Synthesis of *S*-5-Pyrrolo[2,3-*b*]pyridinemethyl and *S*-5- and *S*-6-Pyrrolo[2,3-*d*]pyrimidinemethyl Derivatives of 5'-Deoxy-5'-thioadenosine

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Reaction of 5-dimethylaminomethylpyrrolo[2,3-*b*]pyridine methiodide or 5-dimethylaminomethylpyrrolo-[2,3-*d*]pyrimidin-4-one methiodide with 5'-deoxy-5'-*S*-thioacetyl-N^6-formyl-2',3'-*O*-isopropylideneadenosine in ethanolic sodium hydroxide solution, followed by deprotection of the resulting thiother in 80% formic acid, afforded 5'-deoxy-5'-(5-pyrrolo[2,3-*b*]pyridinemethylthio)adensoine or 5'-deoxy-5'-[5-(pyrrolo[2,3-*d*]pyrimidin-4-one)methylthioadenosine, respectively. Similarly, the methiodide salt of the *iso*-gramine analog, 2-amino-6-dimethylaminomethylpyrrolo[2,3-*d*]pyrimidin-4-one afforded 5'-deoxy-5'-[6-(2-aminopyrrolo[2,3-*d*]pyrimidin-4-one)methylthio]adenosine.

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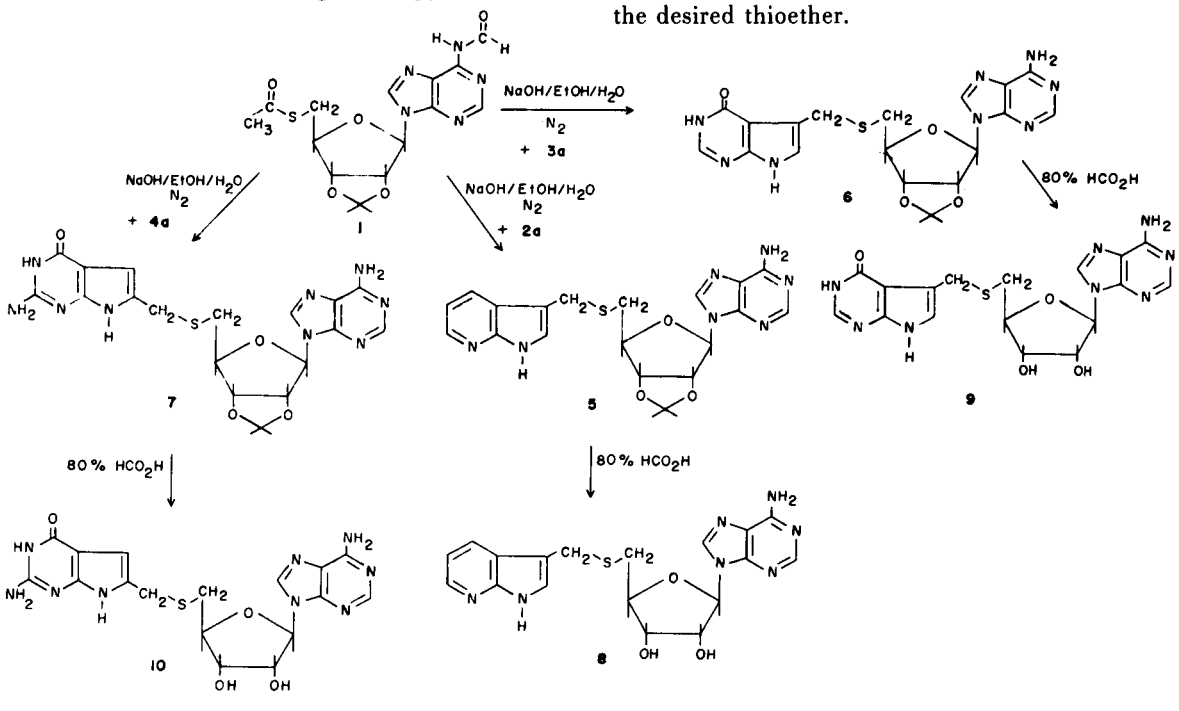
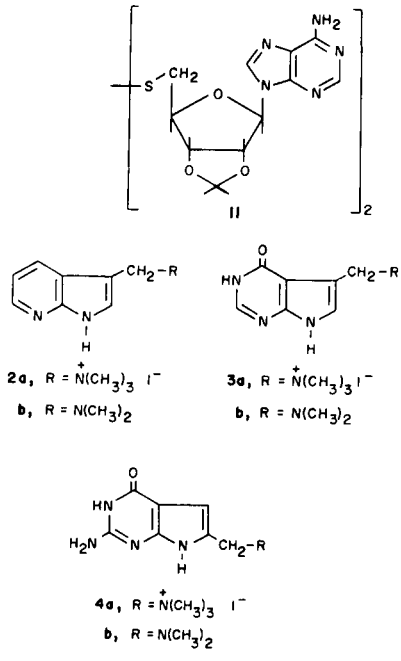
5'-Deoxy-5'-alkyl- or arylthioadenosines can generally be prepared by the reaction of alkyl- or arylthiols with 5'-deoxy-5'-chloroadenosine or with 5'-deoxy-5'-tosyl-2',3'-*O*-isopropylideneadenosine although product yields are sometimes low because of facile formation of *N*-3,5'-cycloadenosine during the course of the reaction (2,3). A recent report from this laboratory (4) describes the reaction of 3-indolemethylthiols with 5'-deoxy-5'-chloroadenosine, and shows that the preparation of 5'-deoxy-5'-(3-indolemethylthio)adenosines *via* this reaction is successful only when the N-1 position of the indole derivative is substituted. Thus, in order to obtain target compounds **8, 9** and **10**, which were regarded as important intermediates in the design of certain enzyme inhibitors, an alternative strategy is necessary.

As an alternative to commencing with 5-pyrrolo[2,3-*b*]-pyridinemethylthiols and 5- or 6-pyrrolo[2,3-*d*]pyrimidinemethylthiols, we decided to investigate a synthetic route to compounds **8, 9** and **10** from 5'-deoxy-5'-*S*-thioacetyl-N^6-formyl-2',3'-*O*-isopropylideneadenosine (**1**) (5,6), a stable 5'-deoxy-5'-thioadenosine precursor. The *in situ* generation of 5'-deoxy-5'-thio-2',3'-*O*-isopropylideneadenosine from **1** in methanolic sodium methoxide solution has been utilized (3,5,7) to prepare a variety of 5'-deoxy-5'-alkylthio-2',3'-*O*-isopropylideneadenosine derivatives from appropriate halogeno compounds. Removal of the isopropylidene blocking group can then be achieved in formic acid to give the 5'-deoxy-5'-thioether. However, substantial amounts of the disulfide **11** are formed in these rections, even when reactions are run in the absence of oxygen. This usually requires the reaction product to be subjected to preparative thin-layer chromatography for isolation of the desired thioether.





We have previously shown that the trimethylammonium group in gramine methiodide derivatives is readily displaced by thiolate ions (4,8). This present communication describes the reaction of **1** with 5-dimethylaminomethylpyrrolo[2,3-*b*]pyridine methiodide (**2a**), 5-dimethylaminomethylpyrrolo[2,3-*d*]pyrimidin-4-one methiodide (**3a**) and 2-amino-6-dimethylaminomethylpyrrolo[2,3-*d*]pyrimidin-4-one methiodide (**4a**) followed by deprotection of the resulting thioethers, to give **8, 9** and **10** respectively.

5-Dimethylaminomethylpyrrolo[2,3-*b*]pyridine (**2b**) was prepared by the method of Robison and Robison (9) and 2-amino-6-dimethylaminomethylpyrrolo[2,3-*d*]pyrimidin-4-one (**4b**) was prepared by the method of Seela and Lupke (10). Both of these compounds were converted to their respective methiodide salts **2a** and **4a**, by reaction with methyl iodide. Compound **3a** was prepared by the method of West (11).

Reaction of **1** with the methiodide **2a** in aqueous ethanolic sodium hydroxide solution at reflux temperature and under a nitrogen atmosphere, afforded the 2′,3′-*O*-isopropylidene derivative **5** in 80% yield. Contrary to previous syntheses of 5′-deoxy-5′-thioethers from the reaction of **1** with halogeno derivatives, problems associated with the formation of the disulfide **11**, were not encountered. Removal of the isopropylidene group of **5** in 80% formic acid gave **8** in 58% yield, without the need for chromatographic purification. In a similar manner, reaction of **1** with methiodide **3a** gave **6** in 75% yield which could be deprotected in formic acid to give good yields of the thioether **9**. The reaction could also be extended to include the coupling of the isogramine methiodide analogue **4a** and **1**. Thus **7** was obtained in 80% yield from this reaction and could be deprotected in formic acid to give **10** in good yield.

EXPERIMENTAL

The ^{1}H-nmr spectra were recorded on a Varian EM 360 spectrometer using tetramethylsilane as an internal reference. All melting points are uncorrected and were taken on a Reichert hot-stage microscope. Evaporations were carried out under reduced pressure on a rotary evaporator. Yields of solids refer to products obtained prior to recrystallization, unless otherwise stated.

5-Dimethylaminomethylpyrrolo[2,3-*b*]pyridine Methiodide (**2a**).

5-Dimethylaminomethylpyrrolo[2,3-*b*]pyridine (**2b**) (9) (0.60 g, 0.00343 mole) was dissolved in a mixture of absolute ethanol (5 ml) and tetrahydrofuran (4 ml) containing glacial acetic acid (0.1 ml). Methyl iodide (0.2 ml, 0.0032 mole) was added to the solution which was stirred at room temperature for 15 minutes and then kept at 4° for 1 hour. The resultant precipitate was filtered off and washed with diethyl ether to give 0.65 g (59.7%) of **2a**, mp 163-164° (from absolute ethanol); ^{1}H-nmr (deuterium oxide): δ 8.01 (dd, H—2, 1H, $J_{2,3}$ = 6 Hz, $J_{2,4}$ = 1 Hz), 7.85 (dd, H—4, 1H, $J_{4,3}$ = 8 Hz, $J_{4,2}$ = 1 Hz), 7.50 (s, H—6, 1H), 7.18-6.88 (m, H—3, 1H), 4.48 (s, CH_2—N^+, 2H), 3.05 (s, $N(CH_3)_3$, 9H).

Anal. Calcd. for $C_{11}H_{16}IN_3$ (317.2): C, 41.65; H, 5.08; N, 13.25. Found: C, 41.53; H, 5.19; N, 13.11.

2-Amino-6-dimethylaminomethylpyrrolo[2,3-*d*]pyrimidin-4-one Methiodide (**4a**).

Methyl iodide (1.0 ml, 0.016 mole) was added to a mixture of 2-amino-6-dimethylaminomethylpyrrolo[2,3-*d*]pyrimidin-4-one (**4b**) (10) (3.0 g, 0.0145 mole) in dimethyl sulfoxide (12 ml). The red solution was stirred at room temperature for 1 hour and then poured into chloroform (250 ml) to give a precipitate which was filtered off and washed with diethyl ether to give 4.5 g (90%) of **4a**, mp 295-298° (from methanol); ^{1}H-nmr (deuterium oxide): δ 6.47 (s, H—5, 1H), 4.35 (s, CH_2—N^+, 2H), 2.98 (s, $^+N(CH_3)_3$, 9H).

Anal. Calcd. for $C_{10}H_{16}IN_5O$ (349.2): C, 34.40; H, 4.62; N, 20.06. Found: C, 34.26; H, 4.71; N, 19.93.

5′-Deoxy-5′-(5-pyrrolo[2,3-*b*]pyridinemethylthio)adenosine (**8**).

A solution of sodium hydroxide (0.11 g, 0.00275 mole) in a mixture of absolute ethanol (7 ml) and water (7 ml) was deoxygenated with a stream of nitrogen at room temperature for 1 hour and **1** (0.50 g, 0.00127 mole) was then added. The stirred reaction mixture was monitored by tlc (silica gel, ethyl acetate) which showed that the starting thioester **1** was converted to the thiol in 30 minutes (R_f(SAc) 0.70 *versus* R_f (SH and S—S) 0.23 and 0.03). After this time **2a** (0.42 g, 0.00133 mole) was added and the solution heated under reflux for 2 hours. The solution was cooled, water (30 ml) was added, and the liberated oil was extracted into chloroform (2 × 30 ml). The combined chloroform extracts were dried with anhydrous magnesium sulfate, decolorised with activated charcoal and evaporated to dryness to give 0.46 g (80%) of **5** as a glassy orange residue, mp 54-55°; R_f (silica gel, ethyl acetate) 0.42; ^{1}H-nmr (deuteriochloroform): δ 11.12 (broad, N—H, 1H, deuterium oxide replaceable), 8.27-8.00 (m, H—2 and adenosyl H—8, 2H), 7.95-7.66 (m, H—4 and adenosyl H—2, 2H), 7.05-6.71 (m, H—6 and H—3, 2H), 6.48 (broad, NH_2, 2H, deuterium oxide replaceable), 5.95 (d, H—1′, 1H, $J_{1',2'}$ = 2 Hz), 5.33 (dd, H—2′, 1H, $J_{2',3'}$ = 7 Hz, $J_{2',1'}$ = 2 Hz), 4.85 (dd, H—3′, 1H, $J_{3',2'}$ = 7 Hz, $J_{3',4'}$ = 2 Hz), 4.29 (t, H—4′, 1H, $J_{4',5'}$ = 6 Hz, $J_{4',3'}$ 2 Hz), 3.80 (s, CH_2—S, 2H), 2.65 (d, H—5′, 2H, $J_{5',4'}$ = 6 Hz), 1.53 (s, CH_3, 3H), 1.32 (s, CH_3, 3H).

Without further purification, **5** (0.4 g, 0.000882 mole) was dissolved in 80% formic acid (5 ml) and left to stand at room temperature for 24 hours. The reaction mixture was evaporated to near dryness *in vacuo* and then repeatedly evaporated with water (2 × 10 ml). Water (10 ml) was added to the oily residue which crystallized on cooling and scratching. The resultant solid was filtered off and recrystallized from absolute ethanol

to give 0.21 (58%) of **8**, mp 157-160°; ^{1}H-nmr (DMSO-d_6): δ 11.20 (broad, N—H, 1H, deuterium oxide replaceable), 8.18 (s, adenosyl H—8, 1H), 8.13-7.96 (m, H—2 and adenosyl H—2, 2H), 7.83 (dd, H—4, 1H, $J_{4,3}$ = 7 Hz, $J_{4,2}$ = 2 Hz), 7.20 (s, H—6, 1H), 7.11 (s, NH_2, 2H, deuterium oxide replaceable), 7.03-6.73 (m, H—3, 1H), 5.80 (d, H—1′, 1H, $J_{1',2'}$ = 5 Hz), 5.28 (broad, 2′—OH and 3′—OH, 2H, deuterium oxide replaceable), 4.92-4.51 (m, H—2′, 1H), 4.33-3.93 (m, H—3′ and H—4′, 2H), 3.86 (s, CH_2—S, 2H), 2.90-2.63 (m, H—5′, 2H, due to non-equivalence of the H's in this grouping).

Anal. Calcd. for $C_{18}H_{19}N_7O_3S\cdot H_2O$ (431.5): C, 50.11; H, 4.91; N, 22.72. Found: C, 50.02; H, 4.95; N, 22.71.

5′-Deoxy-5′-(5-pyrrolo[2,3-*d*]pyrimidin-4-onemethylthio)adenosine (**9**).

A solution of sodium hydroxide (0.11 g, 0.00275 mole) in a mixture of absolute ethanol (7 ml) and water (7 ml) was deoxygenated with a stream of nitrogen at room temperature for 1 hour and **1** (0.50 g, 0.00127 mole) was then added. After stirring at room temperature for 30 minutes, **3a** (11) (0.47 g, 0.00141 mole) was added to the solution which was then heated under reflux for 2 hours. Aqueous sodium hydroxide (1*N*) (15 ml) was added to the cooled solution, the volume of which was then reduced to 15 ml *in vacuo*. Acidification of the solution thus obtained gave a beige precipitate which was filtered off, washed with water and allowed to dry, affording 0.45 g (75%) of **6**, mp 157-158°; ^{1}H-nmr (DMSO-d_6): δ 11.45 (broad, N_7—H, 1H, deuterium oxide replaceable), 8.21 (s, adenosyl H—8, 1H), 8.05 (s, adenosyl H—2, 1H), 7.69 (s, H—2, 1H), 7.21 (broad s, NH_2, 2H, deuterium oxide replaceable), 6.90 (s, N_3—H deuterium oxide replaceable, 1H), 6.81 (s, H—6, 1H), 6.01 (d, H—1′, 1H, $J_{1',2'}$ = 2 Hz), 5.40 (dd, H—2′, 1H, $J_{2',3'}$ = 7 Hz, $J_{2',1'}$ = 2 Hz), 4.86 (dd, H—3′, 1H, $J_{3',2'}$ = 7 Hz, $J_{3',4'}$ = 2 Hz), 4.24 (dt, H—4′, 1H, $J_{4',5'}$ = 6 Hz, $J_{4',3'}$ = 2 Hz), 3.88 (s, CH_2—S, 2H), 2.73 (d, H—5′, 2H, $J_{5',4'}$ = 6 Hz), 1.51 (s, CH_3, 3H), 1.30 (s, CH_3, 3H).

Without further purification **6** (0.4 g, 0.000850 mole) was dissolved in 80% formic acid (5 ml) and allowed to stand at room temperature for 24 hours. The clear solution was evaporated to near dryness *in vacuo* and then repeatedly evaporated with water (2 × 10 ml). The residue was taken up into 1*N* aqueous sodium hydroxide (20 ml) and neutralization of the resulting solution with glacial acetic acid gave a tan precipitate which was filtered off, washed with water, acetone and then diethyl ether to give 0.28 g (77%) of **9**, mp 171-172°; ^{1}H-nmr (DMSO-d_6): δ 11.46 (broad, N_7—H and N_3—H, 2H, deuterium oxide replaceable), 8.19 (s, adenosyl H—8, 1H), 8.00 (s, adenosyl H—2, 1H), 7.64 (s, H—2, 1H), 7.10 (broad, NH_2, 2H, deuterium oxide replaceable), 6.78 (s, H—6, 1H), 5.80 (d, H—1′, 1H, $J_{1',2'}$ = 5 Hz), 5.26 (broad, 2′—OH and 3′—OH, 2H, deuterium oxide replaceable), 4.86-4.50 (m, H—2′, 1H), 4.26-3.86 (m, H—3′ and H—4′, 2H), 3.84 (s, CH_2—S, 2H), 2.93-2.69 (m, H—5′, 2H, due to non-equivalence of the H's in this grouping).

Anal. Calcd. for $C_{17}H_{18}N_8O_4S$ (430.4): C, 47.44; H, 4.22; N, 26.03. Found: C, 47.63; H, 4.51; N, 25.98.

5′-Deoxy-5′-[6-(2-aminopyrrolo[2,3-*d*]pyrimidin-4-one)methylthio]adenosine (**10**).

A solution of sodium hydroxide (0.50 g, 0.0125 mole) in a mixture of absolute ethanol (25 ml) and water (25 ml) was deoxygenated with a stream of nitrogen at room temperature for 1 hour and **1** (2.0 g, 0.00051 mole) was then added. After stirring at ambient temperature for 30 minutes, **4a** (2.0 g, 0.0056 mole) was added to the red solution which was then heated under reflux for 2 hours. Aqueous sodium hydroxide (1*N*, 75 ml) was added to the cooled solution, the volume of which was then reduced to 75 ml *in vacuo*. Acidification of the resulting solution with glacial acetic acid gave a beige precipitate which was filtered off and washed with water to give 2.0 g (81%) of **7**, mp 204-207°; ^{1}H-nmr (DMSO-d_6): δ 10.45 (broad, N_7—H and N_3—H, 2H, deuterium oxide replaceable), 8.36 (s, adenosyl H—8, 1H), 8.19 (s, adenosyl H—2, 1H), 7.38 (s, adenosyl NH_2, 2H, dueterium oxide replaceable), 6.12 (d, H—1′, 1H, $J_{1',2'}$ = 2 Hz), 6.06 (s, H—5, 1H), 5.80 (broad, C_2—NH_2, 2H, deuterium oxide replaceable), 5.44 (dd, H—2′, 1H, $J_{2',3'}$ = 7 Hz, $J_{2',1'}$ = 2 Hz), 4.88 (dd, H—3′, 1H, $J_{3',2'}$ = 7 Hz, $J_{3',4'}$ = 2 Hz), 4.20 (dt, H—4′, 1H, $J_{4',5'}$ = 6 Hz, $J_{4',3'}$ = 2 Hz), 3.64 (s, CH_2—S, 2H), 2.68 (d, H—5′, 2H, $J_{5',4'}$ = 6 Hz), 1.49 (s, CH_3, 3H), 1.28 (s, CH_3, 3H).

Without further purification, **7** (2.0 g, 0.0041 mole) was dissolved in 80% formic acid (15 ml) and allowed to stand at room temperature for 36 hours. The solution was evaporated to near dryness *in vacuo* and the residue was taken up into 1*N* aqueous sodium hydroxide (25 ml). Neutralization of the resulting solution with glacial acetic acid gave a precipitate which was filtered off and washed with water to give 1.3 g (71%) of **10**, mp 213-216° (reprecipitated from 0.5*N* aqueous sodium hydroxide-acetic acid and washed with water); ^{1}H-nmr (DMSO-d_6): δ 10.70 (broad, N_7—H, deuterium oxide replaceable), 10.03 (broad, N_3—H, 1H, deuterium oxide replaceable), 8.16 (s, adenosyl H—8, 1H), 8.00 (s, adenosyl H—2, 1H), 7.10 (broad, adenosyl NH_2, 2H, deuterium oxide replaceable), 5.96 (broad, H—5 and C_2—NH_2, 3H reducing to 1H on addition of deuterium oxide), 5.80 (d, H—1′, 1H, $J_{1',2'}$ = 5 Hz), 5.23 (broad, 2′—OH and 3′—OH, 2H, deuterium oxide replaceable), 4.89-4.48 (m, H—2′, 1H), 4.25-3.83 (m, H—3′ and H—4′, 2H), 3.61 (s, CH_2—S, 2H), 2.93-2.66 (m, H—5′, 2H, due to non-equivalence of the H's in this grouping).

Anal. Calcd. for $C_{17}H_{19}N_9O_4S$ (445.5): C, 45.84; H, 4.27; N, 28.30. Found: C, 45.73; H, 4.38; N, 27.96.

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