

Eric Benghiat and Peter A. Crooks*

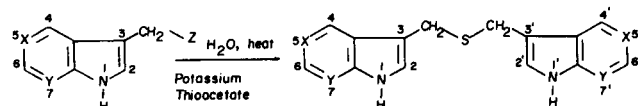
College of Pharmacy, University of Kentucky,
Lexington, KY 40536-0053 U.S.A.

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The S-3-(1-methylindole)methyl and S-3-(1,2-dimethylindole)methyl derivatives of 5'-deoxy-5'-thioadenosine have been prepared by reaction of the appropriate 3-indolemethylthioacetate with 5'-deoxy-5'-chloroadenosine in basic media. 5'-Deoxy-5'-(3-indolemethylthio)adenosines unsubstituted at the indolic nitrogen, cannot be prepared via this route due to facile conversion of the precursor 3-indolemethylthiol derivative to the corresponding 3,3'-diindolemethyl sulfide.

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As part of a program directed towards the preparation of potential enzyme inhibitors, it was necessary to prepare various 3-indolemethyl derivatives linked to the S-atom of 5'-deoxy-5'-thioadenosine, *viz* compounds **6a-e**. A literature survey shows that several 5'-deoxy-5'-alkyl and arylthioadenosines have been readily synthesized in 50-70% yield from the reaction of alkyl or arylthiols with 5'-deoxy-5'-chloroadenosine (1) in 2*N* aqueous sodium hydroxide at 80° (2,3). Similar compounds (4,5) have been prepared

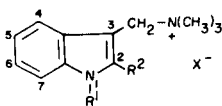
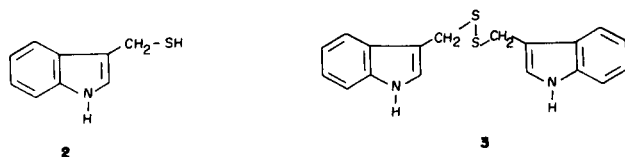


7			6	
X	Y	Z	X	Y
a, CH	N	N(CH ₃) ₂	a, CH	CH
b, N	N	N(CH ₃) ₃ ⁺ I ⁻	b, CH	N
			c, N	N

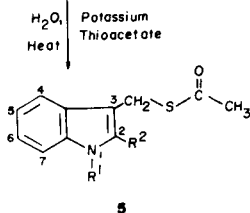
from 5'-deoxy-5'-tosyl-2',3'-*O*-isopropylideneadenosine but their preparation is lengthy and limited because of the facile transformation of the tosyl derivative into the *N*-3',5'-cycloadenosine (6) product. Alkyl thioacetates have also been coupled to 5'-deoxy-5'-chloroadenosine in a mixture of DMSO and 4*N*-aqueous sodium hydroxide at room temperature, the thiolate anion being generated *in situ* (7). Furthermore, several analogs of *S*-adenosylhomocysteine have been prepared from the reaction of *S*-benzyl-L-homocysteine or a derivative of *S*-benzyl-L-homocysteine with the requisite 5'-deoxy-5'-tosyl-2',3'-*O*-isopropylideneadenosine (8-10) or 5'-deoxy-5'-chloroadenosine (11) in sodium and liquid ammonia. However, there is no data in the literature on the reaction of 3-indolemethylthiols with either 5'-deoxy-5'-chloroadenosine or 5'-deoxy-5'-tosyl-2',3'-*O*-isopropylideneadenosine. Indeed, 3-indolemethylthiol (12) (2) is the only such thiol of this class previously reported.

The present communication describes the preparation of the S-3-(1-methylindole) methyl- (6a) and S-3-(1,2-dimethylindole)methyl- (6b) derivatives of 5'-deoxy-5'-thioadenosine and the attempted synthesis of the corresponding S-3-indolemethyl, S-3-(7-azaindole)methyl- and S-3-(5,7-diazaindole)methyl derivatives 6c-e, respectively.

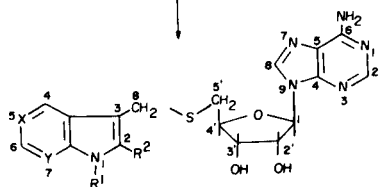
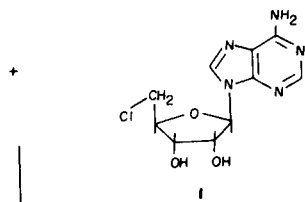
Di-(3-indolemethyl)disulfide (3) was prepared from indole-3-carboxaldehyde in methanolic ammonium sulfide according to Nutting *et al.* (12) and then reduced with amalgamated aluminum to give 3-indolemethylthiol (12). Heating a 1:1 mole ratio of 3-indolemethylthiol and 5'-deoxy-5'-chloroadenosine at 80° in 2*N*-aqueous sodium hydroxide under a nitrogen atmosphere gave, instead of the expected 6c, a quantitative yield of 3,3'-diindole-



R ₁	R ₂	X
a, H	H	CH ₃ SO ₄ ⁻
b, CH ₃	H	I ⁻
c, CH ₃	CH ₃	I ⁻



R ₁	R ₂
a, H	H
b, CH ₃	H
c, CH ₃	CH ₃



R ₁	R ₂	X	Y
a, CH ₃	H	CH	CH
b, CH ₃	CH ₃	CH	CH
c, H	H	CH	CH

R ₁	R ₂	X	Y
d, H	H	CH	N
e, H	H	N	N

methyl sulfide (**8a**), identified by comparison of its infrared and nmr spectrum to that of an authentic sample (14). The reaction between di-(3-indolemethyl) disulfide and 5'-deoxy-5'-chloroadenosine in sodium and liquid ammonia similarly failed to produce **6c**. It was anticipated that alkylation at the 1-position of indole may inhibit the formation of the 3,3'-diindolemethyl sulfide derivative which is probably formed *via* an elimination-addition reaction involving an ethylenic intermediate (15). *N*-1 Substituted indoles are not capable of reacting according to this pathway (16). An alternative route to the synthesis of thiols is *via* a thioacetate precursor which can be transformed into the thiol by basic hydrolysis. Thus in order to obtain the 1-methyl derivative of 3-indolemethylthiol, potassium thioacetate and 1-methylgramine methiodide (17) (**4b**) were heated together under reflux in water to give 3-(1-methylindole)methylthioacetate (**5b**), the desired thiol precursor. Coupling of 3-(1-methylindole)methylthiol, generated *in situ* by basic hydrolysis of **5b**, with 5'-deoxy-5'-chloroadenosine in 2*N* aqueous sodium hydroxide at 80° gave 5'-deoxy-5'-[3-(1-methylindole)methylthio]adenosine (**6a**) in 41% yield. Compound **6a** was also prepared in 75% yield from the reaction of **5b** with 5'-deoxy-5'-chloroadenosine in a mixture of DMSO and 4*N* aqueous sodium hydroxide at room temperature. Similarly 3-(1,2-dimethylindole)methylthioacetate (**5c**), prepared from potassium thioacetate and 1,2-dimethylgramine methiodide (**4c**) (18), was successfully coupled to 5'-deoxy-5'-chloroadenosine in a mixture of DMSO and 4*N* aqueous sodium hydroxide to give **6b**. However, the synthesis of **6b** failed in 2*N* aqueous sodium hydroxide at 80°, possible attributable to the poor water solubility of **5c**. An attempt to prepare 3-(7-azaindole)methylthioacetate from 7-azagramine (**7a**) (19) and potassium thioacetate with the prospect of its subsequent coupling to 5'-deoxy-5'-chloroadenosine, gave 3,3'-di-7-azaindolemethyl sulfide (**8b**) as the major product. Similarly, treatment of 3-dimethylaminomethyl-5,7-diazaindole methiodide (**7b**) (20) with potassium thioacetate gave 3,3'-di-(5,7-diazaindole)methyl sulfide (**8c**), thus precluding the use of this synthetic route in the synthesis of the adenosyl compounds **6d** and **6e**. It may be postulated that in these reactions, the desired thioacetates are formed initially, but then react further to give the sulfides **8b** and **8c**, respectively. Surprisingly, the reaction between gramine methosulfate (**4a**) (21) and potassium thioacetate gave a high yield of 3-indolemethylthioacetate (**5a**). This synthesis of the 3-indolemethylthiol precursor represents a more convenient route to 3-indolemethylthiol prepared previously from **3** (13). In conclusion, it has been shown that 3-indolemethylthiols or their thioacetate precursors will partake in coupling reactions with 5'-deoxy-5'-chloroadenosine only if the 1-position is alkylated. The tendency for the 3-indolemethylthiols unsubstituted at the 1-position to form the symmetrical sulfides of the type **8a-c**, prevents them from

being utilized in the coupling reaction with 5'-deoxy-5'-chloroadenosine to form the desired sulfide ethers **6c-e**, respectively.

EXPERIMENTAL

3-Indolemethylthioacetate (**5a**).

A mixture of gramine methosulfate (21) (2.0 g, 6.66 mmoles) and potassium thioacetate (1.0 g, 8.75 mmoles) in water (10 ml) was heated under reflux, under a nitrogen atmosphere for 15 minutes. The mixture was cooled and extracted with diethyl ether (2 × 30 ml). The combined ethereal extracts were washed with water, dried with anhydrous magnesium sulfate and evaporated to dryness to give a yellow oil which was purified on a silica gel column (30-200 mesh) using ether as eluant to give 1.04 g (76%) of **5a** as a viscous, homogenous oil; ir (Neat): 1645 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 8.07 (bs, 1H, N-H, deuterium oxide replaceable), 7.73-7.48 (m, 1H, H-7), 7.36-7.18 (m, 3H, H-4,5 and 6), 7.08 (d, 1H, H-2, J = 3 Hz), 4.28 (s, 2H, $\text{CH}_2\text{-S}$), 2.27 (s, 3H, SCOCH_3).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{NOS}$ (205.3): C, 64.36; H, 5.40; N, 6.82. Found: C, 64.51; H, 5.44; N, 6.93.

3-(1-Methylindole)methylthioacetate (**5b**).

A solution of 1-methylgramine methiodide (17) (2.9 g, 8.8 mmoles) and potassium thioacetate (1.5 g, 13.2 mmoles) in water (10 ml) was heated under reflux for 2 hours. The reaction mixture was cooled and the oil which had formed was extracted with diethyl ether (2 × 20 ml). The combined ethereal extracts were washed with water, dried with anhydrous magnesium sulfate and evaporated to dryness to afford 1.9 g (99%) of **5b** as a pure viscous yellow oil; ir (neat): 1650 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 7.78-7.43 (m, 1H, H-7), 7.38-7.04 (m, 3H, H-4, 5 and 6), 6.98 (s, 1H, H-2), 4.28 (s, 2H, $\text{CH}_2\text{-S}$), 3.59 (s, 3H, N- CH_3), 2.27 (s, 3H, COCH_3).

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NOS}$ (219.3): C, 65.72; H, 5.97; N, 6.39. Found: C, 65.74; H, 6.02; N, 6.68.

3-(1,2-Dimethylindole)methylthioacetate (**5c**).

A mixture of 1,2-dimethylgramine methiodide (18) (2.0 g, 5.81 mmoles) and potassium thioacetate (1.33 g, 8.70 mmoles) in water (15 ml) was heated under reflux for 45 minutes. The reaction mixture was cooled and then worked up as described for the preparation of **5b** to give a yellow oil which crystallized on standing to afford 1.23 g (9%) of **5c**, mp 41.43° (from petroleum ether 40-60°); ir (Nujol): 1640 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (deuteriochloroform): δ 7.46-7.16 (m, 1H, H-7), 7.13-6.76 (m, 3H, H-4, 5 and 6), 4.25 (s, 2H, $\text{CH}_2\text{-S}$), 3.50 (s, 3H, N- CH_3), 2.31 (s, 3H, C- CH_3 or COCH_3), 2.23 (s, 3H, COCH_3 or C- CH_3).

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NOS}$ (233.3): C, 66.92; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.52; N, 6.00.

5'-Deoxy-5'-[3-(1-methylindole)methylthio]adenosine (**6a**).

Method A.

A mixture of **5b** (0.3 g, 1.37 mmoles) and 5'-deoxy-5'-chloroadenosine (1) (0.35 g, 1.22 mmoles) in 2*N* aqueous sodium hydroxide (4 ml) was heated under reflux, under a nitrogen atmosphere for 1 hour, a white precipitate forming in solution during the last 10 minutes of reflux. The reaction mixture was cooled and precipitation completed by acidification with acetic acid. The resulting solid was filtered off, washed with water then ether and allowed to dry to give 0.24 g (41%) of **6a** as white crystals, mp 111-112° (from methanol); $^1\text{H-nmr}$ (DMSO- d_6): δ 8.40 (s, 1H, adenosyl H-8), 8.18 (s, 1H, adenosyl H-2), 7.59 (dd, 1H, H-7, J = 6 Hz and 1 Hz), 7.40 (dd, 1H, H-4, J = 6 Hz and 1 Hz), 7.32 (s, 2H, NH_2 deuterium oxide replaceable), 7.23-7.12 (m, 2H, H-5 or H-6 and H-2), 7.02 (t, 1H, H-6 or H-5, J = 6 Hz), 5.92 (d, 1H, H-1', J = 5 Hz), 5.64-5.44 (bs, 1H, 2'-OH or 3'-OH, deuterium oxide replaceable), 5.40-5.26 (bs, 1H, 3'-OH or 2'-OH, deuterium oxide replaceable), 4.78 (dd, 1H, H-2', J = 7 Hz and 2 Hz), 4.20 (dd, 1H, H-3', J = 7 Hz, and 2 Hz), 4.13-4.04 (m, 1H, H-4'), 3.90 (s, 2H, H-8), 3.68 (s, 3H, N- CH_3), 2.94-2.68 (m, 2H, H-5', due to non-equivalence of the H-s in this grouping).

Anal. Calcd. for $C_{20}H_{22}O_3N_6S$ (426.5): C, 56.32; H, 5.20; N, 19.70. Calcd. for $C_{20}H_{22}O_3N_6S \cdot 1H_2O$ (444.5): C, 54.04; H, 5.44; N, 18.91. Found: C, 54.12; H, 5.22; N, 18.97.

Method B.

A solution of **5b** (0.80 g, 3.65 mmoles) in DMSO (13 ml) was deoxygenated with a stream of nitrogen for 1 hour, after which time 5'-deoxy-5'-chloroadenosine (0.90 g, 3.15 mole) was added followed by 4*N* aqueous sodium hydroxide (2.8 ml, 11.2 mmoles). The resulting solution was stirred at ambient temperature for 16 hours and then poured into water (75 ml) to give a white precipitate. After cooling at 4° for 30 minutes, the solid was collected by filtration, washed with water and allowed to dry to give 1.03 g (76%) of **6a** which had identical spectral properties and mp to that obtained by method A.

5'-Deoxy-5'-[3-(1,2-dimethylindole)methylthio]adenosine (**6b**).

A solution of **5c** (0.40 g, 1.72 mmoles) in DMSO (7 ml) was deoxygenated with a stream of nitrogen for 1 hour, after which time 5'-deoxy-5'-chloroadenosine (0.49 g, 1.72 mmoles) was added, followed by 4*N* aqueous sodium hydroxide. The resulting solution was stirred at ambient temperature for 16 hours and then poured into water (40 ml) to give a white precipitate. After cooling at 4° for 30 minutes, the solid was collected by filtration, washed with water and allowed to dry to give 0.46 g (61%) of **6b** mp 105-108° (from methanol); ¹H-nmr (DMSO-*d*₆): δ 8.24 (s, 1H, adenosyl H-8), 8.06 (s, 1H, adenosyl H-2), 7.59-6.53 (m, 6H reducing to 4H on addition of deuterium oxide, H-4, 5, 6 and 7, and NH₂), 5.88 (d, 1H, H-1', J = 5 Hz), 5.34 (bs, 2H, 2'-OH and 3'-OH, deuterium oxide replaceable), 4.92-4.50 (m, 1H, H-2'), 4.36-3.86 (m, 2H, H-3' and H-4'), 3.85 (s, 2H, H-8), 3.51 (s, 3H, N-CH₃), 2.77 (d, 2H, H-5', J = 5 Hz), 2.24 (s, 3H, C-CH₃).

Anal. Calcd. for $C_{21}H_{24}O_3N_6S \cdot 1H_2O$: C, 55.01; H, 5.71; N, 18.33. Found: C, 55.39; H, 5.67; N, 18.47.

Attempted Synthesis of **6b** in 2*N* Aqueous Sodium Hydroxide.

A mixture of **5c** (0.4 g, 1.72 mmoles) and 5'-deoxy-5'-chloroadenosine (0.5 g, 1.72 mmoles) in 2*N* aqueous sodium hydroxide (6 ml) was heated at 80° under a nitrogen atmosphere for 1 hour, the solution remaining oily throughout the heating period. Upon cooling, the oily layer crystallized and was filtered off and washed with water to give 0.34 g of an unidentified light brown solid.

Attempted Synthesis of 5'-Deoxy-5'-[3-indolemethylthio]adenosine (**6c**).

Method A.

A mixture of 3-indolemethylthiol (**12**) (1.0 g, 6.12 mmoles) and 5'-deoxy-5'-chloroadenosine (1.75 g, 6.12 mmoles) in 2*N* aqueous sodium hydroxide (14 ml) was heated at 80° under a nitrogen atmosphere for 1 hour. The mixture was cooled and the resulting solid filtered off and washed with water to give 0.88 g (98%) of 3,3'-diindolemethyl sulfide (**8a**), mp 140° (lit mp 142° (14)); ir (Nujol): 3380, 1350, 1210, 1100, 1050, 745 cm⁻¹; ¹H-nmr (acetone-*d*₆): δ 10.11-9.55 (bs, 2H, N-1 and N-1'-H, deuterium oxide replaceable), 7.82-7.53 (m, 2H, H-4 and H-4'), 7.45-6.93 (m, 8H, H-2, 2', 5, 5', 6, 6', 7 and 7'), 3.88 (s, 4H, 2 × CH₂-S).

Method B.

Clean sodium metal was added in small pieces to a stirred mixture of di-(3-indolemethyl) disulfide (**13**) (1.0 g, 3.08 mmoles) in liquid ammonia (30 ml) and immersed in an acetone-dry ice bath, until a blue color persisted for about 20 minutes. The color was dissipated by the addition of a few crystals of ammonium chloride and 5'-deoxy-5'-chloroadenosine (1.75 g, 6.16 mmoles) was added in one portion. The mixture was stirred for 4 hours, the ice-bath was removed and the ammonia was allowed to evaporate slowly. Water (30 ml) was added to the residue. The undissolved solid was filtered off and washed with water to give 0.7 g of a solid which was identified as 3,3'-diindolemethyl sulfide from its ir and nmr spectra. Acidification of the filtrate produced no precipitate which would be expected if **4c** had been formed.

3,3'-Di-7-azaindolemethyl Sulfide (**8b**).

A mixture of 7-azagamine (**19**) (1.0 g, 5.71 mmoles) and potassium thioacetate (1.5 g, 13.1 mmoles) in water (10 ml) was heated under reflux under a nitrogen atmosphere for 1 hour. The mixture was cooled and the solid which had formed in solution during the reflux period, was filtered off, washed with water and allowed to dry, to give 0.82 g (98%) of **8b**, mp 245-246° (from absolute ethanol); ¹H-nmr (DMSO-*d*₆): δ 11.90 (bs, 2H, N-1H and N-1'H deuterium oxide replaceable), 8.38 (dd, 2H, H-6 and H-6', J = 6 Hz and 2 Hz), 8.09 (dd, 2H, H-4 and H-4', J = 7 Hz and 1 Hz), 7.55 (s, 2H, H-2 and H-2'), 7.28-6.95 (m, 2H, H-5 and H-5'), 3.97 (s, 4H, 2 × CH₂-S).

Anal. Calcd. for $C_{16}H_{14}N_4S$ (294.37): C, 65.29; H, 4.76; N, 19.04; S, 10.89. Found: C, 65.28; H, 4.79; N, 18.94; S, 10.98.

3,3'-Di-(5,7-diazaindole)methyl Sulfide (**8c**).

A mixture of 3-dimethylaminomethyl-5,7-diazaindole methiodide (**5b**) (**20**) (0.8 g, 2.51 mmoles) and potassium thioacetate (0.42 g, 3.67 mmoles) in water (5 ml) was heated under reflux under a nitrogen atmosphere for 1 hour. The mixture was cooled and the resulting solid filtered off and washed with water to give 0.28 g (76%) of **8c**, mp 249-250° (from absolute ethanol); ¹H-nmr (perdeuterioacetic acid): δ 12.7 (bs, 2H, N-1H and N-1'H, deuterium oxide replaceable), 9.77 (s, 2H, N-6H and N-6'H), 9.53 (s, 2H, N-4H and N-4'H), 8.17 (s, 2H, N-2H and N-2'H), 4.53 (s, 4H, 2 × CH₂-S).

Anal. Calcd. for $C_{17}H_{14}N_6S$ (296.35): C, 56.74; H, 4.08; N, 28.36; S, 10.82. Found: C, 56.50; H, 4.21; N, 28.44; S, 10.53.

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REFERENCES AND NOTES

- (1) K. Kigugawa and M. Ichino, *Tetrahedron Letters*, **87** (1971).
- (2) K. Kikugawa, K. Iguka, Y. Higuchi, H. Hirayama and M. Ichino, *J. Med. Chem.*, **15**, 387 (1972).
- (3) G. L. Anderson, D. L. Bussolotti and J. K. Coward, *ibid.*, **24**, 1271 (1981).
- (4) J. Baddiley and G. A. Jamieson, *J. Chem. Soc.*, 4280 (1954).
- (5) R. Kuhn and W. John, *Chem. Ber.*, **98**, 1699 (1965).
- (6) J. Baddiley, *J. Chem. Soc.*, 1348 (1951).
- (7) K. C. Tang, R. Mariuzza and J. K. Coward, *J. Med. Chem.*, **24**, 1277 (1981).
- (8) R. T. Borchardt and Y. S. Wu, *ibid.*, **17**, 862 (1974).
- (9) R. T. Borchardt, *ibid.*, **17**, 868 (1974).
- (10) R. T. Borchardt and Y. S. Wu, *ibid.*, **18**, 300 (1975).
- (11) R. T. Borchardt, J. A. Huber and Y. S. Wu, *J. Org. Chem.*, **41**, 565 (1976).
- (12) L. Nutting, R. M. Silverstein and C. M. Himel, U. S. Patent 3,033,875 May 8, (1962), Appl. Sept. 28 (1959); *Chem. Abstr.*, **57**, p12438e (1962).
- (13) L. Nutting, R. M. Silverstein and C. M. Himel, U. S. Patent, 3,041,351 June 26, (1962), Appl. Nov. 4 (1955); *Chem. Abstr.*, **57** p13729f (1962).
- (14) J. J. Licari and G. Dougherty, *J. Am. Chem. Soc.*, **76**, 4039 (1954).
- (15) J. H. Brewster and E. L. Eliel, "Organic Reactions", R. Adams, ed, J. Wiley and Sons, New York Vol VII, 1953, p 99.
- (16) H. R. Synder and J. H. Brewster, *ibid.*, **71**, 1058 (1949).
- (17) H. R. Synder and E. L. Eliel, *ibid.*, **70**, 1703 (1948).
- (18) E. Benghiat and P. A. Crooks, *Synthesis*, submitted, (1982).
- (19) M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, **77**, 457 (1955).
- (20) Wellcome Foundation, British Patent 981,458, Jan 27 (1965), Appl. December 4 (1961); *Chem. Abstr.*, **63** p4309a (1965).
- (21) C. Schopf and J. Thesing, *Angew. Chem.*, **63**, 377 (1951); *Chem. Abstr.*, **48**, 4509e (1954).