Purine Nucleosides. XXIV. A New Method for the Synthesis of Guanine Nucleosides. The Preparation of 2′-Deoxy-α- and -β-guanosines and the Corresponding N^2-Methyl Derivatives[1]

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Diazotization of 2-amino-6-benzyloxypurine in fluoroboric acid produced 2-fluoro-6-benzyloxypurine (1). Acid-catalyzed fusion of 1 with 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose (2) gave the anomeric 2-fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranosyl)purines (3). Treatment of this mixture with alcoholic ammonia (or methylamine) provided the 2-amino- (or 2-methylamino-) 6-benzyloxy-9-(2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines which were resolved into pure anomers by chromatography on Dowex 1-X2. Palladium–carbon-catalyzed hydrogenation of these benzyloxy derivatives gave the desired guanine 2′-deoxynucleosides, which obey Hudson's isorotation rules. The nmr spectra of these 2′-deoxy-D-*erythro*-pentofuranosides had a peak corresponding to an A_2X system which appeared as a "triplet" with $J_{H_1'} = 7$ Hz for the β anomer and a "quartet" with $J_{H_1'} \cong 3.5$ and 7.5 Hz for the α anomer. A facile synthesis of 2-amino-6-benzyloxypurine from 2,4,5-triamino-6-benzyloxypyrimidine is described. Alternative binding mechanisms of actinomycin D to DNA are considered with respect to N^2-methyl-2′-deoxyguanosine.

Interest in the preparation and biological evaluation of certain anomeric purine 2′-deoxynucleosides has been stimulated by the report[2] that 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-thione (α-2′-deoxythioguanosine) is incorporated *per se* into DNA. Since N^2-methylguanosine is a naturally occurring "minor component" nucleoside in RNA,[3] it is of interest to consider N^2-methyl-2′-deoxyguanosine for incorporation into DNA in order to determine physical changes[4] in the macromolecule as well as biological effects. In addition, N^2-methyl-2′-deoxyguanosine (**9**) is a valuable molecule for evaluation of the two suggested models for the binding of actinomycin D to DNA. According to the model of Müller and Crothers,[5] the actinomycin D chromophore is intercalated between the base pairs in the DNA complex adjacent to any guanine–cytosine base pair. The guanine specificity is attributed to electronic interactions in the intercalated π complex. In contrast, a free 2-amino group of guanine is required for hydrogen bonding in the actinomycin D–DNA complex model of Reich and coworkers.[6] Therefore a synthetically polymerized DNA with N^2-methyl-2′-deoxyguanosine (**9**) in place of 2′-deoxyguanosine (**8**) could not bind actinomycin D by the Reich mechanism[6] but should bind to some extent (uv spectra of **8** and **9** are qualitatively and quantitatively similar) by the π-complex[5] mechanism.

Several approaches have been employed in the synthesis of nucleosides of the guanine ring system.[7] However, certain of these procedures involve high-temperature amination and/or acidic deamination steps and are somewhat unsuited for the preparation of deoxyguanosines. Indeed, 2′-deoxyguanosine (**8**) has been prepared previously in 1.5%[7b] and 4.4%[7e] over-all yields based on purine starting materials.

Success in the fusion procedure[8] of deoxynucleoside synthesis[9] suggested a new approach to the problem. The synthesis of 2′-deoxyguanosine (**8**) and its α anomer **10** (obtained for the first time) has now been accomplished in 14 and 16% yields, respectively, from starting purine **1** *via* the fusion method (Scheme I). This procedure also precluded any toxic mercury ion contamination.[10]

The starting material base chosen for the fusion procedure was 2-fluoro-6-benzyloxypurine which has a group at the 2 position readily susceptible to nucleophilic displacement[11,12] and the benzyloxy function at the 6 position which can be readily converted to keto oxygen by hydrogenation at neutral pH. Ring closure of 2,4,5-triamino-6-benzyloxypyrimidine[13] with diethoxymethyl acetate[14] gives a convenient alternative synthesis of 2-amino-6-benzyloxypurine.[15] Treatment of 2-amino-6-benzyloxypurine with sodium nitrite in aqueous fluoroboric acid according to the general procedure of Montgomery and Hewson[16] gave 2-fluoro-6-benzyloxypurine (**1**), the desired base for fusion coupling in 48% yield.

Acid-catalyzed fusion of **1** and 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erthro*-pentofuranose[9] (**2**) gave 2-fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines (**3**) in at least 40% yield as a syrupy mixture. Treatment of this product with methanolic ammonia at 80° gave 2-amino-6-benzyloxy-9-(2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines

(1) This work was supported by Research Grant CA 08109 from the National Cancer Institute of the National Institutes of Health.

(2) G. A. LePage and I. G. Junga, *Mol. Pharmacol.*, **3**, 37 (1967).

(3) R. H. Hall, *Biochemistry*, **4**, 661 (1965), and references therein.

(4) See, for example, P. R. Srinivasan and E. Borek, *Science*, **145**, 548 (1964); A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o, *J. Amer. Chem. Soc.*, **89**, 3612 (1967).

(5) W. Müller and D. M. Crothers, *J. Mol. Biol.*, **35**, 251 (1968).

(6) E. Reich and I. H. Goldberg, *Prog. Nucleic Acid Res. Mol. Biol.*, **3**, 183 (1964); A. Cerami, E. Reich, D. C. Ward, and I. H. Goldberg, *Proc. Natl. Acad. Sci. U. S.*, **57**, 1036 (1967).

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(12) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **11**, 48 (1968).

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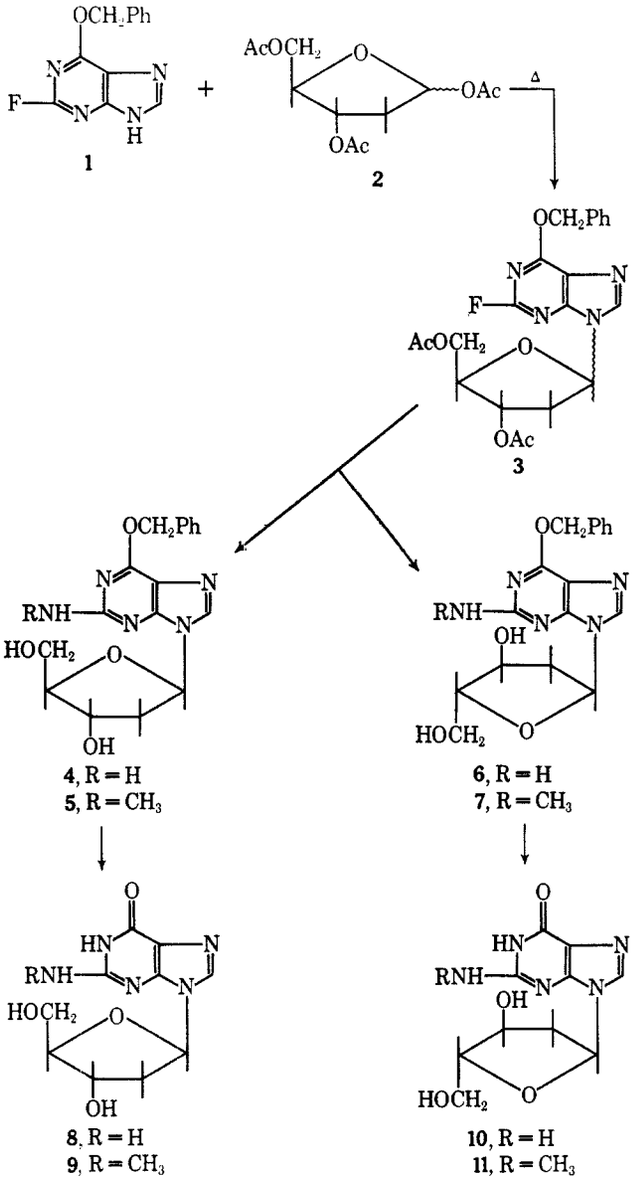
(16) J. A. Montgomery and K. Hewson, *J. Amer. Chem. Soc.*, **82**, 463 (1960).

SCHEME I



(6 and 4) in contrast to results reported with analogous treatment of 2-chloro-6-methoxy-9-β-D-ribofuranosylpurine.[17] In the latter case the 6-alkoxy function was selectively replaced by ammonia and thus the successful choice of the 2-fluoro leaving group is suggested. The anomers **4** and **6** were resolved on a Dowex 1-X2 (OH^-) column.[18] The α anomer was crystallized and characterized by elemental analysis and uv spectroscopic comparison with the β-D-ribofuranose analog.[11] The β anomer **4** was compared with **6** spectroscopically and by thin layer chromatography (tlc) and was converted directly to 2′-deoxyguanosine (**8**) by palladium-catalyzed hydrogenation without further purification. The properties of synthetic and naturally occurring **8** were rigorously compared and found to be identical. This confirms the position of attachment and configuration of synthetic **8** and the other nucleosides obtained from the intermediate **3**. Compound **6** was similarly hydrogenated to give the first reported synthesis of 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purin-6-one (α-2′-deoxyguanosine) (**10**).

(17) H. J. Schaeffer and H. J. Thomas, *J. Amer. Chem. Soc.*, **80**, 3738 (1958).

(18) C. A. Dekker, *ibid.*, **87**, 4027 (1965).

For the synthesis of the N^2-methyl-2′-deoxyguanosines, the syrupy mixture containing the anomeric 2-fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranosyl)purines (**3**) was treated with methanolic methylamine at room temperature to give 2-methylamino-6-benzyloxy-9-(2-deoxy-α- and -β-D-*erythro*-pentofuranosyl)purines (**7** and **5**). Anomeric resolution of **5** and **7** was accomplished on Dowex 1-X2 (OH^-). These anomers had tlc behavior similar to **4** and **6** and had uv absorption comparable to the riboside analog.[11] Compound **5** was catalytically hydrogenated to the desired 2-methylamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-one (**9**) without further purification. Compound **7** was transformed to 2-methylamino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)-purin-6-one (**11**) by the same procedure. The anomers **9** and **11**, obtained in 17 and 21% over-all yield, respectively, exhibit uv spectra almost identical with those of N^2-methylguanosine.[11] The tlc migrations of **9** and **11** are identical with those of 2′-deoxyguanosine (**8**) and α-2′-deoxyguanosine (**10**), respectively (see Experimental Section). Examination of the nmr spectra of the 2′-deoxynucleosides **6** and **8**–**11** demonstrated results in accord with A_2X splitting patterns previously observed for purine 2′-deoxy-*erythro*-pentofuranosides.[9] These anomeric 2′-deoxynucleosides **8**–**11** were found to obey Hudson's isorotation rule[19] in dimethylformamide.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra were determined on a Varian A-60 instrument with sodium 5,5-dimethyl-5-silapentanesulfonate as internal standard. Uv spectra were determined on a Beckman DK-2 instrument. Hydrogenations were effected using a Parr hydrogenation apparatus at specified hydrogen gas pressure. Evaporations were accomplished using a Büchler rotating evaporater under reduced pressure unless otherwise specified. Thin layer chromatography (tlc) was run on glass plates coated with SilicAR-7GF (Mallinckrodt Chemical Works) using the upper phase of ethyl acetate–*n*-propyl alcohol–water (4:1:2) unless specified otherwise.

2,4,5-Triamino-6-benzyloxypyrimidine.[13]—A solution of 50 g (0.20 mol) of 2,4-diamino-5-nitroso-6-benzyloxypyrimidine[13] in 1500 ml of 95% EtOH was reduced as previously described. The resulting solution was evaporated to dryness under a nitrogen stream. The brown residue was added to boiling EtOH–H_2O and this mixture was treated with Norit and filtered. The filtrate was cooled at 0° for 18 hr and the resulting yellow crystals (40 g, 85%) which separated were filtered. A small sample for analysis was recrystallized from EtOH–H_2O to give crystals: mp 149–151°; uv $\lambda_{max}^{pH\ 1}$ 277 mμ (ε 12,500), $\lambda_{sh}^{pH\ 1}$ 224 mμ (ε 8900), $\lambda_{max}^{pH\ 11}$ 283, 243 mμ (ε 7870, 8660), λ_{max}^{EtOH} 285, 245 mμ (ε 7230, 8660).

Anal. Calcd for $C_{11}H_{13}N_5O \cdot 0.5H_2O$: C, 55.00; H, 5.87; N, 29.16. Found: C, 55.00; H, 5.92; N, 29.14.

2-Amino-6-benzyloxypurine.[15]—To 15 g (0.093 mol) of diethoxymethyl acetate[14] was added 4.62 g (0.02 mol) of crude 2,4,5-triamino-6-benzyloxypyrimidine while stirring magnetically. The resulting red-brown solution was placed in an oil bath preheated to 185°. Vigorous boiling was moderated by raising the flask periodically. After heating for 25 min, the flask was removed from the oil bath and the thick pasty mass was allowed to cool to about 100° and then was evaporated to dryness. Water (20 ml) was added to the brown residue and NaOH pellets were added slowly until all solid material dissolved. This solution (pH >12) was refluxed for 15 min, treated with Norit, refluxed 5 min, and filtered through a Norit–Celite pad. The hot filtrate was acidified to pH ~6 with HOAc and the resulting mixture was cooled at 0° for 18 hr. The orange crystalline solid

(19) C. S. Hudson, *ibid.*, **31**, 66 (1909); *Advan. Carbohydrate Chem.*, **3**, 1 (1948).

(3.90 g, 81%) was filtered and recrystallized from EtOH–H_2O (using Norit) to yield 3.0 g (62%) of crystals, mp 197–200°, chromatographically homogeneous (tlc) and identical with authentic 2-amino-6-benzyloxypurine.[15] A small sample was recrystallized from EtOH–H_2O to give needles: mp 204–206°; uv $\lambda_{max}^{pH\ 1}$ 286 mμ (ε 12,100), $\lambda_{max}^{pH\ 11}$ 282 mμ (ε 9400), λ_{max}^{MeOH} 282, 241 mμ (ε 9200, 7500); lit.[15] mp 202–204°, mmp 203–205°.

Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.59; H, 4.36; N, 29.13.

2-Fluoro-6-benzyloxypurine (1).—To 90 ml of 48% fluoroboric acid precooled to −25° in an *i*-PrOH–Dry Ice bath was added 7.3 g (0.03 mol) of 2-amino-6-benzyloxypurine with vigorous stirring. A solution of 3.5 g (0.05 mol) of $NaNO_2$ in 4.5 ml of H_2O was added dropwise over a period of 20 min to the vigorously stirred mixture and the reaction temperature was carefully maintained at −20 to −25°. The mixture was allowed to stir an additional 20 min at −25 to −18° and then was carefully neutralized to pH ~6 with 50% aqueous NaOH solution while keeping the inside temperature −15 to −10°. The mixture was allowed to stand at 0° for 15 hr and then was filtered to give 6.3 g of solid after air drying. This solid was finely powdered and continuously extracted with absolute Et_2O for 10 days (while protected from moisture). The ether was evaporated to yield 4.4 g of yellow solid which was recrystallized from absolute EtOH to yield 3.54 g (48%) of 2-fluoro-6-benzyloxypurine (1): mp 184–185°; uv $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 13,400), $\lambda_{max}^{pH\ 11}$ 263 mμ (ε 12,900), λ_{max}^{MeOH} 256 mμ (ε 12,700), λ_{Sh}^{MeOH} 270.5, 260.5, 239 mμ (ε 3540, 11,400, 7600).

Anal. Calcd for $C_{12}H_9FN_4O$: C, 59.01; H, 3.71; F, 7.78; N, 22.94. Found: C, 58.84; H, 3.78; F, 7.95; N, 22.73.

Acid-Catalyzed Fusion of 2-Fluoro-6-benzyloxypurine (1) and 1,3,5-Tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose (2).—To 3.50 g (0.0135 mol) of 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose (1,3,5-tri-*O*-acetyl-2-deoxy-D-ribose)[9] (2) in a 25-ml round-bottom flask was added 2.0 g (0.0082 mol) of finely powdered 2-fluoro-6-benzyloxypurine (1). This mixture was stirred well and placed in an oil bath preheated to 145°. The mixture was stirred several minutes and then 5 drops of dichloracetic acid was added with vigorous stirring. Stirring was continued until a clear amber melt formed. An oil pump was then attached to the reaction flask and fusion was continued at 145° (*in vacuo*) for 25 min. The melt was removed from the oil bath and allowed to cool to about 100° and then was dissolved in 50 ml of EtOAc. This solution was cooled in ice–H_2O and then extracted with two 30-ml portions of ice-cold saturated aqueous Na_2CO_3 solution, ice–H_2O to pH ~6, and dried over Na_2SO_4. The mixture was filtered using a Norit–Celite bed and the filtrate was evaporated to a viscous oil. The uv spectra of this syrup had λ_{max} 255.5 mμ with no shift from acidic to basic solution in EtOH. Tlc (SilicAR-7GF $CHCl_3$–Me_2CO, 9:1) showed the presence of one major uv quenching spot and several minor products. This syrup containing the anomeric mixture **3** did not crystallize and was used directly for amine displacements.

2-Amino-6-benzyloxy-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (4) and 2-Amino-6-benzyloxy-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine (6).—The above syrup containing **3** was dissolved in 20 ml of MeOH, and 130 ml of MeOH presaturated with NH_3 at −10° was added. This solution was heated at 80° in a stainless steel bomb for 4.5 hr. To the cooled ammoniacal solution was added 8 ml (0.008 mol) of 1 *N* NaOH and this solution was evaporated to dryness. The residue was partitioned between 75 ml of EtOAc and 25 ml of H_2O. The aqueous phase was extracted with two 30-ml portions of EtOAc and the combined organic phase was washed with 40 ml of H_2O and 40 ml of saturated aqueous NaCl solution. The EtOAc layer was dried over Na_2SO_4, filtered, and evaporated to yield an off-white solid foam. This material was dissolved in 9 ml of glyme and 11 ml of H_2O was added. This solution was applied to a column (1 × 35 in., 500 ml) of Dowex 1-X2 (OH^-), 200–400 mesh resin packed in glyme–water (45:55). The column was eluted with the same solvent mixture and 10-ml fractions were collected. Fractions 1–74 were discarded. Fractions 75 to 87 were pooled and evaporated to dryness to yield 0.67 g (23%) of crude **6**. This product was dissolved in hot *i*-PrOH and cooled at 0° for several days to yield 0.4 g (14%) of **6** as white needle clusters. A small sample was recrystallized from *i*-PrOH to give needles of **6**: mp 158–160°, uv $\lambda_{max}^{pH\ 1}$ 287 mμ (ε 12,500), $\lambda_{max}^{pH\ 11}$ 280, 249 mμ (ε 12,000, 10,000), λ_{max}^{MeOH} 282, 249 mμ (ε 12,500, 10,900); the nmr spectrum in DMSO-d_6 was consistent with the assigned structure with an A_2X "quartet" with $J_{H_1'-H_2',H_2''}$ = 3.0 and 7.5 Hz (peak width 10.5 Hz) at δ 6.37 corresponding to the anomeric proton of a 2′-deoxy-α-*erythro*-pentofuranoside.[9]

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 56.91; H, 5.38; N, 19.67.

Fractions 88–97 from the above column separation were pooled and evaporated to dryness to yield 0.22 g (7.5 %) of solid which was found by tlc and nmr to consist of an approximately 65:35 mixture of the α and β anomers **6** and **4**, respectively. Fractions 98–128 were pooled and evaporated to dryness to yield 0.65 g (22%) of solid **4**. The uv spectrum of this product in alcohol was essentially the same as recorded for **6**. The nmr spectrum was similar with an A_2X "pseudotriplet" corresponding to the peak for the anomeric proton.[9] The tlc R_4/R_6 = 1.1. Crude **4** was hydrogenated to give 2′-deoxyguanosine (**8**) which conclusively confirmed structure **4**.

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-one (2′-Deoxyguanosine) (8).—To a solution of 0.60 g (0.0017 mol) of crude **4** in 30 ml of EtOH and 60 ml of H_2O was added 0.3 g of 5% palladium on charcoal and the mixture was hydrogenated at 48 psi for 7.5 hr. The catalyst was removed by filtration using a Norit–Celite bed and the filtrate was evaporated to dryness. The crystalline solid was recrystallized from 10 ml of H_2O to yield 0.33 g (69% based on crude **4**, 14% based on starting 1) of **8** monohydrate: $[\alpha]^{26}D$ −20.3° (*c* 1.2, DMF); uv $\lambda_{max}^{pH\ 1}$ 255 mμ (ε 12,100), $\lambda_{sh}^{pH\ 1}$ 272 mμ (ε 8460), $\lambda_{max}^{pH\ 11}$ 258–266 mμ (broad) (ε 12,000), λ_{max}^{MeOH} 253 mμ (ε 14,500), λ_{Sh}^{MeOH} 267 mμ (ε 10,600); nmr (DMSO-d_6, D_2O) δ 6.28 (t, 1, $J_{H_1'-H_2',H_2''}$ = 7 Hz, H_1') plus the remainder of a usual 2′-deoxy-β-*erythro*-pentofuranoside spectrum.[9] These physical characteristics were essentially identical with those determined on a similarly recrystallized commercial sample of 2′-deoxyguanosine; tlc R_8(synthetic)/R_8(natural) = 1.0.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.90; H, 5.25; N, 24.65.

2-Amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purin-6-one (10).—To a solution of 0.40 g (0.0011 mol) of crude **6** in 25 ml of EtOH and 50 ml of H_2O was added 0.2 g of 5% palladium on charcoal and the mixture was hydrogenated at 48 psi for 15 hr. The mixture was treated as in the preparation of **8** above to yield 0.22 g (71% based on crude **6**, 16% based on starting 1) of crystalline **10** hemihydrate: $[\alpha]^{26}D$ +102.4° (*c* 0.99, DMF); uv $\lambda_{max}^{pH\ 1}$ 254.5 mμ (ε 10,700), $\lambda_{Sh}^{pH\ 1}$ 274 mμ (ε 7710), $\lambda_{max}^{pH\ 11}$ 259–267 mμ (broad) (ε 9960), λ_{max}^{MeOH} 253 mμ (ε 12,000), λ_{Sh}^{MeOH} 268 mμ (ε 8830); nmr (DMSO-d_6, D_2O) δ 6.24 (q, 1, $J_{H_1'-H_2',H_2''}$ = 3.5 and 7.5 Hz, H_1'); tlc R_8/R_{10} = 1.2.

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C, 43.47; H, 5.11; N, 25.35. Found: C, 43.24; H, 5.07; N, 25.57.

Reaction of Methylamine with Syrupy 2-Fluoro-6-benzyloxy-9-(3,5-di-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranosyl)purine.—A fusion of 2-fluoro-6-benzyloxypurine and 1,3,5-tri-*O*-acetyl-2-deoxy-D-*erythro*-pentofuranose was effected in a manner identical with that described above. The syrupy product containing **3** obtained after the extraction procedure was dissolved in a minimum volume of MeOH and treated with a solution of 30 ml of liquid $MeNH_2$ in 70 ml of MeOH. The resulting yellow solution was allowed to stir at room temperature for 2 hr and 8 ml (0.008 mol) of 1 *N* NaOH was added. This solution was evaporated to dryness and the residue was partitioned between EtOAc and H_2O as described above for the preparation of the 2-amino analogs **4** and **6**. The off-white solid foam obtained by evaporating the combined, dried EtOAc phase was dissolved in 9 ml of glyme, and 11 ml of H_2O was added. This solution was applied to a column (1 × 35 in., 500 ml) of Dowex 1-X2 (OH^-) (200–400 mesh) resin packed in glyme–H_2O (45:55). Elution of the column with the same solvent mixture was begun and 10-ml fractions were collected. Fractions 1–57 were discarded. Fractions 58–82 were pooled and evaporated to dryness to yield crude 2-methylamino-6-benzyloxy-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)-purine (**7**). This product had similar uv absorption spectra to those reported[11] for 2-methylamino-6-benzyloxy-9-β-D-*ribo*-pentofuranosylpurine. The tlc migration and nmr (of the carbohydrate portion) spectrum of this product were similar to those of **6**. Fractions 83–86 contained essentially no product and were discarded. Fractions 87–130 were pooled and evaporated to dryness to yield crude 2-methylamino-6-benzyloxy-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (**5**). Again the uv spectra were similar to those reported for the riboside analog[11] and tlc migration and nmr (sugar portion) were comparable to those of **4**. These chromatographically homogeneous intermediates were

hydrogenated directly to the desired guanine-type nucleosides without further purification.

2-Methylamino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purin-6-one (9).—A solution of 0.90 g (0.0024 mol) of crude **5** in 35 ml of EtOH and 70 ml of H_2O was hydrogenated at 47 psi for 6.5 hr with 0.5 g of 5% palladium on charcoal. This mixture was treated as in the preparation of **8** above to yield 0.41 g [55% based on crude **5**, 17% based on starting 2-fluoro-6-benzyloxypurine (**1**)] of crystalline **9** hemihydrate: $[\alpha]^{26}D$ −15.2° (*c* 1.64, DMF); uv $\lambda_{max}^{pH\ 1}$ 258 mμ (ε 13,400), $\lambda_{Sh}^{pH\ 1}$ 281 mμ (ε 7370), $\lambda_{max}^{pH\ 11}$ 258 mμ (ε 11,200), $\lambda_{Sh}^{pH\ 11}$ 270 mμ (ε 10,200), λ_{max}^{MeOH} 254 mμ (ε 14,500), λ_{Sh}^{MeOH} 273 mμ (ε 9150); nmr (DMSO-d_6, D_2O) δ 6.28 (t, 1, $J_{H_1'-H_2',H_2''}$ = 7 Hz, H_1'), 2.92 (s, 3, 2-NHCH$_3$); tlc R_9/R_8 (natural) = 1.0.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.5H_2O$: C, 45.51; H, 5.56; N, 24.13. Found: C, 45.32; H, 5.58; N, 24.38.

2-Methylamino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purin-6-one (11).—A solution of 1.0 g (0.0027 mol) of crude **7** in 40 ml of EtOH and 80 ml of H_2O was hydrogenated at 48 psi for 15 hr with 0.5 g of 5% palladium on charcoal. This mixture was treated as in the preparation of **8** above to yield 0.50 g (64% based on crude **7**, 21% based on starting **1**) of crystalline **11** hemihydrate: $[\alpha]^{26}D$ +94.1° (*c* 1.55, DMF); uv $\lambda_{max}^{pH\ 1}$ 257 mμ (ε 11,400), $\lambda_{Sh}^{pH\ 1}$ 279.5 mμ (ε 6380), $\lambda_{max}^{pH\ 11}$ 257 mμ (ε 10,200), $\lambda_{Sh}^{pH\ 11}$ 269 mμ (ε 8980), λ_{max}^{MeOH} 254 mμ (ε 13,100), λ_{Sh}^{MeOH} 273 mμ (ε 8260); nmr (DMSO-d_6, D_2O) δ 6.27 (q, 1, $J_{H_1'-H_2',H_2''}$ = 3.5 and 8.0 Hz, H_1'), 2.91 (s, 3, 2-NHCH$_3$); tlc R_9/R_{11} = 1.2.

Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot 0.5H_2O$: C, 45.51; H, 5.56; N, 24.13. Found: C, 45.38; H, 5.44; N, 24.17.

Registry No.—2,4,5-Triamino-6-benzyloxypyrimidine, 19916-72-4; 2-amino-6-benzyloxypurine, 19916-73-5; **1**, 19916-74-6; **6**, 19916-75-7; **8**, 961-07-9; **9**, 19916-77-9; **10**, 19916-78-0; **11**, 19916-79-1.

Reactions of Carbohydrates with (Halomethylene)dimethyliminium Halides and Related Reagents. Synthesis of Some Chlorodeoxy Sugars[1]

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The reaction of (chloromethylene)- and (chloroethylidene)dimethyliminium chloride with selected carbohydrate derivatives containing hydroxyl, epoxide, and unsaturated functions has been investigated. Primary hydroxyl groups are converted into formate esters or are replaced by a chlorine atom, depending on the reaction conditions. Acetal and ketal groups migrate in certain cases, especially when the hydroxyl group is secondary. The reagent reacts with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside to give the *trans*-2-chlorodeoxy-3-formate derivative, as a result of nucleophilic attack of chloride ion on the epoxide function. At elevated temperature a second chlorine atom is incorporated into the molecule with acetal migration to give methyl 3,4-*O*-benzylidene-2,6-dichloro-2,6-dideoxy-α-D-altropyranoside. The mechanism of the reaction is discussed.

Relatively few methods are available for the direct replacement of a hydroxyl group (except at C-1) in a sugar derivative by a halogen atom.[3,4] Among the methods that are considered to be of synthetic utility are the reactions of suitably blocked sugars with sulfuryl chloride,[5,6] and with triphenyl phosphite halides.[7,8] In both of these methods the halogen atom is incorporated by SN2-type reactions leading to inversion of configuration in those cases where secondary hydroxyl groups are involved. Selective chlorination of the primary hydroxyl group in some methyl hexopyranosides has been accomplished with reagents such as sulfur monochloride[9] and *N,N*-dimethylformamide–methanesulfonyl chloride adducts.[10]

In a preliminary communication[11] we reported on the utility of halomethyleneiminium halide reagents[12] in the preparation of certain chlorodeoxy sugars. We now wish to disclose details of this work and to comment on some synthetic and mechanistic aspects of the reaction.

The strongly electrophilic character of amide halide reagents such as (chloromethylene)dimethyliminium chloride[13,14] **2** has been exploited in a wide variety of reactions.[12–15] Some applications which are pertinent to synthetic carbohydrate chemistry include the reaction of **2** with various alcohols to give formate esters[13,14a] and chlorodeoxy sugar derivatives.[11] The sequence of reactions leading to formylation and chlorination of alcohols is illustrated in Scheme I. The precise nature of the addition product from an alcohol and **2** cannot be readily established since an equilibrium such as A ⇌ B is possible. Only one case[13] is known where the primary adduct (type B) of *t*-butyl alcohol was actually isolated as the perchlorate salt. When solutions of the adducts of simple alcohols are heated in chlorinated hydrocarbons, the corresponding alkyl halides and presumably *N,N*-dimethylformamide are formed.[15] Although the reaction is of preparative significance, its application has not been extended to more complex systems. Furthermore, the stereochemical course of the reaction has not been established. Some analogy can be drawn from the pyrolysis of simple imino ester hydrochlorides to the corresponding alkyl halides, which has been shown[16] to proceed by a bimolecular mechanism. The conversion of optically

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