76.14, 76.84, 78.25, and 80.24, C_q 109.04 (2 C), 109.41, 110.58, 111.68, and 169.96. Anal. Calcd for $C_{27}H_{44}O_{12}$: C, 57.84; H, 7.91. Found: C, 57.96; H, 8.09.

2,3:4,5:6,7:8,9:10,11-Penta-*O*-isopropylidene-D-*glycero*-D-*talo*-L-*talo*-undecose (9). The reaction was conducted as described for heptose **5**, by starting with 1.0 g (1.78 mmol) of methyl ester **8**. This furnished the crude aldehyde **9**, which was purified by flash chromatography on silica gel (70:30 hexane/ethyl acetate) to give pure undecose **9** (0.76 g, 81%) as a colorless oil: $[\alpha]_D$ = -42.5° (c 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (d, J = 1.5 Hz, 1 H), 4.65 (dd, J = 6.6, 1.5 Hz, 1 H), 4.56 (dd, J = 9.6, 6.6 Hz, 1 H), 4.46 (dd, J = 7.8, 4.8 Hz, 1 H), 4.36 (t, J = 5.1 Hz, 1 H), 4.34 (m, 1 H), 4.30 (t, J = 6.3 Hz, 1 H), 4.25 (t, J = 5.1 Hz, 1 H), 4.17 (dd, J = 9.9, 5.1 Hz, 1 H), 4.06 (dd, J = 8.1, 6.3 Hz, 1 H), 3.98 (dd, J = 8.1, 7.0 Hz, 1 H), 3.92 (dd, J = 10.0, 5.1 Hz, 1 H), 1.55, 1.53, 1.49, 1.43, 1.41, 1.40, 1.38, 1.37, 1.36, and 1.34 (10 s, each 3 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) DEPT sequence, CH_3 δ 25.51, 25.55, 25.56, 25.63, 26.36, 27.09, 27.72, 27.97, 28.01, and 28.07, CH_2 δ 65.31, CH δ 75.13 (2 C), 75.25, 75.94 (2 C), 76.10, 78.19, 80.37, 82.18, and 198.56, C_q δ 109.25, 109.49 (2 C), 110.64, and 111.86; FTIR ($CDCl_3$) 1738 cm^{-1}. Anal. Calcd for $C_{26}H_{42}O_{11}$: C, 58.85; H, 7.98. Found: C, 58.70; H, 7.69.

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Registry No. 1, 15186-48-8; 2, 132046-98-1; *epi*-2, 132047-05-3; 3, 132046-99-2; 3 2,3-*O*-isopropylidene-5-desilyl derivative, 132047-06-4; 4, 132047-00-8; 5, 132077-98-6; 6, 132047-01-9; *epi*-6, 132047-07-5; 7, 132047-02-0; 8, 132047-03-1; 9, 132047-04-2; TMSOF, 61550-02-5; volemitol, 488-38-0; volemitol heptaacetate, 6893-85-2.

A Simple and Efficient Synthesis of 9-Substituted Guanines. Cyclodesulfurization of 1-Substituted 5-[(Thiocarbamoyl)amino]imidazole-4-carboxamides under Aqueous Basic Conditions

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5-Aminoimidazole-4-carboxamide (AICA) (**1a**) is 1-alkylated by an improved method. The resulting 5-amino-1-alkylimidazole-4-carboxamides (**1b-i**) are converted to the corresponding 1-alkyl-5-[(thiocarbamoyl)amino]imidazole-4-carboxamides (**3**). These compounds are ring closed under alkaline conditions to 9-substituted guanines (**5**) in very high yields by treatment with heavy-metal salts in aqueous sodium hydroxide, or, in somewhat lower yields, by S-oxidation with hydrogen peroxide or sodium perborate in aqueous sodium hydroxide.

Introduction

The search for new or improved synthetic routes leading to nucleoside analogues of guanosine has attracted much attention during recent years.[1]

One of the classic routes to 9-substituted guanines is the Yamazaki ring closure. In 1967 Yamazaki and co-workers first reported the synthesis of guanosine from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA-riboside) (**1b**),[2] and since then Yamazaki as well as others have attempted to improve this method or to develop new, related methodologies.[3-6]

There are several examples in the literature of cyclodesulfurization of thioureas leading to various heterocyclic compounds. Among reagents used in this type of reactions are dicyclohexylcarbodiimide (DCC) and mercury salts. These ring closure reactions are believed to proceed via intermediate cyanamides or carbodiimides, respectively.[7] However, attempts to prepare guanines by direct cyclodesulfurization of thioureido derivatives of 5-aminoimidazole-4-carboxamides have failed. Thus Yamazaki was unsuccessful in an attempt to prepare guanine by desulfurization of **3a** using mercury(II) oxide, although he was able to demonstrate that **4a**, prepared by another route, underwent cyclization when treated with aqueous base. An interesting finding was that the ring closure product was dependent on base strength, viz. guanine was formed in 6 N sodium hydroxide, while **4a** ring closed to isoguanine in 0.1 N sodium hydroxide. Different reaction mechanisms were suggested. The formation of isoguanine was explained by the initial cyclization to an unstable [1,3]-oxazine derivative with subsequent ring opening to 5-[(carbamoyl)amino]imidazole-4-carbonitrile, the ring closure of which would lead to the observed isoguanine.[3] The proposed mechanism has later been supported by other workers. Townsend et al. unexpectedly isolated 5-[[*N'*-(methoxycarbonyl)carbamoyl]amino]imidazole-4-carbonitrile riboside after treatment of 1-ribosyl-5-[[*N'*-(methoxycarbonyl)(thiocarbamoyl)]amino]imidazole-4-carboxamide with DCC. Isotope labeling experiments indicated

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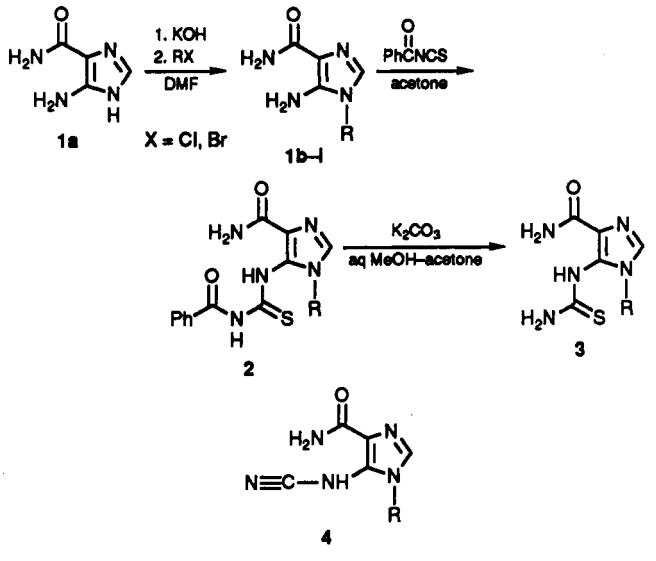
Scheme I



1a 1b–i 2 3 4

a: R = H
b: R = 1-β-D-ribofuranosyl
c: R = methyl
d: R = ethyl
e: R = 1-propyl
f: R = phenylmethyl
g: R = [2-(acetyloxy)ethoxy]methyl*
h: R = (2-hydroxyethoxy)methyl*
i: R = (1,3-dihydroxy-2-propoxy)methyl
* 2g → 3h

the presence of an intermediate [1,3]-oxazine derivative.[5] Reese et al. isolated a protected 1-ribosyl-5-(carbamoylamino)imidazole-4-carbonitrile derivative after treatment of the corresponding 5-[(thiocarbamoyl)amino]imidazole-4-carboxamide with mercury(II) perchlorate in the presence of pyridine in THF. Reese et al. as well as Chern et al. have demonstrated that this type of compounds very easily ring close to isoguanines.[8]

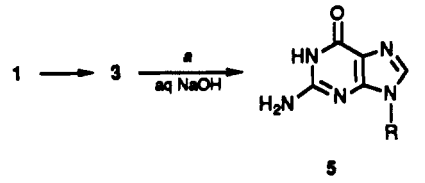
We now report that desulfurization of **3** in aqueous base, by using heavy-metal salts or by S-oxidation, effects a direct ring closure to 9-substituted guanines even at 0 °C.

Results and Discussion

The 1-substituted 5-[(thiocarbamoyl)amino]imidazole-4-carboxamides (**3**) were prepared as outlined in Scheme I.

1-Alkylations of 5-aminoimidazole-4-carboxamide (AICA) (**1a**) are reported in the literature,[9] but yields are generally low, and in many instances a relatively high content of the undesired 3-isomer makes chromatographic purification necessary. By preparing the potassium salt of **1a** in DMF using KOH powder followed by addition of the alkylating agent, we were able to isolate the crystalline 1-isomers from the reaction mixtures in yields up to 65%. Treatment of these compounds with benzoyl isothiocyanate in acetone afforded the corresponding 1-alkyl-5-[[*N'*-benzoyl(thiocarbamoyl)]amino]imidazole-4-carboxamides (**2**) in high yields. The compounds **2** could be isolated or hydrolyzed in situ under mild conditions to the corresponding thioureas (**3**). **3a** has been described earlier,[2] while the 1-substituted compounds **3b–i** are hitherto unknown.

Scheme II



5

[a] Method A: heavy-metal salt (Cu^{2+}, Ag^{+}, Hg^{2+}) in aqueous NaOH. Method B: 35% H_2O_2/Na_2WO_4 in aqueous NaOH.

Table I. Effects of Metal Ion, the Amount and Concentration of Base, and the Temperature on the Reaction Time and Yield of Acyclovir (5h)

3h $\xrightarrow{M^{n(+)}/NaOH}$ **5h**

metal ion[a]	conc NaOH, N	NaOH/ **3h** ratio	temp, °C	time, h	yield,[b] %
Cu^{2+}	0.1	4	100	2	42
Cu^{2+}	0.1	8	100	1	80
Cu^{2+}	0.1	12	100	1	88
Cu^{2+}	1	6	25	45	94
Cu^{2+}	1	6	100	1	97
Cu^{2+}	1	12	100	0.5	100 (77)[c]
Cu^{2+}	2	4	25	24	74
Cu^{2+}	3	6	100	1	100 (92)[d]
Cu^{2+}	3	12	0	45	95
Cu^{2+}	3	12	25	4	100
Cu^{2+}	3	12	100	0.5	100
Cu^{2+}	6	12	25	2	100 (85)[c]
Ag^{+}	3	12	100	2	100
Hg^{2+}	3	12	100	2	87
Pb^{2+}	3	12	100	2	26
Zn^{2+}	3	12	100	24	16
Bi^{2+}	3	12	100	2	9
Fe^{2+}	3	12	100	2	0

[a] 1.15 equiv of metal ion to 1 equiv of **3h**. [b] Yields determined by HPLC. [c] Isolated and recrystallized. [d] Isolated.

In the accomplishment of the cyclodesulfurization (Scheme II) by use of a heavy-metal salt (method A), **3** was added to a suspension of a slight excess of the metal salt in aqueous sodium hydroxide. The reaction proceeds at 0 °C, but heating to reflux shortens the reaction time appreciably. The highest yields were obtained with copper and silver salts, while mercury salts afforded somewhat lower yields. Lead, zinc, and bismuth salts gave only poor yields, and ferro salts did not work at all (Table I).

The molar ratio of hydroxyl ions to compound **3** turned out to be essential for the yield of the ring-closure reaction, the preferable ratio being 6 equiv of hydroxyl ions to 1 equiv of **3** (Table I). The molar concentration of hydroxyl ions has, on the other hand, only a small effect on the yield. Table I summarizes the effect of the metal ion, the amount and concentration of base, and the temperature on the reaction times and yields of the 9-substituted guanine **5h**.

In order to carry out the ring closure by S-oxidation (method B), 3 was suspended in aqueous sodium hydroxide together with a catalytic amount of sodium tungstate, and an excess of 35% hydrogen peroxide was added dropwise at a temperature between 5 and 15 °C. Yields were generally lower than yields obtained by using heavy-metal salts. Similar results could be obtained by using sodium perborate as an oxidant. Yields of 9-substituted guanines prepared by either of the two ring closure methods are summarized in Table II.

Conclusions

A new, simple, and efficient synthesis of 9-substituted guanines from AICA has been developed. Having several merits over hitherto known methods, i.e. fewer reaction

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Table II. Ring Closure of 1-Alkyl-5-[(thiocarbamoyl)amino]imidazole-4-carboxamides (3) to 9-Alkylguanines (5)

		isolated yield,[a] %	
thiourea (3)	guanine (5)	method A	method B
3b	**5b**	53[b]	
3c	**5c**	96	40
3d	**5d**	83	34
3e	**5e**	91	42
3f	**5f**	93	54
3h	**5h**	92	50
3i	**5i**	61	

[a] Method A: Cu^{2+}/aqueous NaOH. Method B: 35% H_2O_2/Na_2WO_4/aqueous NaOH. [b] Based on AICA-riboside (**1b**).

steps, mild reaction conditions, higher yields, and easy workup procedures, the methodology reported should find wide application to the preparation of guanosine-type nucleoside analogues from 1-substituted AICA.

Experimental Section

General Methods. Melting points were obtained on a Büchi SMP-20 melting point apparatus and are uncorrected. ^1H and ^{13}C NMR were recorded on a JEOL FX 90Q 89.55-MHz spectrometer. Unless otherwise stated, NMR spectra were recorded in DMSO-d_6. Microanalyses were carried out by Mr. Preben Hansen in the Microanalytical Department of the H. C. Ørsted Institute, Copenhagen. All known compounds gave satisfactory microanalyses.

Reactions were followed by high-performance liquid chromatography (HPLC) carried out on Philips/Pye Unicam HPLC equipment with UV detector using a Nucleosil 10 C-18 column (Mikrolab) eluted with methanol–water mixtures and monitoring at 240 nm.

Materials. 2-(Chloromethoxy)ethyl acetate[10] and [1,3-bis(benzyloxy)-2-propoxy]methyl chloride[11] were prepared as described in the literature. Other starting materials were commercially available and were used without further purification.

5-Amino-1-methyl-1*H*-imidazole-4-carboxamide (1c). To a precooled suspension of AICA, HCl (16.3 g, 0.1 mol) in DMF (150 mL) was added 86% KOH powder (13.0 g, 0.2 mol). After the mixture was stirred for 4 h on an ice bath, during which period the mixture turned violet, methyl bromide (9.5 g, 0.1 mol) was bubbled in over 1 h at 0–8 °C. After additional stirring on an ice bath for 2 h, the solid product was filtered off, washed with cold DMF, and then stirred with water at 0 °C. Filtration, washing with water, and drying afforded 55% yield of the title compound **1c** (7.7 g) as a reddish solid: mp 251–5 °C (dec, softening from 250 °C) (lit. mp 251.5–3.5 °C,[12] mp 260 °C,[13] mp 254 °C[14]), a sample recrystallized from water had mp 260 °C dec; ^1H NMR δ 7.06 (s, 1, imidazole-H), 6.67 (br s, 2, $CONH_2$), 5.57 (br s, 2, NH_2), 3.38 (s, 3, CH_3).

5-Amino-1-propyl-1*H*-imidazole-4-carboxamide (1e). The same procedure as described for **1c** was used with *n*-propyl bromide to give 39% of **1e**: mp 240–4 °C dec, a sample recrystallized from 1-propanol had mp 243–5 °C dec; ^1H NMR δ 7.08 (s, 1, imidazole-H), 6.64 (br s, 2, $CONH_2$), 5.76 (br s, 2, NH_2), 3.74 (t, 2, NCH_2), 1.61 (m, 2, CCH_2C), 0.83 (t, 3, CH_3). Anal. Calcd for $C_7H_{12}N_4O$: C, 49.98; H, 7.19; N, 33.31. Found: C, 49.64; H, 7.28; N, 32.88.

5-Amino-1-(phenylmethyl)-1*H*-imidazole-4-carboxamide (1f). To a precooled suspension of AICA, HCl (32.6 g, 0.2 mol) in DMF (300 mL) was added 86% KOH powder (26.0 g, 0.4 mol). After the mixture was stirred for 4 h on an ice bath, benzyl chloride (25.4 g, 0.2 mol) was added dropwise to the violet reaction mixture over 3 h at 0–5 °C. The resulting suspension was stirred overnight at ambient temperature and then on an ice bath for 2 h. The solid product was filtered off, washed with cold DMF, and then stirred with water at 20 °C. Filtration, washing with water, and drying gave 65% (28.0 g) of **1f** as a grayish solid: mp 253–9 °C dec (lit. mp 254–7 °C,[12] mp 249–51 °C,[15]), a sample recrystallized from DMF had mp 261–3 °C; ^1H NMR δ 7.1–7.4 (m, 6, aromatic), 6.68 (br s, 2, $CONH_2$), 5.81 (br s, 2, NH_2), 5.07 (s, 2, NCH_2).

5-Amino-1-[[2-(acetyloxy)ethoxy]methyl]-1*H*-imidazole-4-carboxamide (1g). To a precooled suspension of AICA, HCl (196 g, 1.2 mol) in DMF (1.8 L) was added 86% KOH powder (156 g, 2.4 mol). The suspension was stirred on an ice bath for 5 h. To the resulting violet mixture was added 2-(chloromethoxy)ethyl acetate (184 g, 1.2 mol) dropwise over 1 h at 0–8 °C. After additional stirring for 0.5 h the reaction mixture was concentrated first in water-jet vacuum and then in oil pump vacuum. The residue was stirred in methanol (150 mL), and acetone (1 L) was added. The mixture was filtered through silica gel (450 g), and the silica gel was washed with acetone–methanol, 15:1. The combined filtrate and wash was evaporated on a rotary evaporator to leave a solid, which was recrystallized from ethanol to give 41% (119 g) of **1g**, mp 131–4 °C. Another recrystallization from ethanol raised the mp to 135–6 °C: ^1H NMR δ 7.24 (s, 1, imidazole-H), 6.73 (br s, 2, $CONH_2$), 5.86 (br s, 2, NH_2), 5.27 (s, 2, NCH_2), 4.10 + 3.62 (dbl t, 2 + 2, CH_2CH_2), 1.99 (s, 3, CH_3). Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.62; H, 5.83; N, 23.13. Found: C, 44.43; H, 5.76; N, 23.20.

5-Amino-1-ethyl-1*H*-imidazole-4-carboxamide (1d). The same procedure as described for **1g** was used with ethyl bromide to give 27% of **1d**: mp 226–8 °C dec (lit. mp 223.5–226 °C,[12] mp 230–2 °C,[13]); ^1H NMR δ 7.13 (s, 1, imidazole-H), 6.81 (s, 2, $CONH_2$), 5.81 (s, 2, NH_2), 3.82 (q, 2, NCH_2), 1.25 (t, 3, CH_3).

5-Amino-1-[(2-hydroxyethoxy)methyl]-1*H*-imidazole-4-carboxamide (1h). A solution of **1g** (6.05 g, 25 mmol) in ethanol (60 mL) and 25% aqueous NH_3 (30 mL) was stirred at ambient temperature for 65 h. The solvent was removed in vacuo, and the residue was crystallized from acetone to give pure **1h** (4.50 g, 90%) as a white solid: mp 132–3 °C (lit. mp 130–1 °C[9a]); ^{13}C NMR (90 MHz, D_2O) δ 165.8 ($CONH_2$), 141.4 (C-5), 130.2 (C-2), 109.4 (C-4), 70.9 (OCH_2N), 67.1 ($HOCH_2CH_2$), 57.7 ($HOCH_2CH_2$).

5-Amino-1-[(1,3-dihydroxy-2-propoxy)methyl]-1*H*-imidazole-4-carboxamide (1i). To a precooled suspension of AICA, HCl (16.3 g, 0.1 mol) in DMF (150 mL) was added 86% KOH powder (13.0 g, 0.2 mol). After stirring on an ice bath for 3 h, [1,3-bis(benzyloxy)-2-propoxy]methyl chloride was added dropwise to the violet mixture over 1 h at 0–5 °C. After additional stirring for 0.5 h the reaction mixture was concentrated first in water-jet vacuum and then in oil pump vacuum. The residue was stirred with acetone (400 mL) for 45 min and filtered through silica gel. The silica gel was washed with acetone, and the combined filtrate and wash was evaporated on a rotary evaporator. The residue was extracted with hexane (100 mL). The hexane phase was washed with water, whereupon removal of the solvent in vacuo afforded crude 5-amino-1-[[1,3-bis(benzyloxy)-2-propoxy]methyl]-1*H*-imidazole-4-carboxamide (28.6 g, 75%) as a yellow oil. This oil was dissolved in 80% aqueous methanol (1.7 L) and hydrogenated over 10% Pd–C (10 g) at 10 atm of H_2 pressure, 80 °C, for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo and the residues filtered through silica gel. The silica gel was washed with acetone–methanol, 2:1. The combined filtrate and wash was evaporated on a rotary evaporator, and the residue was crystallized from 2-propanol to yield **1i** (4.2 g, 18% based on AICA) as a white solid: mp 126.0–8.5 °C; ^1H NMR δ 7.24 (s, 1, imidazole-H), 6.80 (br s, 2, $CONH_2$), 5.80 (br s, 2, NH_2), 5.34 (s, 2, NCH_2O), 4.75 (t, 2, OH), 3.45 (br s, 5, $CH(CH_2OH)_2$). Anal. Calcd for $C_8H_{14}N_4O_4$: C, 41.73; H, 6.13; N, 24.34. Found: C, 41.67; H, 6.23; N, 24.17.

5-[[*N'*-Benzoyl(thiocarbamoyl)]amino]-1-methyl-1*H*-imidazole-4-carboxamide (2c). **1c** (6.3 g, 45 mmol) and benzoyl isothiocyanate (7.7 g, 47 mmol) were refluxed in acetone (90 mL) under nitrogen for 4 h. Cooling on an ice bath, filtration, washing with acetone, and drying afforded **2c** (13.0 g, 95%) as a white solid: mp 194–6 °C.

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Compounds **2d–f** were prepared by the same procedure:

5-[[*N'*-Benzoyl(thiocarbamoyl)]amino]-1-ethyl-1*H*-imidazole-4-carboxamide (2d): yield 92%; mp 178–80 °C.

5-[[*N'*-Benzoyl(thiocarbamoyl)]amino]-1-propyl-1*H*-imidazole-4-carboxamide (2e): yield 94%; mp 163–4 °C.

5-[[*N'*-Benzoyl(thiocarbamoyl)]amino]-1-(phenylmethyl)-1*H*-imidazole-4-carboxamide (2f): yield 88%; mp 181.0–2.5 °C.

1-Methyl-5-[(thiocarbamoyl)amino]-1*H*-imidazole-4-carboxamide (3c). To **2c** (12.1 g, 40 mmol) in acetone–methanol (1:1, 200 mL) was added potassium carbonate (2.8 g, 20 mmol) in water (12 mL). The mixture was heated to reflux under nitrogen for 6 h, whereupon acetic acid (2.9 g, 48 mmol) was added. After cooling on an ice bath the solid product was filtered off, washed, and dried to give **3c** (7.7 g, 96%) as a white solid: mp 270–4 °C dec. A sample recrystallized from water had mp 280–3 °C (dec, conversion begins about 220 °C): ^{13}C NMR δ 184.0 (C=S), 163.9 ($CONH_2$), 134.8 (C-5), 130.2 (C-2), 127.3 (C-4), 30.9 (CH_3). Anal. Calcd for $C_6H_9N_5OS$: C, 36.17; H, 4.55; N, 35.16. Found: C, 36.06; H, 4.53; N, 35.05.

Compounds **3d–f** were prepared by the same procedure.

1-Ethyl-5-[(thiocarbamoyl)amino]-1*H*-imidazole-4-carboxamide (3d): yield 93%; mp 265–8 °C dec; ^{13}C NMR δ 183.8 (C=S), 163.9 ($CONH_2$), 133.8 (C-5), 129.1 (C-2), 127.8 (C-4), 39.0 (CH_3CH_2), 15.2 (CH_3CH_2). Anal. Calcd for $C_7H_{11}N_5OS$: C, 39.42; H, 5.20; N, 32.84. Found: C, 39.37; H, 5.19; N, 32.71.

1-Propyl-5-[(thiocarbamoyl)amino]-1*H*-imidazole-4-carboxamide (3e): yield 92%; mp 197–8 °C dec; ^{13}C NMR δ 183.8 (C=S), 163.9 ($CONH_2$), 134.4 (C-5), 129.2 (C-2), 127.7 (C-4), 45.7 ($CH_3CH_2CH_2$), 22.7 ($CH_3CH_2CH_2$), 10.8 ($CH_3CH_2CH_2$). Anal. Calcd for $C_8H_{13}N_5OS$: C, 42.27; H, 5.77; N, 30.81. Found: C, 42.16; H, 5.84; N, 30.86.

1-(Phenylmethyl)-5-[(thiocarbamoyl)amino]-1*H*-imidazole-4-carboxamide (3f): yield 88%; mp 264–6 °C dec; ^{13}C NMR δ 183.8 (C=S), 163.9 ($CONH_2$), 136.5 (C-5), 134.5 (Ph), 129.6 (C-2), 128.6 (Ph), 127.7 (C-4), 127.4 (Ph), 47.6 ($PhCH_2$). Anal. Calcd for $C_{12}H_{13}N_5OS$: C, 52.34; H, 4.76; N, 25.44. Found: C, 52.31; H, 4.73; N, 25.52.

1-[(2-Hydroxyethoxy)methyl]-5-[(thiocarbamoyl)amino]-1*H*-imidazole-4-carboxamide (3h). 1g (44.0 g, 182 mmol) and benzoyl isothiocyanate (29.7 g, 182 mmol) were refluxed in acetone (430 mL) under nitrogen for 1 h. To the resulting solution was added methanol (430 mL) and potassium carbonate (14.9 g, 108 mmol) in water (45 mL). The mixture was heated to reflux for 4 h, and after cooling to room temperature the pH was adjusted to 8 by adding acetic acid. After the mixture was cooled to 0 °C, the solid product was filtered off, washed with acetone, and then stirred with water (100 mL) at 0 °C for 10 min. Filtration, washing with water, and drying at 70 °C afforded **3h** (39.2 g, 83%) as a white solid: mp 181–3 °C dec, a sample recrystallized from water had mp 182–3 °C dec; ^{13}C NMR δ 183.9 (C=S), 163.7 ($CONH_2$), 134.9 (C-5), 129.3 (C-2), 127.9 (C-4), 74.0 (OCH_2N), 70.4 ($HOCH_2CH_2$), 59.7 ($HOCH_2CH_2$). Anal. Calcd for $C_8H_{13}N_5O_3S$: C, 37.06; H, 5.05; N, 27.01; S, 12.37. Found: C, 36.92; H, 5.07; N, 27.30; S, 12.28.

1-[(1,3-Dihydroxy-2-propoxy)methyl]-5-[(thiocarbamoyl)amino]-1*H*-imidazole-4-carboxamide (3i). The title compound was prepared from **1i** by the same method as described for **3h**: yield 31%; mp 185 °C dec; ^{13}C NMR δ 183.8 (C=S), 163.9 ($CONH_2$), 134.8 (C-5), 129.2 (C-2), 127.9 (C-4), 80.2 ($(HOCH_2)_2CH$), 73.5 (OCH_2N), 60.7 ($HOCH_2CH$). Anal. Calcd for $C_9H_{15}N_5O_4S$: C, 37.36; H, 5.23; N, 24.21; S, 11.08. Found: C, 37.34; H, 5.16; N, 23.81; S, 10.76.

Preparation of Compounds 5. Method A. 9-Methylguanine (5c).[16] **3c** (3.98 g, 20 mmol) was dissolved in 1 N aqueous sodium hydroxide (160 mL). Copper(II) acetate, H_2O (4.6 g, 23 mmol) was added, and the mixture was heated to reflux for 1 h. After being allowed to cool to 50 °C, the formed copper(II) sulfide was filtered off (Whatman GF/F), and the filter cake was washed with 1 N sodium hydroxide. The filtrate was acidified with acetic acid to pH 5.0. The resulting product was filtered off, washed with water, and dried to yield **5c** (3.16 g, 96%) as a white solid: mp >300 °C; ^{13}C NMR (1 N NaOD) δ 170.7 (C-6), 163.6 (C-2), 154.0 (C-4), 141.4 (C-8), 120.0 (C-5), 32.2 (CH_3).

Compounds **5d–f** were prepared by the same procedure.

9-Ethylguanine (5d):[17] yield 83%; mp >300 °C.

9-Propylguanine (5e):[16] yield 91%; mp >300 °C; ^{13}C NMR δ 156.8 (C-6), 153.3 (C-2), 151.0 (C-4), 137.4 (C-8), 116.5 (C-5), 44.2 ($CH_3CH_2CH_2$), 22.7 ($CH_3CH_2CH_2$), 10.8 ($CH_3CH_2CH_2$).

9-(Phenylmethyl)guanine (5f): yield 93% mp 305–8 °C (crystallized from DMF) (lit.[16] mp 303–4 °C); ^{13}C NMR δ 157.0 (C-6), 153.8 (C-2), 151.2 (C-4), 137.6 (C-8), 137.3 (Ph), 128.7 (Ph), 127.6 (Ph), 127.2 (Ph), 116.6 (C-5), 45.9 ($PhCH_2$).

9-[(2-Hydroxyethoxy)methyl]guanine (Acyclovir) (5h).[18]

1. 3h (10.0 g, 38.6 mmol) was added to a suspension of copper(II) sulfate (7.0 g, 44 mmol) in 6 N sodium hydroxide (80 mL). The mixture was stirred at ambient temperature for 4 h, after which time HPLC indicated formation of **5h** in 100% yield. Formed copper(II) sulfide was filtered off (Whatman GF/F), and the filter cake was washed with 1 N sodium hydroxide. The filtrate was acidified with 50% aqueous acetic acid. The solution was heated to reflux for a few minutes and then cooled to 5 °C. The product was filtered off and recrystallized from water using activated charcoal to give pure **5h**·$^3/_4H_2O$ (7.8 g, 85%) as a white solid: mp ca. 250 °C dec; ^{13}C NMR δ 156.8 (C-6), 153.8 (C-2), 151.4 (C-4), 137.8 (C-8), 116.5 (C-5), 72.1 (OCH_2N), 70.4 ($HOCH_2CH_2$), 59.9 ($HOCH_2CH_2$).

2. 3h (10.0 g, 38.6 mmol) was added to a suspension of copper(II) acetate, H_2O (8.1 g, 40.5 mmol) in 3 N sodium hydroxide (80 mL). The mixture was heated to reflux for 1 h. After being allowed to cool to 35 °C the formed copper(II) sulfide was filtered off (Whatman GF/F) and washed with 1 N sodium hydroxide. The filtrate was acidified with 37% hydrochloric acid until pH 5.1. Cooling to 5 °C, filtration, washing with water, and drying gave **5h**·$^3/_4H_2O$ (8.5 g, 92%) as an off-white solid. HPLC indicated 99% purity.

9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine (Ganciclovir) (5i).[11,19] **3i** (0.58 g, 2.0 mmol) was added to a suspension of copper(II) sulfate (0.32 g, 2.3 mmol) in 3 N sodium hydroxide (8 mL). The mixture was heated to reflux for 1 h, after which time HPLC indicated formation of **5i** in 100% yield. After cooling to room temperature copper(II) sulfide was filtered off (Whatman GF/F), and the filter cake was washed with 1 N sodium hydroxide. The filtrate was acidified with 50% aqueous acetic acid. The solution was heated to reflux with activated charcoal and filtered hot. The product separated upon cooling to 5 °C. Filtration, washing with water, and drying afforded **5i**·$^3/_4H_2O$ (0.33 g, 61%) as a white solid: mp ca. 245 °C dec; ^{13}C NMR δ 157.0 (C-6), 153.9 (C-2), 151.3 (C-4), 137.6 (C-8), 116.3 (C-5), 79.9 ($(HOCH_2)_2CH$), 71.4 (OCH_2N), 60.8 ($HOCH_2CH$).

9-β-D-Ribofuranosylguanine (Guanosine) (5b). AICA riboside **1b** (4.96 g, 19.2 mmol) and benzoyl isothiocyanate (3.26 g, 20 mmol) were dissolved in DMF (50 mL). The mixture was stirred at room temperature overnight. Removal of the solvent in vacuo afforded an oily residue (13.9 g) which was dissolved in acetone (40 mL) and methanol (40 mL). Potassium carbonate (1.59 g, 11.5 mmol) in water (8 mL) was added, and the mixture was heated to reflux for 5 h. Removal of the solvent in vacuo afforded crude **3b** (14.6 g) as an oil.

The oil was dissolved in 3 N NaOH (52 mL). Copper(II) acetate, H_2O (4.19 g, 21 mmol) was added, and the mixture was heated to reflux for 1.5 h, after which time HPLC indicated formation of **5b** in 71% yield. After cooling to room temperature, copper(II) sulfide was filtered off (Whatman GF/F), and the filter cake was washed with 1 N sodium hydroxide. The filtrate was acidified with 37% hydrochloric acid until pH 5.0. Cooling to 5 °C, filtration, washing with water and acetone, and drying gave crude **5b** (5.62 g) as a greenish solid. HPLC indicated 59% purity. Recrystallization from water (treating with activated charcoal)

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afforded **5b**·H_2O (3.00 g, 53% based on **1b**) as a grayish solid. HPLC indicated 95% purity. The product was shown to be identical with an authentic sample of guanosine H_2O.

Method B. 9-(Phenylmethyl)guanine (5f). **3f** (2.75 g, 10 mmol) and sodium tungstate (0.1 g) were suspended in 6 N sodium hydroxide (20 mL) at 5 °C; 35% hydrogen peroxide (4.0 mL, 44 mmol) was added dropwise at 5–15 °C over 30 min. Water (60 mL) was added to the resulting mixture, and after additional stirring on an ice bath for 1 h, the pH was adjusted to 5 with dilute HCl. The product separated and was isolated by filtration, washed with water, and dried to afford pure **5f** (1.30 g, 54%). The product was identical with **5f** prepared by method A. Compounds **5c–e** were prepared in similar yields by the same procedure.

9-[(2-Hydroxyethoxy)methyl]guanine (Acyclovir) (5h). **3h** (2.59 g, 10.0 mmol) and sodium tungstate (0.05 g) were dissolved in 6 N sodium hydroxide (20 mL) at 5 °C; 35% hydrogen peroxide (4.0 mL, 44 mmol) was added dropwise at 5–15 °C over 15 min, and stirring on an ice bath was continued for additionally 15 min, after which time HPLC indicated formation of the title compound in 59% yield. The pH was adjusted to 5.5 with 4 N acetic acid, and the product was isolated by filtration, washed with water, and dried to afford **5h**·$^3/_4H_2O$ (1.13 g, 50%) as a white solid identical with **5h** prepared by method A.

Registry No. **1a**, 360-97-4; **1**·HCl, 72-40-2; **1b**, 2627-69-2; **1c**, 21343-04-4; **1d**, 67790-32-3; **1e**, 61507-88-8; **1f**, 3815-69-8; **1g**, 118966-30-6; **1h**, 77856-29-2; **1i**, 131490-62-5; **2c**, 131490-63-6; **2d**, 131490-64-7; **2e**, 131490-65-8; **2f**, 131490-66-9; **3c**, 131490-67-0; **3d**, 131490-68-1; **3e**, 131490-69-2; **3f**, 131490-70-5; **3h**, 131490-71-6; **3i**, 131490-72-7; **5b**, 118-00-3; **5c**, 5502-78-3; **5d**, 879-08-3; **5e**, 22917-85-7; **5f**, 14937-72-5; **5h**, 59277-89-3; **5i**, 82410-32-0; MeBr, 74-83-9; PrBr, 106-94-5; $PhCH_2Cl$, 100-44-7; $ClCH_2OCH_2CH_2OAc$, 40510-88-1; EtBr, 74-96-4; $(PhCH_2OCH_2)_2CHOCH_2Cl$, 74564-16-2; PhCONCS, 532-55-8.

1-(Carbazol-9-ylmethyl)benzotriazole Anion: A Formyl Anion Equivalent

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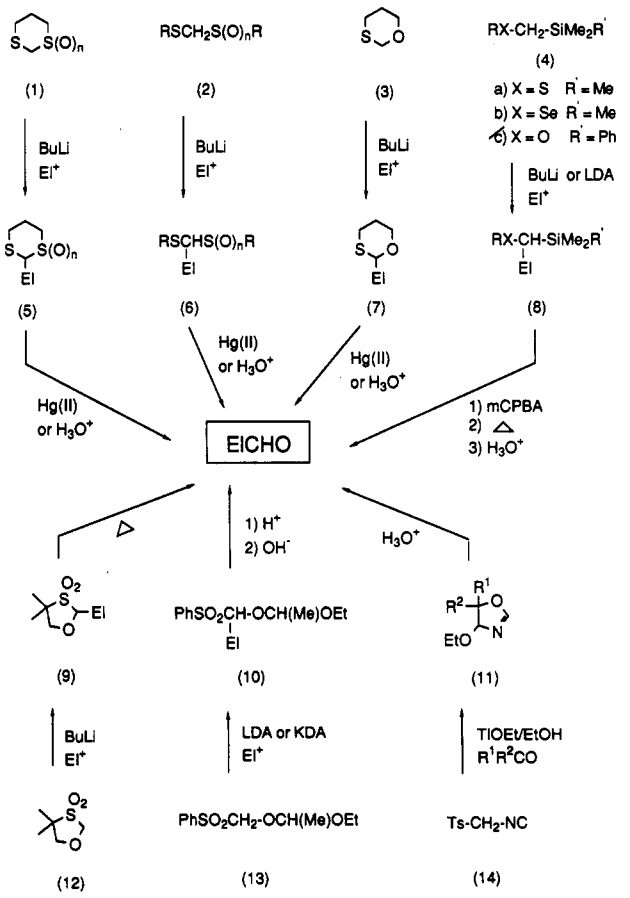
The title anion, readily available as its lithium derivative, smoothly reacts with a wide range of electrophiles to give well-characterized products which are easily hydrolyzed to the corresponding aldehydes in high overall yields. The method is compared with currently available routes.

Introduction

As lack of stability greatly limits the use of formyl ($^-$C-H=O) and acyl ($^-$CR=O) anions,[1] various masked synthons have been developed.[2] Important formyl anion equivalents are of the type XYCH$^-$ where X and Y are heteroatoms (Scheme I). Dithioformyls employed include the 1,3-dithione[3] (**1**; n = 0), and bis(alkylthio)[4] (**2**; R = alkyl, n = 0), bis(arylthio)[5] (**2**; R = Ar, n = 0), and cyclic[6] analogues. Thioacetals with one sulfur atom oxidized (e.g., **1**, **2**; n = 1) have also been used.[7] Anions generated by e.g. treatment with n-butyllithium,[8] or by lithium or sodium amide in liquid ammonia,[4] with electrophiles give the corresponding thioacetals (**5–7**), which are converted to the aldehydes by complex formation with a metal ion (usually mercury(II) salts[9]) or by making one sulfur atom more electrophilic through oxidation.[10]

Other sulfur analogues used include 1,3-oxathianes[11] (**3**), α-thio silanes[12] (**4a**), α-functionalized sulfones[13,14] (**12**, **13**)

Scheme I



and TosMIC[15] (**14**). Oxidation of **8** followed by a sila-Pummerer rearrangement affords the *O*-(trimethylsilyl)-

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