## Communications to the Editor

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# CONVERSION OF GUANOSINE INTO 2-AMINOMETHYLINOSINE (2-HOMOGUANOSINE)

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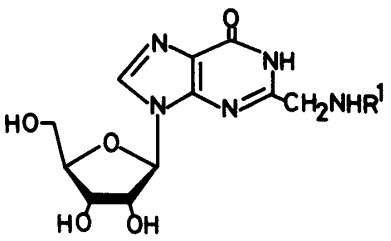
2-Aminomethylinosine (1), a one-carbon extended homolog of an exocyclic amino group of guanosine, was synthesized from guanosine by the use of a newly developed protection and deprotection method. Introduction of a methoxy group into the 6-position of 2-benzenesulfonyl-purine riboside facilitated a nucleophilic substitution with cyanide to afford 2-cyano-6-methoxypurine riboside (11) which was subsequently hydrogenated and demethylated with trimethylsilyl iodide to afford 1.

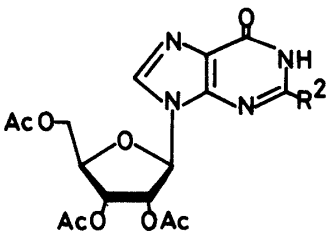
KEYWORDS—— 2-substituted purine nucleoside; 2-homoguanosine; guanosine; cyanation; benzenesulfonyl group; trimethylsilyl iodide; demethylation; non-aqueous diazotization

Efforts have been directed to the synthesis of nucleoside and nucleobase antimetabolites for chemotherapeutic drugs. A least modification of the parent structure would be necessary for designing active antimetabolites such as 5-fluorouracil, 6-mercaptopurine, and 1-β-D-arabinofuranosylcytosine. As one of the possible designs, we have developed the homologation of exocyclic amino functions in the base moiety of nucleosides, such as 6-homoadenosine analogues.[1] In this communication, we describe the synthesis of 2-aminomethylinosine (1), 2-homoguanosine, a one-carbon unit extended homolog of an exocyclic amino group of guanosine.

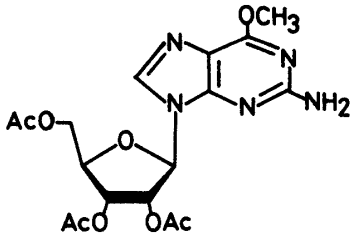
The most straightforward approach to 2-homoguanosine (1) would appear to be to utilize 2-methanesulfonylinosine derivative (3), which is readily obtained from its adenosine counterpart[2] by hydrolytic deamination, as one of the starting materials. In contrast to 2-methanesulfonyladenosine, however, this inosine analog (3) failed in reaction with cyanide to afford the 2-cyanoinosine derivative (4),[3] from which 1 could be directly obtained by subsequent catalytic reduction of the cyano group. Although we have reported[2,4,5] that a methanesulfonyl group as a leaving group is superior to a halogeno group in the 2-,6-, and 8-positions of purine nucleosides for the nucleophilic substitution reaction with carbon nucleophiles, this inertness of 3 could be explained by the presence of a dissociable N-1 proton interfering with the reaction. This difficulty could be circumvented by introducing a methoxy group in the 6-position of the purine nucleoside to block the dissociable proton if the methyl group could be removed at the final stage of the



1 : $R^1$ = H
2 : $R^1$ = Ac



3 : $R^2$ = $SO_2Me$
4 : $R^2$ = CN
5 : $R^2$ = $NH_2$



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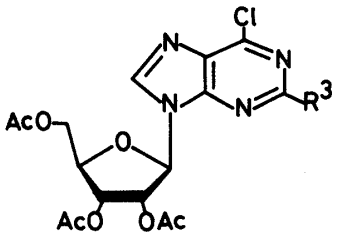
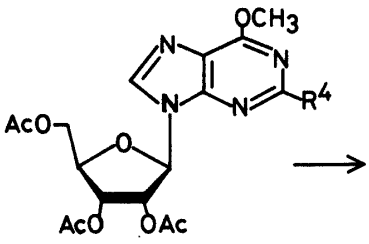
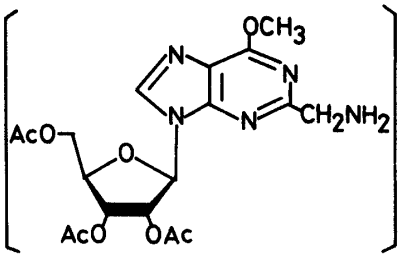


7 : $R^3$ = $NH_2$
8 : $R^3$ = SPh



9 : $R^4$ = SPh
10 : $R^4$ = $SO_2Ph$
11 : $R^4$ = CN
12 : $R^4$ = $CONH_2$



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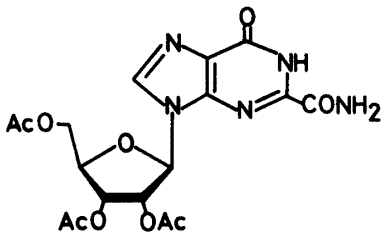

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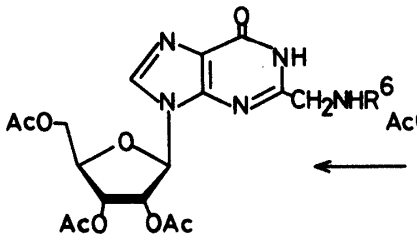
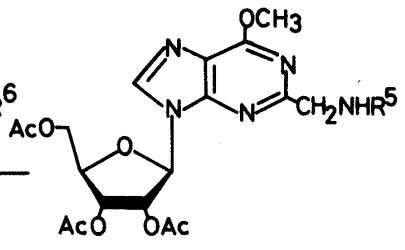


16 : $R^6$ = Ac
17 : $R^6$ = $COCF_3$



14 : $R^5$ = Ac
15 : $R^5$ = $COCF_3$

reaction sequences without affecting other functionalities, especially the glycosidic linkage. Therefore demethylation of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-amino-6-methoxypurine (6) was investigated first. Treatment of 6 with trimethylsilyl iodide (prepared from trimethylsilyl chloride and sodium iodide in acetonitrile)[6] at room temperature for 1 h gave the guanosine derivative (5) in 90% yield. This experiment clearly shows that trimethylsilyl iodide is capable of effecting complete deblocking of the methyl function without cleaving the glycosidic linkage and is promising for preparation of 1 using this strategy.

Introduction of a sulfur function of appropriate purine nucleosides at the 2-position was accomplished by the non-aqueous diazotization-substitution method[7] which has been successfully utilized to introduce halogeno and carbon functionalities at the 2-and 6-positions of purine nucleosides. When 7, used as the starting material obtained in two steps from guanosine,[8] was heated with diphenyl disulfide in the presence of isoamyl nitrite in acetonitrile, 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-chloro-2-phenylthiopurine (8) was isolated as a yellowish foam [57%; $M^+$ m/z 520] after chromatographic purification over a silica gel column. A subsequent treatment of 8 with NaOMe in MeOH followed by acetylation of the sugar portion afforded 9 [98%, foam; $M^+$ m/z 516; δ 3.94 (s,3H,OMe)[9]]. The sulfur function of 9 was oxidized with $KMnO_4$ in aqueous acetic acid to give the 2-phenylsulfone [10, foam; $M^+$ m/z 548; δ 4.10 (s,3H,OMe)] in 92% yield. Compound 10 was allowed to react with NaCN in DMF at ambient temperature for 5 h and 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-cyano-6-methoxypurine (11) was isolated in 71% yield as a crystalline solid [mp 188-189°C (MeOH); $M^+$ m/z 433; IR $\nu_{max}^{KBr}$ $cm^{-1}$: 2235 (CN)]. Thus, it is clear that inertness of 3 towards reaction with cyanide is due to the presence of the dissociable N-1 proton.

The cyano group in 11 was subsequently converted to an aminomethyl group by hydrogenation over Pd/C in ethanolic acetic acid. Isolation of 13 was tedious and concurrent demethylation of crude 13 with trimethylsilyl iodide gave a complex mixture due to the O N acetyl migration. These observations suggested that blocking the primary amino group should be necessary for further conversions. Therefore 13 was acetylated first with $Ac_2O$ to 14 which was subjected to demethylation with trimethylsilyl iodide. After short-column chromatography, demethylated product (16) was isolated as a colorless foam in 87% yield. Treatment of 16 with MeOH-$NH_3$ led to crystallization of 2-acetamidomethylinosine (2) as one of the desired products in 91% yield, mp 195-196°C (MeOH-AcOEt). The $^1$H-NMR spectrum of 2 [δ 1.91 (s,3H,-$CH_2$NHAc), 4.22 (d,2H,-$\underline{CH_2}$NHAc), 8.33 (t,1H,-$CH_2\underline{NH}$Ac, exchangeable), 12.16 (br s,1H,NH, exchangeable)] is in good agreement with its structure. In a similar way, trifluoroacetylation of 13 was carried out, then 15 was demethylated as above. Deacylation of 17 (foam, 76% yield from 11) afforded the desired 2-homoguanosine [1, 38%,[10] mp 150-153°C (eff.); δ 3.17 (s,2H,-$\underline{CH_2}NH_2$); positive ninhydrin test]. Purification of 17 by silica gel column chromatography was crucial in order to obtain pure 1.

Attempted demethylation of 11 prior to catalytic reduction of the cyano group caused glycosidic bond cleavage. On the other hand, carboxamide (12),[11] which was derived from 11 by alkaline hydrolysis, was smoothly demethylated into 18 in 88% yield by the treatment with trimethylsilyl iodide.[12]

Thus, introduction of a methoxy group at the 6-position facilitated nucleo-

philic substitution of the 2-phenylsulfone with cyanide and removal of its methyl group was easily achieved by use of trimethylsilyl iodide to regenerate the lactam functionality in the base moiety of oxypurine nucleosides. This methodology provides convenient access to 2-carbon substituted inosines and may also be applied to the oligonucleotide synthesis to avoid undesirable side reactions in oxypurine moieties.

## REFERENCES AND NOTES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8) For a recent method, see: M. J. Robins and B. Uznanski, Can. J. Chem., 59, 2601 (1981).
9) The $^1$H-NMR spectra given in this paper were measured in DMSO-$d_6$.
10) The yield of this compound was not optimal. Biological activity of the compounds described here will be reported elsewhere.
11) Compound 12 was isolated as a colorless foam; $M^+$ m/z 451; δ 4.19 (s,3H,OMe), 7.84, 8.13 (br s each, 2H,-CO$\underline{NH}_2$, exchangeable).
12) Compound 18 was obtained as crystals [mp 208-209°C (EtOH); $M^+$ m/z 437; δ 8.16, 8.29 (br s each, 2H,-CO$\underline{NH}_2$, exchangeable), 12.10 (br s, 1H, NH, exchangeable)]. Deacetylation of 18 with MeOH-$NH_3$ afforded a free inosine 2-carboxamide as a crystalline solid [mp 250-251°C ($H_2O$); δ 8.11, 8.30 (br s each, 2H,-CO$\underline{NH}_2$, exchangeable), 12.10 (br s, 1H, NH, exchangeable)].


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