yield) of VIII, bp 11–12.5°. Infrared bands were obtained at 2860–3000 (CH_3, weak), 1740–1790 ($C{=}CF_2$, strong), and 1075–1160 cm^{-1} (C–F, strong). Structure was confirmed by nmr: fluorine spectra at 56.4 Mcps = 64.2 ppm (CF_3, quartet), 80.3 ppm ($C{-}F_2$, complex multiplet, *trans* to CF_3), 84.7 ppm ($C{-}F_1$, complex multiplet *cis* to CF_3) with trichlorofluoromethane as internal reference; proton spectra at 60 Mcps = 8.22 τ (CH_3, triplet) with tetramethylsilane as internal reference.

Preparation of 1,1-Difluoro-2-(chlorodifluoromethyl)prop-1-ene (X).—The same experimental procedure given for VIII was followed. To a cold (−70°) stirred solution of 4.75 g (0.125 mole) of lithium aluminum hydride dissolved in 200 ml of dry tetrahydrofuran was added, over a 20-min period, 49.2 g (0.25 mole) of dry II in 50 ml of dry tetrahydrofuran. Fractionation of the resultant liquid gave 22.9 g (56% yield) of X, bp 42–44°. Structure was confirmed by nmr. When the above reaction was repeated at a reaction temperature of −10°, the yield of product, bp 42–44°, rose to 75% of theory. Vapor phase chromatography[7] (vpc) was used to purify samples for elemental analysis and refractive index. Infrared bands were obtained at 2860-3000 (CH_3, weak), 1740–1780 ($C{=}CF_2$, strong), 1060–1150 (C–F, strong), and 685 cm^{-1} (C–Cl, medium).

Anal. Calcd for X ($C_4H_3ClF_4$): C, 29.55; H, 1.86; Cl, 21.81; F, 46.76. Found: C, 29.70; H, 1.87; Cl, 21.59; F, 46.86.

Preparation of 1,1-Difluoro-2-(difluoromethyl)prop-1-ene (IX).—The equipment and technique used were generally the same as for VIII. A 20% lithium aluminum hydride–diethyl ether solution (103.5 ml, 0.50 mole of $LiAlH_4$) diluted with 100 ml of dry diethyl ether was treated with 49.2 g (0.25 mole) of dry II diluted with 100 ml of dry diethyl ether over a 2-hr period, with stirring, at 0–10°. The yield of IX, bp 19–20°, was 20.8 g, which is 65% theory. Vpc was used to purify an analytical sample. Infrared bands were obtained at 2850–3000 ($-CH_3$, medium), 1750–1780 ($C{=}CF_2$, strong), and 1030–1090 cm^{-1} (C–F, strong). Structure was confirmed by nmr: fluorine spectra at 56.4 Mcps = 118.1 ppm (CF_2H, pair of doublets), 89.6 and 88.2 ppm ($C{-}F_2$, *cis* to CF_2H, and $C{-}F_1$, *trans* to CF_2H, respectively; AB quartet, J_{AB} = 42 cps) with trichlorofluoromethane as internal reference; proton spectra at 60.0 Mcps = τ 8.30 (CH_3, complex multiplet) and τ 3.62 (CF_2H, 55 cps, triplet); with tetramethylsilane as internal reference.

Anal. Calcd for IX ($C_4H_4F_4$): C, 37.51; H, 3.14; F, 59.34. Found: C, 37.60; H, 3.21; F, no consistent values.

Preparation of 1,1-Difluoro-2-(trifluoromethyl)but-1-ene (XI).—Dry 1-trifluoromethyl-1-(chlorodifluoromethyl)prop-1-ene (XII) (97.3 g, 0.5 mole) in 100 ml of dry tetrahydrofuran was treated at 5° with 4.75 g (0.125 mole) of lithium aluminum hydride dissolved in 100 ml of dry tetrahydrofuran. The technique used was the same as for VIII. The yield of XI, bp 31.5–32°, was 29.5 g, a 43% yield. Infrared bands were obtained at 2860–3000 (saturated C–H, medium), 1725–1760 ($C{=}CF_2$, strong), and 1100–1150 cm^{-1} (C–F, strong). Structure was confirmed by nmr: fluorine spectra at 56.4 Mcps = 63.3 ppm (CF_3 quartet), 79.2 ppm ($C{-}F_2$, complex multiplet, *trans* to CF_3), 84.6 ppm ($C{-}F_1$, complex multiplet, *cis* to CF_3) with chlorotrifluoromethane as internal reference; proton spectra at 60 Mcps = τ 8.86 (CH_3 triplet), τ 7.77 (CH_2) with tetramethylsilane as internal reference.

Anal. Calcd for XI ($C_5H_6F_5$): C, 37.51; H, 3.15; F, 59.34. Found: C, 37.68; H, 3.33; F, 59.06.

Preparation of 1,1-Difluoro-2-(trifluoromethyl)oct-1-ene (XIII).—A dry, 250-ml, three-necked, round-bottomed flask fitted as for VIII was charged with 40.2 g (0.157 mole) of dry 1-trifluoromethyl-1-(chlorodifluoromethyl)hept-1-ene (XIV) in 80 ml of dry diethyl ether. The solution was cooled to 0° and 16.3 ml (0.078 mole) of 20% lithium aluminum hydride in diethyl ether was introduced over a 15-min period with stirring. A white precipitate formed almost at once. Upon complete addition, the suspension was stirred at room temperature for 20 min and then cooled to −180° with liquid nitrogen. A 0.5–1-mm pressure was established in the pot and cold trap and the apparatus was sealed off. The pot contents were then rewarmed and distilled into the cold trap. Fractionation of the trap contents on a 2-ft spinning-band column yielded 21.3 g (a 61.5% yield) of XIII, bp 47–48° (32 mm). Infrared bands were obtained at 2850–3000 (saturated C–H, strong), 1725–1755 ($C{=}CF_2$, strong), and 1100–1150 cm^{-1} (C–F, strong).

Anal. Calcd for XIII ($C_9H_{13}F_5$): C, 50.00; H, 6.06; F, 43.94. Found: C, 50.16; H, 6.13; F, 44.09.

Registry No.—VIII, 2253-00-1; IX, 13369-09-0; X, 13395-59-0; XI, 13369-10-3; XIII, 13369-11-4.

Acknowledgment.—The investigation by nmr techniques of the structure of many of the compounds described in this paper was carried out by Mr. Donald W. Moore, Research Department, U. S. Naval Ordnance Test Station, China Lake, Calif., for which we are grateful. This research was financed by the Bureau of Naval Weapons Project No. RRMA-03-065/216-1/R007-03-01, J. J. Gurtowski, Project Engineer.

(7) A 3/8 in. × 20 ft aluminum vpc column, packed with Chromasorb W impregnated with 30% by weight of SE-30 (Aerograph methylsilicone gum ubber).

Purine Nucleosides. XV. The Synthesis of 8-Amino- and 8-Substituted Aminopurine Nucleosides[1]

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The direct bromination of 2′-deoxyguanosine to furnish 8-bromo-2′-deoxyguanosine has been accomplished and treatment of xanthosine under similar reaction conditions with saturated bromine–water has provided a new and direct preparation of 8-bromoxanthosine. Nucleophilic displacement of bromine from 8-bromoxanthosine, 8-bromoguanosine, 8-bromoinosine, 8-bromo-2′-deoxyadenosine, 8-bromoadenosine, and 8-bromo-2′-deoxyguanosine has provided the corresponding 8-amino- and 8-substituted aminopurine ribonucleosides. Possible biochemical significance of these nucleosides is discussed. The application of proton magnetic resonance spectroscopy for the assignment of anomeric configuration to 2′-deoxyribofuranosyl nucleosides is discussed.

Halogenation has been shown[2–6] to produce significant biochemical modifications of certain nucleic acids and has prompted the synthesis[7–10] of several 8-halogenated purine nucleosides and their derivatives.

8-Aminoguanosine and 8-aminoadenosine have demonstrated effective inhibition of a *Streptococcus faecalis*

(1) This work was supported by Contract No. PH 43-65-1041 with the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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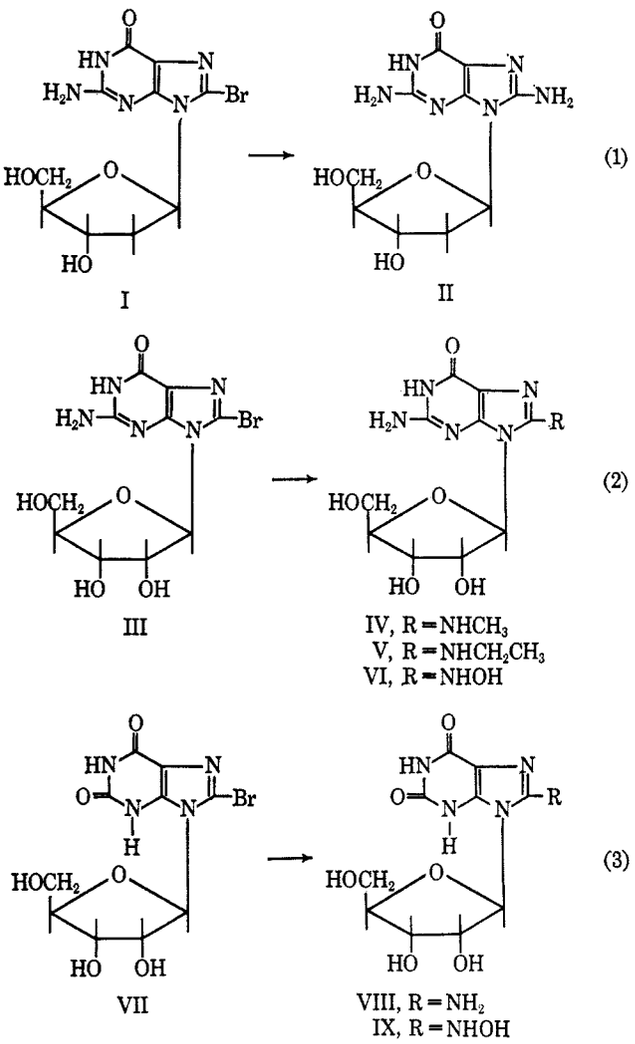
test system. 8-Aminoadenosine has exhibited[11] only slight inhibition of leukemia L-1210 but significant inhibition of sarcoma S-180 ascites cells and complete resistance toward adenosine deaminase, thus preventing its conversion to the biologically inactive inosine analog. 8-Aminopurine nucleosides are also of interest at the present time because of their structural similarity to a paralytic poison, saxitoxin,[12] isolated from certain shellfish. The present work describes the synthesis of several new and interesting 8-amino- and 8-substituted aminopurine nucleosides from the corresponding 8-bromopurine nucleosides.

The bromination of 2′-deoxyguanosine or 3′,5′-di-*O*-acetyl-2′-deoxyguanosine utilizing previous[7,8] bromination procedures proved most unsatisfactory primarily because of the lability of the glycosidic bond. However, a recently reported[13] procedure for the bromination of guanosine has been successfully applied, with certain modifications, to the direct bromination of 2′-deoxyguanosine. Treatment of 2′-deoxyguanosine with saturated bromine–water produced a compound in 46% yield which was assigned the structure of 8-bromo-2′-deoxyguanosine (I) on the basis of ultraviolet absorption and proton magnetic resonance spectroscopy. The reaction conditions, especially temperature and reaction time, are very critical if cleavage of the glycosidic bond is to be avoided. In fact, cleavage of the glycosidic bond has been observed in the process of recrystallization of I from boiling water.

Treatment of I with aqueous hydrazine, using reaction conditions previously reported[8] for the preparation of 8-aminoguanosine, produced cleavage of the glycosidic bond. It was found, however, that addition of methanol to the reaction mixture resulted in a sufficient lowering of the reaction temperature to afford 8-hydrazino-2′-deoxyguanosine which was immediately treated with Raney nickel to yield 8-amino-2′-deoxyguanosine (II) (eq 1). The ultraviolet absorption spectra of II was essentially identical with that reported for 8-aminoguanosine.[8] Treatment of 8-bromoguanosine (III) with aqueous methylamine at an elevated temperature in a sealed vessel provided 8-methylaminoguanosine (IV), but considerable decomposition was observed. It was later found that a minimum of side reactions with an increase in total yield of product could be obtained by simply using anhydrous reaction conditions. When III was allowed to react with methylamine (liquefied) in anhydrous methanol at 115° in a sealed vessel, a 55% yield of 8-methylaminoguanosine (IV) was obtained (eq 2). Similar treatment of III with ethylamine (liquefied) produced a good yield of 8-ethylaminoguanosine (V) (eq 2). The preparation of 8-hydroxylaminoguanosine (VI) was accomplished smoothly by treatment of III with hydroxylamine in anhydrous methanol at 100° in a sealed vessel (eq 2). Recrystallization of VI from water produced a gelatinous mass which was found to assume a more crystalline form on trituration with acetone.

The preparation of 8-bromoxanthosine (VII) has been previously accomplished by the deamination of 8-bromoguanosine[7] (III). However, an improved and new procedure for the preparation of VII was developed during the course of this investigation. Treatment of xanthosine with saturated bromine–water, similar to the procedure employed for the preparation of 8-bromo-2′-deoxyguanosine (I), has produced a good yield of VII which proved to be identical with 8-bromoxanthosine (VII) prepared from III. When 8-bromoxanthosine (VII) was treated with methanolic hydroxylamine at 110°, nucleophilic displacement of the bromo group occurred to afford 8-hydroxylaminoxanthosine (IX) (eq 3). Preparation of hydroxylamino derivatives is of interest since a number of hydroxylaminopurine nucleosides have recently demonstrated[14] significant activity as antineoplastic agents, especially against various types of leukemia. The same reaction conditions required for the preparation of 8-aminoguanosine, *i.e.*, refluxing aqueous hydrazine, were utilized for the successful preparation of 8-aminoxanthosine (VIII) (eq 3).



The preparation of 8-amino-2′-deoxyadenosine (XI) *via* the 8-azido derivative was successful, utilizing reaction conditions reported[8] for the preparation of 8-aminoadenosine. It was found, however, that a substitution of *N*,*N*-dimethylformamide for dimethyl

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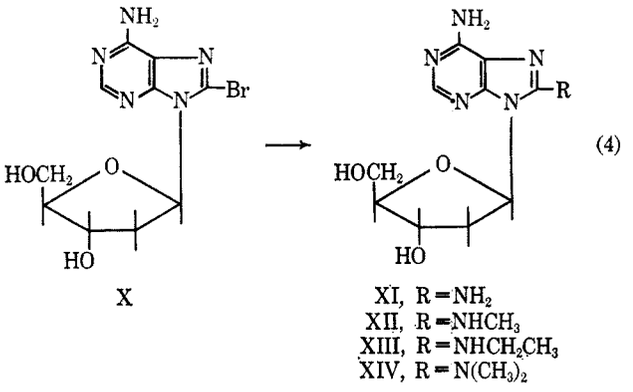
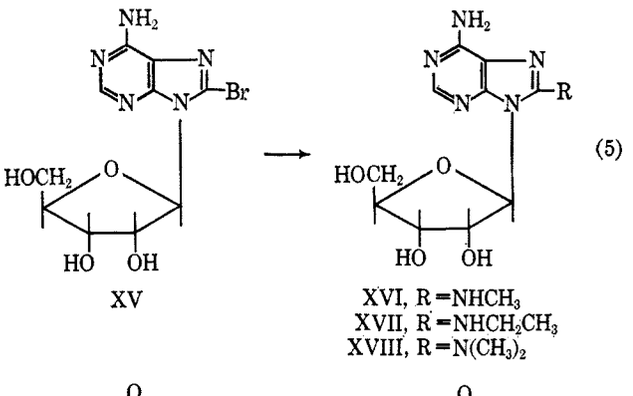
sulfoxide affords better isolation of the 8-azido intermediate. This intermediate was characterized by the infrared absorption band at 2180 cm^{-1} and immediately hydrogenated in the presence of palladium on carbon to afford 8-amino-2′-deoxyadenosine (XI). Treatment of X with liquefied methylamine or liquefied ethylamine in anhydrous ethanol at refluxing temperature furnished 8-methylamino-2′-deoxyadenosine (XII) and 8-ethylamino-2′-deoxyadenosine (XIII), respectively. 8-Dimethylamino-2′-deoxyadenosine (XIV) was obtained when X was treated with anhydrous dimethylamine in methanol at room temperature (eq 4).



(4)

X

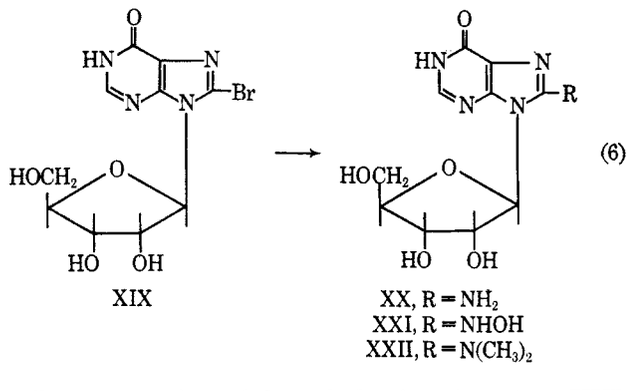
XI, R = NH_2
XII, R = $NHCH_3$
XIII, R = $NHCH_2CH_3$
XIV, R = $N(CH_3)_2$



(5)

XV

XVI, R = $NHCH_3$
XVII, R = $NHCH_2CH_3$
XVIII, R = $N(CH_3)_2$



(6)

XIX

XX, R = NH_2
XXI, R = NHOH
XXII, R = $N(CH_3)_2$

The preparation of 8-methylaminoadenosine (XVI) was attempted *via* the nucleophilic displacement of the 8-bromo group from XV with aqueous methylamine at reflux temperature (eq 5). Although nucleophilic displacement of the 8-bromo group occurred, the product was accompanied by considerable decomposition and was difficult to purify. It was found that, when XV was treated with liquefied methylamine in anhydrous ethanol under reflux, there was obtained a good yield of 8-methylaminoadenosine (XVI) which could be readily purified by recrystallization. The increase in nucleophilicity of the dimethylamine resulted in the facile replacement of the 8-bromo group from XV with anhydrous dimethylamine in anhydrous methanol at room temperature to yield 8-dimethylaminoadenosine (XVIII) (eq 5).

More vigorous reaction conditions were required for the preparation of the inosine derivatives, presumably owing to the ready removal of the proton from N-1 to produce an anion which resulted in increased difficulty of nucleophilic attack. It was found that nucleophilic displacement of the 8-bromo group from XIX with anhydrous dimethylamine in methanol to furnish 8-dimethylaminoinosine (XXII) (eq 6) required an elevation of the temperature, to reflux in direct contrast to room temperature for the corresponding adenosine derivative. Treatment of XIX with hydroxylamine and anhydrous methanol in a sealed vessel at 100° produced 8-hydroxylaminoinosine (XXI) (eq 6). The preparation of 8-aminoinosine was approached from two different routes. Preparation of the 8-azido derivative of XIX was followed by catalytic hydrogenation to afford 8-aminoinosine (XX) (eq 6). The preparation of XX was accomplished in better yield directly by prolonged treatment with refluxing aqueous hydrazine. It is of interest that the 8-substituted inosine derivatives appear to be more soluble than the corresponding 8-substituted adenosine derivatives.

Several 2′-deoxy-D-ribofuranose nucleosides have displayed[15-17] a noncompliance with Hudson's rules[18] of isorotation which correlate optical rotation and anomeric configuration. The configuration of thymidine and its α anomer was determined[19] on a theoretical consideration of the proton-splitting patterns of the 2′-deoxyribofuranosyl moiety and these splitting patterns were found to be within allowable limits for the values predicted by the Karplus equation.[20] The splitting patterns or coupling constants of adjacent hydrogens have been shown to be a function of several diverse factors.[21-23] In a recent study[24] it has been observed that the anomeric configuration of 2′-deoxy-D-ribofuranosyl nucleosides in general could be correlated with the splitting pattern and coupling constants observed for the anomeric proton. This observation was made on the basis of an inspection of the proton magnetic resonance spectra of several 6-substituted, 2,6-disubstituted, and 2,6,8-trisubstituted 2′-deoxy-D-ribofuranosylpurines prepared in our laboratory and by inspection of commercially available 2′-deoxy-β-D-ribofuranosyl nucleosides. It was noted that proton magnetic resonance spectroscopy could be utilized for an assignment of absolute configuration of 2′-deoxy-D-ribofuranosylpurines since the β anomer displayed a splitting pattern (Figure 1) for the anomeric proton which was a "pseudo-triplet" while the α anomer exhibited a multiplet of four for the anomeric proton.

(15) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959).
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(17) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961).
(18) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909); W. Pigman, "The Carbohydrates," Academic Press Inc., New York, N. Y., 1957, p 70.
(19) R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).
(20) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(21) R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **42**, 893 (1964).
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(24) M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 4934 (1965).

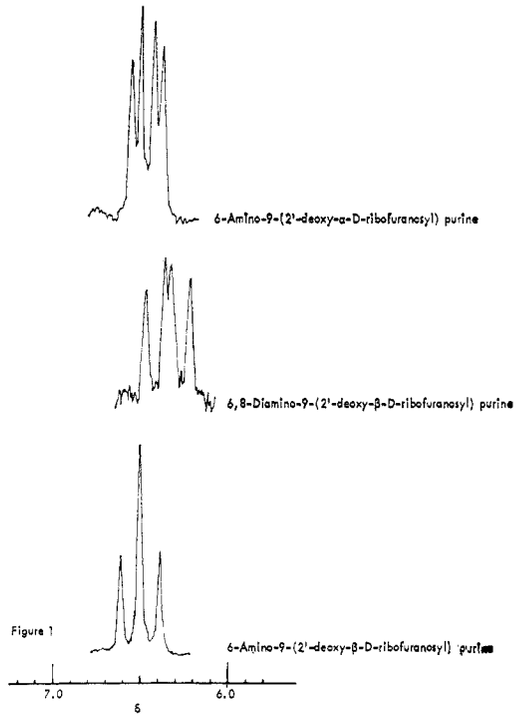

Figure 1.—Splitting patterns observed for the anomeric proton of certain 2′-deoxyribofuranosyl nucleosides.

This observation was subsequently utilized[25] for the assignment of anomeric configuration for a series of 2′-deoxy-D-ribofuranosylbenzimidazoles. In the course of obtaining routine proton magnetic resonance spectra for the present series of compounds, there was observed, for 8-amino-2′-deoxyadenosine (XI), a splitting pattern (multiplet of four) for the anomeric proton which was different from the usually observed splitting pattern ("pseudo-triplet") for a 2′-deoxy-β-D-ribofuranoside. Similar splitting patterns were subsequently observed for 8-methylamino-2′-deoxyadenosine (XII) and 8-ethylamino-2′-deoxyadenosine (XIII). It was assumed that the slight increase in coupling constant observed in these cases was due to the proton residing on the exocyclic nitrogen at position 8. Presumably this proton could be hydrogen bonded to the carbohydrate moiety, thereby causing a slight change in its conformation with a concomitant alteration of the dihedral angles between the protons attached to C-1′ and C-2′. This assumption prompted the preparation of 8-dimethylamino-2′-deoxyadenosine (XIV) which, although it still retains the basic amine at position 8, does not possess a proton which might hydrogen bond. The pmr spectrum of XIV displayed a splitting pattern (multiplet of four) very similar to the splitting pattern observed (for example, see Table I) for XI, XII, and XIII. Thus, apparently hydrogen bonding of the 8-amino protons does not affect the conformation. Hydrogen bonding between the amine group at position 8 and the anomeric proton has been tentatively eliminated since hydrogen bonding results[26] in a shift of the proton signal to a lower field and there was observed no significant chemical shift (in reference to 2′-deoxyadenosine) for the anomeric proton in the preceding pmr spectra. The increased peak width 15.2 cps (see Table I) compared to ≈14 cps for the β anomer[24] with the increased coupling constant could be due to steric hindrance caused by the insertion of a large group in position 8. Another possibility is the formation of a hydrogen bond between a proton of the carbohydrate moiety and the basic exocyclic group at position 8.

(25) C. P. Whittle and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 4940 (1965).
(26) R. H. Shoup, H. T. Miles, and E. D. Becker, *Biochem. Biophys. Res. Commun.*, **23**, 194 (1966).

TABLE I

PROTON MAGNETIC RESONANCE SPLITTING PATTERNS FOR THE H-1′ PROTON OF SOME 6-AMINO-8-SUBSTITUTED 9-(2′-DEOXY-β-D-RIBOFURANOSYL)PURINES[a]

8 Substituent	Absorption[b]	$J_{H-1'}$, cps	Peak width, cps	Solvent
$-NH_2$	Q	6.6, 8.6	15.2	D_2O
$-NHCH_3$	Q	6.0, 9.2	15.2	DMSO-d_6–D_2O
$-NHC_2H_5$	Q	6.4, 8.6	15.0	D_2O
$-N(CH_3)_2$	Q	6.0, 9.2	15.2	D_2O

[a] All spectra were obtained with a Varian A-60 nmr spectrometer. [b] Q = multiplet of four.

It is of interest that several 8-substituted purine nucleosides have demonstrated the ability to form anhydro linkages between the thio group at position 8 and the carbohydrate moiety.[27-29] The present series of compounds may possess a suitable juxtaposition to accommodate certain specific interactions of the sugar and base. Investigation of the increased coupling constants as possibly resulting from certain favorable *syn* or *anti* conformations[30] is a subject presently under study in our laboratory.

The difference between the splitting pattern (multiplet of four) for the anomeric proton of 8-substituted 9-(2′-deoxy-β-D-ribofuranosyl)purines and the splitting pattern (multiplet of four) for the anomeric proton of the previously reported 2-, 6-, and 2,6-disubstituted 9-(2′-deoxy-α-D-ribofuranosyl)purines[24] can be readily ascertained from a visual inspection (see Figure 1) of the pmr spectra in the δ 6–7 region. The peak width of the α anomers is 10.4 ± 0.4 cps while the peak width of the four 8-substituted β anomers prepared in this investigation (Table I) is 15.15 ± 0.15 cps. The compounds prepared in this investigation were prepared from 2′-deoxyadenosine and are all known β anomers. It is apparent that anomeric configuration of a 2′-deoxyribofuranosylpurine may still be readily assigned on the basis of coupling constants, but it should be pointed out as previously stated[24] that this assignment is based on particular conformational restrictions of the furanose ring and factors influencing such conformation should be carefully considered.

It would be particularly helpful to study certain 8-substituted 9-(2′-deoxy-α-D-ribofuranosyl)purines to determine the influence of the 8-amino group in the α anomer.

Ultraviolet spectra of certain 8-substituted purine nucleosides are given in Table II.

Experimental Section[31]

8-Bromo-2′-deoxyguanosine (I).—Bromine (1 ml) was added to 50 ml of water and stirred at room temperature for 2–3 min

(27) M. Ikehara and H. Tada, *J. Am. Chem. Soc.*, **85**, 2344 (1963).
(28) M. Ikehara and H. Tada, *ibid.*, **87**, 606 (1965).
(29) M. Ikehara, H. Tada, K. Muneyama, and M. Kaneko, *ibid.*, **88**, 3165 (1966).
(30) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967).
(31) Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF CERTAIN 8-SUBSTITUTED PURINE NUCLEOSIDES

Purine nucleosides	pH 1 λ_{max}, mμ	pH 1 ε	pH 11 λ_{max}, mμ	pH 11 ε
8-Bromo-2′-deoxyguanosine (I)	261	16,600	270	15,225
8-Amino-2′-deoxyguanosine (II)	287.5	12,100	285 (sh)	18,600
	250	23,120	257.5	9,850
8-Methylaminoguanosine (IV)	289	9,360	278	11,860
	252	16,225	261	16,350
8-Ethylaminoguanosine (V)	288	9,100	261	15,000
	253	16,300		
8-Hydroxylaminoguanosine (VI)	287.5	9,700	275 (sh)	12,250
	250	16,000	258	14,400
8-Aminoxanthosine (VIII)	277.5	11,960	291	10,760
	237.5	12,560	249	12,860
8-Hydroxylaminoxanthosine (IX)	278.5	13,200	291	13,200
	234	12,560	246	11,350
8-Amino-2′-deoxyadenosine (XI)	270	12,500	272	16,500
8-Methylamino-2′-deoxyadenosine (XII)	272.5	19,600	277	17,360
8-Ethylamino-2′-deoxyadenosine (XIII)	274	13,200	278.5	16,750
8-Dimethylamino-2′-deoxyadenosine (XIV)	287	11,760	274	15,580
	270 (sh)	10,300		
8-Methylaminoadenosine (XVI)	275	14,800	278	18,350
8-Ethylaminoadenosine (XVII)	274	17,360	278.5	13,485
8-Dimethylaminoadenosine (XVIII)	280	14,600	274	16,700
8-Aminoinosine (XX)	253	13,300	261.5	13,900
8-Hydroxylaminoinosine (XXI)	253.5	14,350	262.5	15,250
8-Dimethylaminoinosine (XXII)	262	17,400	267	15,200

(all of the bromine does not dissolve). 2′-Deoxyguanosine (5.0 g) was suspended in 25 ml of water at room temperature with stirring. To this rapidly stirring suspension was added bromine–water (decanted from the above preparation) dropwise, allowing the yellow color to fade after each addition. When the yellow persisted, the solid was immediately collected by filtration and washed with 50 ml of ice water. The solid was suspended in hot methanol (50 ml) and dissolved by the addition of boiling water while the temperature was maintained below 80° at all times. The solution was allowed to stand overnight at 5° and the solid which had separated was collected by filtration and dried to the air to yield 2.96 g (46%) of I, mp 210° dec.

Anal. Calcd for $C_{10}H_{12}BrN_5O_4$: C, 34.67; H, 3.47; N, 20.23; Br, 23.12. Found: C, 34.82; H, 3.61; N, 20.03; Br, 23.30.

8-Amino-2′-deoxyguanosine (II).—8-Bromo-2′-deoxyguanosine (3.54 g) was suspended in a mixture of water (50 ml) and methanol (100 ml) and to this suspension was added 20 ml of 97% hydrazine. The solution was heated at reflux for 24 hr and the solid removed by filtration and discarded. The filtrate was evaporated to dryness *in vacuo*, keeping the temperature of the water bath below 70°. Ethanol was added to the residue and the solvent was then removed *in vacuo*. The above process was repeated three times and the resulting solid (1.3 g, 42%) was dissolved in boiling methanol, filtered, and the filtrate reduced to one-fourth of the original volume. The solution was allowed to stand at 5° for 18 hr and the solid which had separated was collected by filtration. This solid was dissolved in a mixture of water (60 ml) and methanol (100 ml) and to this solution was added 10.0 g (wet weight) of washed Raney nickel W-4. This mixture was heated at reflux and stirred vigorously for 18 hr. The hot solution was filtered through Celite to remove the catalyst and the catalyst was washed with 800 ml of a boiling methanol–water mixture (1:1) in 150-ml portions. The filtrate and washings were evaporated to dryness *in vacuo* (temperature of the water bath below 70°). The resulting solid was recrystallized from a methanol–water mixture to furnish 1.0 g (81%) of product. A small sample was recrystallized from a methanol–water mixture for analysis. The product turned brown at approximately 235°, mp >300°.

Anal. Calcd for $C_{10}H_{14}N_6O_4$: C, 42.55; H, 4.96; N, 29.79. Found: C, 42.30; H, 5.09; N, 29.55.

8-Methylaminoguanosine (IV).—8-Bromoguanosine[7] (5.0 g) was dissolved in 150 ml of anhydrous methanol containing liquefied anhydrous methylamine (60 ml). The solution was then heated in a sealed vessel for 18 hr at 115°. After the solution was cooled to room temperature, the solid was collected by filtration and dissolved in hot water. This hot solution was treated with decolorizing carbon, filtered, and the filtrate allowed to stand in the refrigerator overnight to furnish 2.36 g (55%) of product, dec pt >200°.

Anal. Calcd for $C_{11}H_{16}N_6O_5$: C, 40.00; H, 5.45; N, 25.45. Found: C, 40.04; H, 5.36; N, 26.01.

8-Hydroxylaminoguanosine (VI).—8-Bromoguanosine[7] (10.0 g) was dissolved in anhydrous methanol (150 ml) containing 10.0 g of hydroxylamine.[32] This solution was heated in a sealed vessel for 18 hr at 100°. The solid which had separated from the cooled reaction vessel was collected by filtration and dissolved in boiling water. The hot solution was treated with decolorizing carbon, filtered, and allowed to stand at 5° for 18 hr. The solid which separated was collected by filtration and suspended in rapidly stirring acetone (300 ml) at room temperature. The solid was collected by filtration and air dried to furnish 3.41 g (39%) of product. A small sample was prepared for analysis by recrystallization from water followed by trituration with acetone; it decomposed at >260°.

Anal. Calcd for $C_{10}H_{14}N_6O_6$: C, 38.22; H, 4.46; N, 26.75. Found: C, 38.35; H, 5.05; N, 26.38.

8-Hydroxylaminoxanthosine (IX).—Reaction conditions similar to those utilized for the preparation of VI furnished a 28% yield of IX. A small sample was recrystallized from water for analysis, mp >300°.

Anal. Calcd for $C_{10}H_{13}N_5O_7 \cdot H_2O$: C, 36.10; H, 4.50; N, 21.01. Found: C, 36.12; H, 4.37; N, 21.80.

8-Hydroxylaminoinosine (XXI).—Reaction conditions similar to those utilized for the preparation of VI furnished a 34% yield of XXI. A small sample was recrystallized from methanol–water for analysis, mp 210° dec.

Anal. Calcd for $C_{10}H_{13}N_5O_6$: C, 40.13; H, 4.35; N, 23.40. Found: C, 40.96; H, 4.94; N, 23.34.

8-Bromoxanthosine (VII).—Xanthosine (10.0 g) was suspended in water (50 ml) at room temperature and bromine water (decanted from 8 ml of bromine dissolved in 400 ml of water at room temperature) was added over 2–3 min. The reaction mixture became very thick and was difficult to stir. The solid was collected by filtration and washed with 75 ml of ice water. The solid was recrystallized from water to afford 6.37 g (46%) of 8-bromoxanthosine. This product was found to possess the same ultraviolet absorption and pmr spectra as the 8-bromoxanthosine prepared *via* the deamination of 8-bromoguanosine.[7]

8-Aminoxanthosine (VIII).—To a suspension of 8-bromoxanthosine (5.0 g) in water (200 ml) was added 2.0 ml of 97% hydrazine. The resulting solution was heated to reflux for 18 hr and finally evaporated to dryness *in vacuo*. Ethanol (100 ml) was added to the residue and the solvents were removed *in vacuo*. This process was repeated three times and the resulting solid was dissolved in hot ethanol by the slow addition of boiling water. This solution was treated with decolorizing carbon, filtered to remove the carbon, and the filtrate reduced in volume by one-half. The solid which separated on cooling was collected by filtration and the volume of the filtrate again reduced by one-half. The solid which separated was again collected by filtration. The combined solid was triturated with acetone (300 ml) and air dried to yield 1.90 g (46%) of product. A small sample was recrystallized from water for analysis, mp 250° dec.

Anal. Calcd for $C_{10}H_{13}N_5O_6$: C, 40.02; H, 4.35; N, 23.41. Found: C, 39.44; H, 4.44; N, 23.43.

8-Amino-2′-deoxyadenosine (XI).—8-Bromo-2′-deoxyadenosine (4.0 g) and sodium azide (2.4 g) were added to *N*,*N*-dimethylformamide (75 ml) and the reaction mixture was heated for 16 hr at 75°. The solvent was removed on a steam bath *in vacuo*. Anhydrous methanol (100 ml) was added to the residue and then evaporated to dryness *in vacuo*. This process was repeated three times and the resulting solid dissolved in boiling ethanol (100 ml)

(32) C. D. Hurd, *Inorg. Syn.*, **1**, 87 (1939).

by the slow addition of water. The solution was allowed to stand at 5° for 18 hr and the 8-azido-2′-deoxyadenosine (1.85 g, 52%) which had separated from the solution was collected by filtration. To a mixture of water (100 ml) and methanol (100 ml) containing 8-azido-2′-deoxyadenosine (1.85 g) was added 1.5 g of 5% palladium on carbon. This solution was exposed to hydrogen for 3 hr at 50 psi at room temperature. The catalyst was removed by filtration through a Celite pad and the catalyst washed with 300 ml of a boiling ethanol–water mixture (1:1). The filtrate and washings were evaporated to dryness *in vacuo* and the resulting solid was crystallized from an ethyl acetate–methanol mixture to afford 1.11 g (66%) of product. A small sample was recrystallized from the same solvent pair for analysis, mp 138–140°.

Anal. Calcd for $C_{10}H_{14}N_6O_3$: C, 45.11; H, 5.26; N, 31.58. Found: C, 45.02; H, 5.50; N, 31.30.

8-Ethylamino-2′-deoxyadenosine (XIII).—8-Bromo-2′-deoxyadenosine[7] (4.0 g) was dissolved in anhydrous ethanol (100 ml) containing liquefied ethylamine (70 ml). This solution was heated at reflux temperature for 18 hr and the solvent was removed *in vacuo* on a steam bath. Anhydrous methanol (100 ml) was added to the residue and then removed *in vacuo* on a steam bath. This process was repeated two times and the residue was dissolved in a boiling ethyl acetate–methanol mixture. This solution was treated with decolorizing carbon, filtered, and the filtrate allowed to stand at 5° for 18 hr. The solid which separated was collected by filtration to afford 1.46 g (41%) of product. A small sample was recrystallized from acetone–methanol mixture for analysis, mp 201–203° dec.

Anal. Calcd for $C_{12}H_{16}N_6O_3$: C, 49.00; H, 6.12; N, 28.57. Found: C, 48.93; H, 6.12; N, 28.69.

8-Methylaminoadenosine (XVI).—8-Bromoadenosine[7] (2.0 g) was dissolved in anhydrous ethanol (150 ml) containing liquefied methylamine (50 ml). This solution was heated at reflux temperature for 18 hr and the solvent then removed *in vacuo* on a steam bath. Anhydrous methanol (100 ml) was added to the residue and then evaporated to dryness *in vacuo* on a steam bath. The above process was repeated three times and the resulting residue was dissolved in boiling methanol by the slow addition of water. This solution was allowed to stand at 5° for 18 hr and the solid which separated from solution was collected by filtration to furnish 1.09 g (63%) of product, mp 250° dec.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.45; N, 28.39. Found: C, 44.46; H, 5.41; N, 28.61.

8-Methylamino-2′-deoxyandenosine (XII).—Reaction conditions similar to those utilized for the preparation of XVI furnished a 63% yield of XII. A small sample was recrystallized from an ethanol–methanol mixture for analysis, mp 225–226° dec.

Anal. Calcd for $C_{11}H_{16}N_6O_3$: C, 47.14; H, 5.71; N, 30.00. Found: 47.29; H, 6.04; N, 29.60.

8-Ethylaminoadenosine (XVII).—8-Bromoadenosine[7] (2.0 g) was dissolved in 70% aqueous ethylamine (150 ml) and this solution heated in a sealed vessel for 18 hr at 125°. The solution was then evaporated to dryness *in vacuo* on a steam bath. Anhydrous methanol (100 ml) was added to the residue and then evaporated to dryness *in vacuo* on a steam bath. The above process was repeated three times and the resulting residue was recrystallized from an ethanol–water mixture to afford 1.14 g (63% yield) of product. A small sample was recrystallized from ethanol–water for analysis, mp 257° dec.

Anal. Calcd for $C_{12}H_{18}N_6O_4$: C, 46.45; H, 5.81; N, 27.09. Found: C, 46.13; H, 5.91; N, 27.55.

8-Dimethylaminoadenosine (XVIII).—8-Bromoadenosine[7] (2.0 g) was dissolved in anhydrous methanol (100 ml) containing 10 ml of anhydrous dimethylamine. The solution was stirred at room temperature for 26 hr and the solution evaporated to dryness *in vacuo*. Absolute methanol (120 ml) was added and removed *in vacuo*. This process was repeated three times and the resulting residue was dissolved in boiling ethanol, treated with decolorizing carbon, filtered, and cooled in the refrigerator overnight. The solid which separated was collected by filtration to yield 1.05 g (58%) of product. A small sample was recrystallized from ethanol for analysis, mp 300° dec.

Anal. Calcd for $C_{12}H_{18}N_6O_4$: C, 46.45; H, 5.81; N, 27.10. Found: C, 46.05; H, 5.79; N, 26.90.

8-Dimethylaminoinosine (XXII).—Reaction conditions similar to those utilized for the preparation of XVIII, except heated at reflux temperature, furnished a 44% yield of XXII. A small sample was recrystallized from methanol for analysis, mp 208–212° dec, on preheated block.

Anal. Calcd for $C_{12}H_{17}N_5O_5$: C, 46.30; H, 5.47; N, 22.51. Found: C, 46.21; H, 5.64; N, 22.25.

8-Dimethylamino-2′-deoxyadenosine (XIV).—Reaction conditions similar to those utilized for the preparation of XVIII, except the residue was recrystallized from a mixture of methanol–ethyl acetate, furnished a 31% yield of XIV. An analytical sample was prepared by two successive recrystallizations from ethyl acetate–methanol, mp 176–177°.

Anal. Calcd for $C_{12}H_{18}N_6O_3$: C, 48.98; H, 6.12; N, 28.57. Found: C, 48.82; H, 6.13; N, 28.53.

8-Aminoinosine (XX). Method 1.—A solution of 8-bromoinosine[7] (1.0 g in 20 ml of H_2O) and hydrazine (0.4 ml, 97%) was refluxed for 72 hr. The solution was reduced to dryness *in vacuo* over steam. Ethanol (100 ml) was added and removed *in vacuo*. This process was repeated three times. The solid was recrystallized from ethanol–water to yield 0.44 g (54%). An analytical sample was prepared by a further crystallization from an ethanol–methanol mixture. The product melted at 190° dec.

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot 1.5H_2O$: C, 39.10; H, 5.16; N, 22.80. Found: C, 38.80; H, 4.58; N, 22.66.

The pmr spectrum showed peaks for the 1.5 mole of H_2O present.

Method 2.—To 8-bromoinosine[7] (5.0 g) and sodium azide (3.0 g) was added 50 ml of dimethyl sulfoxide. The resulting solution was stirred in an oil bath at 65° for 18 hr. The solvent was removed *in vacuo*, with water added to azeotrope. The resulting solid was recrystallized from an ethanol–water mixture to yield 3.35 g (75%) of 8-azidoinosine. The product was dissolved in 200 ml of ethanol and 10 ml of water. To this solution was added 2.0 g of Pd–C (5%). The resulting mixture was hydrogenated for 3.5 hr at 50 psi, heated to boiling, and filtered. The carbon was washed with 200 ml of boiling water and the combined filtrate reduced to dryness *in vacuo*. The resulting solid was recrystallized from an ethanol–methanol mixture to yield 1.60 g (52%) of 8-aminoinosine, identical with that produced by method 1.

Registry No.—I, 13389-03-2; II, 13389-04-3; IV, 13389-05-4; V, 13389-06-5; VI, 13389-07-6; VIII, 13389-08-7; IX, 13440-70-5; XI, 13389-09-8; XII, 13389-10-1; XIII, 13389-11-2; XIV, 13389-12-3; XVI, 13389-13-4; XVII, 13389-14-5; XVIII, 13389-15-6; XX, 13389-16-7; XXI, 13421-41-5; XXII, 13389-17-8.

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