtained from the reaction mixture indicated the presence of **8** and **9**, and a slow moving

component **10**. Preparative tlc of the extract on silica gel using chloroform-methanol (4:1) as the developing solvent gave a very small quantity of **10**. In methanol, **10** had uv maxima at 325 and 238 nm. The ir spectrum showed peaks at 3300 and 1650  $\text{cm}^{-1}$ . Similar results were obtained when a 1:2 ratio of **8** to Na was used.

Reaction of 2-Amino-5-bromopyrazine (**6**) [16] with Sodium Hydrosulfide.

Sodium (0.136 g, 0.006 g-atom) was dissolved in absolute ethanol (10 ml) and the solvent was evaporated. The residue was dissolved in DMF (20 ml) and the solution was saturated with hydrogen sulfide gas at 0°. The mixture was warmed to room temperature, **6** (0.5 g, 0.003 mole) was added with stirring, and the stirring was continued at room temperature for 16 hours. Thin-layer chromatography of the reaction mixture indicated that only starting material **6** was present. The mixture was, therefore, heated at 100° for 50 hours. Thin-layer chromatography of the mixture still indicated the presence of **6**. After removal of the solvent, the residue was crystallized from water-ethanol (40:6) to recover 0.42 g of **6**.

The reaction was repeated, however, the reaction mixture was refluxed for 24 hours. After the mixture was cooled to room temperature, the solvent was removed *in vacuo* and the residue was separated by preparative tlc on silica gel using chloroform-methanol (4:1) as the developing solvent. The faster moving band gave 0.15 g of the starting material **6** and the slower moving band gave 0.175 g of yellow crystals, mp 246-247.5°; uv (methanol):  $\lambda$  max (log  $\epsilon$ ), 267 nm (4.30), 342.5 nm (3.94); ir (potassium bromide):  $\nu$  max 3340, 3320  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  6.62 (s, 4H), 7.83 (s, 2H), 7.92 (s, 2H).

The yellow crystals were identified as *bis*-(2-aminopyrazine) 5-sulfide (**11**).

Anal. Calcd. for  $\text{C}_8\text{H}_8\text{N}_6\text{S}$ : C, 43.62; H, 3.66; N, 38.16; S, 14.55. Found: C, 43.28; H, 3.65; S, 14.30.

### 2,5-Dichloropyrazine (**13**).

The procedure of Palamidessi and Bernardi [13] was followed for the synthesis of 2,5-dichloropyrazine (**13**). Compound **12** (2.0 g, 0.015 mole) was suspended in 30 ml of phosphoryl chloride and refluxed for 2 hours. After cooling to room temperature, the mixture was carefully poured onto 300 g of crushed ice to destroy the excess phosphoryl chloride. The aqueous solution was extracted with methylene chloride. The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of methylene chloride afforded 0.205 g (9%) of **13**. The aqueous layer was evaporated to a small volume (~100 ml) and extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and evaporated to recover 1.3 g of the starting material **12**.

The above reaction was repeated, however, the suspension was heated at 130° in a sealed tube for 6 hours. After work-up, 1.7 g of crude product **13** was obtained. The crude product was separated by column chromatography on silica gel, using chloroform as eluent. Fractions (~25 ml each) number 3 through 6 were collected. Removal of chloroform afforded 1.53 g (69% yield) of pure **13** as colorless liquid;  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  8.32 (s).

### 2,5-Dichloropyrazine 1-Oxide (**14**).

#### 1. Oxidation with *m*-Chloroperbenzoic Acid.

2,5-Dichloropyrazine (**13**) (0.44 g, 0.003 mole) was dissolved in dry 1,2-dichloroethane (20 ml) and 85% *m*-chloroperbenzoic acid (0.68 g) was added with stirring to this solution. The mixture was heated at 95° (bath temperature) for 13 hours. The reaction solution was cooled to room temperature and kept in the refrigerator overnight. *m*-Chlorobenzoic acid was filtered and the filtrate was washed with saturated sodium bicarbonate solution (2 x 15 ml) and water (1.5 ml). The sodium bicarbonate and water washes were extracted with chloroform (3 x 20 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and evaporated to give 0.38 g of a yellow syrup. The syrup was separated by preparative tlc on silica gel using chloroform as the developing solvent. The band corresponding to the product was extracted with dichloromethane-methanol (1:1). Removal of the solvent gave 0.098 g (20%) of a slightly yellow solid which was crystallized from aqueous methanol to give 0.061 g of white crystals, mp 99-101°; uv (methanol):  $\lambda$  max (log  $\epsilon$ ), 241 nm (4.16), 276 nm (3.96), 315 nm (3.24); ir (potassium bromide):  $\nu$  max 1260, 850  $\text{cm}^{-1}$  (N → O);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  8.29 (s, 1H), 8.42 (s, 1H).

Anal. Calcd. for  $\text{C}_4\text{H}_2\text{N}_2\text{Cl}_2\text{O}$ : C, 29.12; H, 1.22; N, 16.98; Cl, 42.98. Found: C, 29.15; H, 1.25; N, 16.89; Cl, 42.81.

#### 2. Oxidation with Hydrogen Peroxide in Acetic Acid.

2,5-Dichloropyrazine (**13**) (0.171 g, 0.001 mole) was dissolved in glacial acetic acid (3 ml). To this solution, 30% hydrogen peroxide (0.45 ml) was added with stirring and the mixture was heated at 75-85° for 44 hours. The solution was cooled to room temperature and evaporated to give 0.013 g (7%) of **14**.

#### 3. Oxidation with Hydrogen Peroxide in Trifluoroacetic Acid.

Hydrogen peroxide (30%, 1.1 ml) was added with stirring to a mixture of **13** (1.18 g, 0.008 mole) in trifluoroacetic acid (25 ml). The solution was heated at 65° for 3 hours, cooled to room temperature, and evaporated to remove excess trifluoroacetic acid. The residue was suspended in saturated sodium bicarbonate solution (15 ml) and the mixture was extracted with chloroform. The chloroform extract was washed with water and dried (magnesium sulfate). Chloroform was evaporated and the crude product (1.16 g) was separated by dry column chromatography on silica gel using chloroform-acetone (30:1). The band corresponding to the product was extracted with dichloromethane-methanol (1:1). After removal of the solvent, the residue was dissolved in methylene chloride, filtered, and evaporated to give 0.95 g (72%) of pure **14**.

#### 2-Benzylthio-5-chloropyrazine 1-Oxide (**15**) and 2,5-Dibenzylthiopyrazine 1-Oxide (**17**).

Sodium (0.151 g, 0.007 g-atom) was dissolved in absolute ethanol (20 ml), the clear solution was evaporated, and the residue was dissolved in dry DMF (40 ml). After stirring for a few minutes, benzylmercaptan (0.72 g, 0.68 ml, 0.006 mole) was added, the mixture was stirred for 5 minutes and **14** (0.95 g, 0.006 mole) was added. Stirring was continued for 1 hour at room temperature, the solvent was removed *in vacuo*, and the residue was separated by dry column chromatography on silica gel using chloroform-acetone (30:1) as the eluent. The band corresponding to the product was divided into 3 parts. The top third, 0.47 g, was shown to be a mixture of **15** and 2,5-dibenzylthiopyrazine 1-oxide (**17**). The middle and bottom bands gave 0.78 g of a white residue showing the expected spectra and analysis of compound **15** (see below).

The mixture of **15** and **17** (0.47 g) was separated by preparative tlc on silica gel using chloroform-acetone (30:1) as the developing solvent. The upper band gave 0.09 g of **17** and the lower band yielded 0.36 g of **15**.

The total yield of **15** was 1.14 g (75%). The white residue of **15** was crystallized from methanol, mp 141-143°; uv (methanol):  $\lambda$  max (log  $\epsilon$ ), 255 nm (4.32), 278 nm (4.09), 353 nm (3.32); ir (potassium bromide):  $\nu$  max 1250, 830  $\text{cm}^{-1}$  (N  $\rightarrow$  O);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  4.25 (s, 2H), 7.32 (s, 5H), 8.08 (s, 1H), 8.14 (5, 1H).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_9\text{N}_2\text{SClO}$ : C, 52.29; H, 3.59; N, 11.08; S, 12.69; Cl, 14.03. Found: C, 52.25; H, 3.61; N, 11.16; S, 12.76; Cl, 13.97.

The yield of **17** was 0.09 g, mp 164-166°; uv (methanol):  $\lambda$  max (log  $\epsilon$ ), 260 nm (4.25), 278 nm (4.40), 369 nm (3.64); ir (potassium bromide):  $\nu$  max 1250, 870  $\text{cm}^{-1}$  (N  $\rightarrow$  O);  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  4.22 (s, 2H), 4.32 (s, 2H), 7.28 (s, 5H), 8.00 (s, 1H), 8.13 (s, 1H).

To obtain an analytical sample, **17** was crystallized from methanol-chloroform.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{S}_2\text{O}$ : C, 63.50; H, 4.74; N, 8.23; S, 18.84. Found: C, 63.66; H, 4.79; N, 8.21; S, 18.91.

#### 5-Benzylthio-1,2-dihydro-2-oxopyrazine 4-Oxide (**16**).

Compound **15** (0.218 g, 0.0009 mole) was suspended in a solution of sodium hydroxide (0.046 g, 0.00012 mole) in water (10 ml) and the suspension was refluxed for 1.5 hours. While still hot, the mixture was filtered. The filtrate was cooled to room temperature and neutralized with 2 *N* hydrochloric acid to give a yellow precipitate. The precipitate was separated by preparative tlc on silica gel using chloroform-methanol (4:1) as the developing solvent. The band corresponding to the product was extracted with dichloromethane-methanol (1:1). Removal of the solvent gave 0.13 g (64%) of a yellow compound which was recrystallized from chloroform-methanol to give 0.115 g of yellow needles, mp 229-231°; uv (methanol):  $\lambda$  max (log  $\epsilon$ ), 237 nm (4.16), 255 nm (s) (4.09), 356 nm (3.39); ir (potassium bromide):  $\nu$  max 1700 (amide,

C=O), 1255, 840  $\text{cm}^{-1}$  (N  $\rightarrow$  O);  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  4.05 (s, 2H), 7.32 (s, 5H), 7.51 (s, 1H), 7.67 (s, 1H).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{SO}_2$ : C, 56.40; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.28; H, 4.34; N, 11.91; S, 13.58.

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