Table VIII

No.	3'-Substituent	% Yield	Mp, °C	DMF, ml/g	λ_{max}, mμ[a]	ϵ	Formula
XIIIa	H	86	189–191	18			[b]
XIIIb	Me	81	194–196	6	237.5	21,400	$C_6H_{11}N_3S_3$
XIIIc	Pr	88	169–170	[c]			$C_8H_{15}N_3S_3$
XIIId	CH_2CH_2OH	84	181–182	2[d]	245	15,000	$C_7H_{13}N_3OS_3$

[a] In MeOH. [b] Lit.[12] mp 200–201°. [c] Readily soluble in hot MeOH. [d] Analytical sample from MeOH.

dissolves fairly slowly in hot EtOH and some insoluble material is often formed, and for reaction with TSC's the following modification of the published method[12] is more convenient.

A mixture of XII (7.6 g, 0.05 mol; prepared as above) and the TSC (0.05 mol) was treated with EtOH (100 ml), H_2O (60 ml), and AcOH (3 ml). The suspension was heated under reflux on the water bath, and after 1–2 min a clear solution resulted. Heating was continued for 10 min in all, and on cooling, a mass of colorless crystals separated; in the case of TSC itself, the product crystallized from the clear solution during the heating. Next day the product was collected and washed with EtOH. For recrystallization, each of the derivatives XIIIa,b,d was dissolved in the indicated volume of DMF at 100° and the solution treated with 5–6 vol of boiling MeOH. The recovery was good and the melting point (dec) raised only a few degrees. *Anal.* C, H, N, S for the compounds with formulas recorded (Table VIII).

Acknowledgments.—We are grateful to the following organizations who supported this work financially: May & Baker Ltd., Dagenham, England; Arthur Guinness, Son and Co. (Dublin) Ltd.; Irish Cancer Society; Tenovus; and Irish Hospitals Trust Ltd.

2-Fluoropurine Ribonucleosides[1]

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Received November 3, 1969

The preparation of the 2-fluoro derivative of the anticancer agent 6-methylthiopurine ribonucleoside from *S*-methylthioguanosine is described. A number of other 2-fluoropurine ribonucleosides were synthesized by the selective displacement of the 6-fluorine of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine followed by treatment with MeOH–NH_3 to remove the O-Ac groups. The cytotoxicity of these nucleosides is discussed.

Because of the high degree of broad-spectrum biologic activity of 2-fluoroadenosine,[2-13] a number of other nucleosides of 2-fluoroadenine were prepared and evaluated for cytotoxicity with interesting results.[14] This paper describes the synthesis and evaluation of another type of structural variants of 2-fluoroadenosine.

N-Methyladenosine and *N*,*N*-dimethyladenosine are readily phosphorylated by adenosine kinase to the 5'-monophosphates,[10] but the 5'-monophosphate of *N*-methyladenosine is not a substrate for adenylate kinase[15] and, therefore, is not converted in whole cells into the di- and triphosphates,[15] a conversion requisite for incorporation into RNA (presumably the same holds true for *N*,*N*-dimethyladenosine). It is reasonable to assume that 2-fluoro-*N*-methyladenosine (**11**) and 2-fluoro-*N*,*N*-dimethyladenosine (**12**) would probably be converted also into the 5'-monophosphates only and not incorporated into RNA, although *in vivo* demethylation to 2-fluoroadenosine might occur. These compounds and other 2-fluoropurine ribonucleosides have been prepared for biologic evaluation.

S-Methylthioguanosine (**2**) was converted into the 2-fluoro analog (**5**) of the anticancer agent, 6-(methylthio)purine ribonucleoside,[16] by the modified Schiemann reaction.[2] To prepare 2-fluoro-*N*-methyladenosine (**11**) by this method, 2-amino-6-chloro-9-β-D-ribofuranosylpurine (**1**) was treated with $MeNH_2$ to obtain the requisite intermediate, 2-amino-*N*-methyladenosine (**3**). In addition to **3**, 2-methylamino-*N*-methyladenosine (**4**), resulting from the displacement of the 2-NH_2 as well as the 6-Cl, was formed. When 2-amino-*N*-methyladenosine (**3**) was subjected to the modified Schiemann reaction a complex reaction mixture resulted from which an impure sample of the desired 2-fluoro-*N*-methyladenosine (**12**) was isolated by column chromatography. Fortunately the availability of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine (**6**)[17] provided an alternative route to this and other 2-

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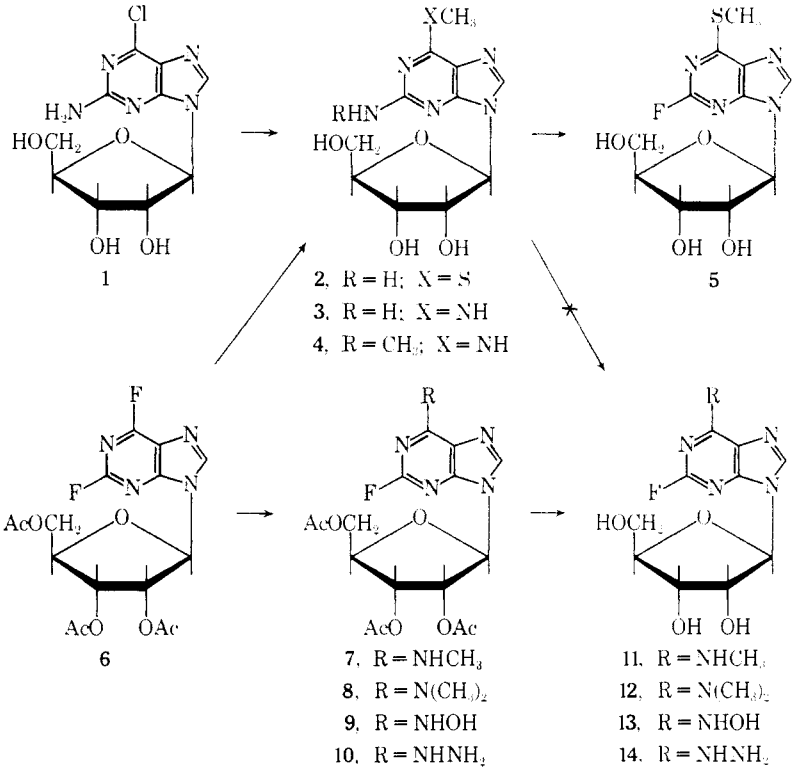
SCHEME I



fluoropurine ribonucleosides. However, treatment of **6** with excess ethanolic $MeNH_2$ at 5° for 3 days, conditions that with NH_3 provide a good yield of 2-fluoroadenosine,[17] gave only 2-methylamino-*N*-methyladenosine (**4**) by replacement of both fluorines of **6**. Treatment of **6** with 1 equiv of $MeNH_2$ at 5° for 18 hr resulted in replacement of the 6-F only giving 2′,3′,5′-tri-*O*-acetyl-2-fluoro-*N*-methyladenosine (**7**). This interesting result caused us to investigate the reaction of 9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloropurine with $MeNH_2$ under mild conditions and, indeed, displacement of the less reactive 6-Cl could be effected without concomitant debenzoylation giving 2′,3′,5′-tri-*O*-benzoyl-2-chloro-6-methyladenosine. The Ac groups of **7** were removed by treatment with ethanolic NH_3 at 5° for 3 days. In a similar manner 2-fluoro-*N*,*N*-dimethyladenosine (**12**) was prepared by the reaction of 1 equiv of Me_2NH with **6** followed by deacetylation of **8** with ethanolic NH_3. To effect replacement of the 6-F of **6** with hydroxylamine and hydrazine to give **9** and **10**, it was necessary to use almost 2 equiv of both reagents in ethanol at 5° for 1 hr. Thus the utility of this route for the preparation of 2-fluoropurine nucleosides has been demonstrated. In addition these reactions show the greater susceptibility of the 6-F to nucleophilic displacement reactions relative to the 6-Cl of purines, which is in keeping with the earlier observation of the greater reactivity of the 2-F compared with the 2-Cl of purines[2] and with the general observation that an activated fluorine is an excellent leaving group.[18]

Although deacetylation of **9** and **10** was accomplished with ethanolic NH_3 as described for **7** and **8**, the ribonucleosides **13** and **14** proved to be quite unstable and decomposed during attempted isolation. Even so a low yield of pure **14** was obtained.

Cytotoxicity Data.—2-Fluoro-*N*-methyladenosine (**11**) is only 1/1150 as cytotoxic as 2-fluoroadenosine and 2-fluoro-*N*,*N*-dimethyladenosine (**12**) is even less cytotoxic. At the same time the cytotoxicity of **11** is only slightly less than that of *N*-methyladenosine (see Table I), which appears to support the view that the triphosphate of 2-fluoroadenosine is responsible for its great cytotoxicity. 2-Fluoro-6-(methylthio)purine ribonucleoside is only 1/70 as cytotoxic as 6-(methythio)-purine ribonucleoside, probably because it is a relatively poor substrate for adenosine kinase.[10] On the other hand 2-fluoro-*N*-hydroxyadenosine triacetate (**9**) is about 33 times as cytotoxic as *N*-hydroxyadenosine. It was necessary to test this structure as the triacetate **9** because of the instability of **13**. The validity of evaluating the triacetate of **13** (and **14**) is supported by previous work which has shown that, because of widespread occurrence of nonspecific esterases, nucleoside acetates tend to show the same biologic properties as the parent nucleoside.[19] Furthermore in this study the triacetate of 2-fluoroadenosine was found to be highly cytotoxic, even though somewhat less so than 2-fluoroadenosine itself. The triacetate of *N*-amino-2-fluoroadenosine was only slightly less cytotoxic than *N*-aminoadenosine. It is not clear at this time why the introduction of F in the 2 position of two nucleosides so similar in structure and biologic activity (*N*-hydroxyadenosine and *N*-aminoadenosine) should have such a different effect on their activities. The triacetate of 2,6-difluoro-9-β-D-ribofuranosylpurine showed moderate cytotoxicity.

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Table I
Cell Culture Cytotoxicity Data[a]

Compound	ED_{50}, μmol/l.[b]
2-Fluoroadenosine	0.020
2-Fluoroadenosine triacetate	0.15
N-Methyladenosine	14
N,*N*-Dimethyladenosine	>340
2-Fluoro-*N*-methyladenosine (11)	23
2-Fluoro-*N*,*N*-dimethyladenosine (12)	>130
N-Hydroxyadenosine	32
2-Fluoro-*N*-hydroxyadenosine triacetate (9)	0.97
N-Aminoadenosine	1.8
N-Amino-2-fluoroadenosine triacetate (10)	6.7
2-Fluoro-6-(methylthio)purine ribonucleoside (5)	19
6-(Methylthio)purine ribonucleoside	0.30
2,6-Difluoropurine ribonucleoside triacetate (6)	31

[a] Human epidermoid carcinoma cells No. 2. [b] The concentration of compound required to inhibit the growth of treated cells to 50% of that of untreated controls as measured by colony counts.[11]

Experimental Section

SilicAR-TLC-7 (Mallinckrodt) was used for column and tl (1 mm) chromatographic purifications. Silica gel H (Brinkmann) was used for thin-layer (0.25 mm) analyses (tlc). Chromatographic homogeneity was established for all reported compounds using the solvent systems indicated. Spots were detected with either uv light after spraying the plates with Ultraphor (WT, highly concentrated) (BASF Colors & Chemicals, Inc., Charlotte, N. C.) or heat charring after spraying with $(NH_4)_2SO_4$. The uv spectra were determined in 0.1 *N* HCl, 0.1 *N* NaOH, and pH 7 buffer with a Cary Model 14 spectrophotometer. The ir spectra were determined in pressed KBr disks with a Perkin-Elmer Model 521 spectrophotometer, and the pmr spectra were determined in $CHCl_3$-*d* or DMSO-d_6 with a Varian A-60A spectrometer (Me_4Si) (these spectra, which are in agreement with the assigned structures, are not presented). Melting points, unless otherwise noted, were determined on a Kofler–Heizbank and are corrected.

2-Methylamino-*N*-methyladenosine (4).—A solution of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine[17] (**6**, 500 mg, 1.1 mmol) in EtOH (50 ml, dried over Linde 3A sieve) was saturated at 5° with dry $MeNH_2$ and the reaction solution was refrigerated for 3 days before it was evaporated to dryness *in vacuo* [10–15 (mm), 25°]. The residue was triturated with $CHCl_3$ and the crystals that formed were collected in several crops to give the crude product. Two recrystallizations of the crude product from EtOH gave the pure material as hydrated crystals: yield 103 mg (33%); mp 125° (Mel-Temp); tlc (3:1 $CHCl_3$–MeOH); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 1, 255 (13.2), 297 (10.0); pH 7, 228 (20.2), 263 (10.7), 286 (10.8); pH 13, 226 (21.0), 263 (10.6), 287 (11.1). *Anal.* ($C_{12}H_{18}N_6O_4 \cdot H_2O$) C, H, N.

2-Fluoro-6-(methylthio)-9-β-D-ribofuranosyl)purine (5).—A solution of *S*-methylthioguanosine[20] (**2**, 1.5 g, 4.8 mmol) in 48% HBF_4 (15 ml) was cooled to −10° and stirred during the addition (in small portions) of $NaNO_2$ (560 mg, 8.1 mmol). After the addition was complete (10 min), the reaction mixture was stirred at −10 to −5° for 30 min. The solution temperature was lowered to −20°, H_2O-saturated *n*-BuOH (5 ml) was added, and the resulting mixture was neutralized (pH 5–6) with 50% NaOH not allowing the temperature to exceed −10°. The neutral mixture was diluted with H_2O-saturated *n*-BuOH (50 ml) and the layers were allowed to separate. The *n*-BuOH layer was washed with *n*-BuOH-saturated H_2O (3 × 5 ml) before it was evaporated to dryness *in vacuo*. The residue was dissolved in boiling H_2O (10–15 ml). The solution was clarified by filtration through dry Celite and the filtrate was allowed to stand until crystallization was complete. The crystals were collected by filtration, washed, and dried *in vacuo*. The filtrate and washings were combined and extracted with *n*-BuOH-saturated H_2O (30–40 ml). The *n*-BuOH extract was evaporated to dryness and the residue was dissolved in EtOH (1 ml) for purification by tlc. The EtOH solution was streaked on two silica gel coated plates (1 × 200 mm) and the plates were developed with 4:1 $CHCl_3$–MeOH. The major band from each plate was combined, eluted with EtOH, and the EtOH solution was evaporated to dryness *in vacuo* to give additional purified product. The two portions of purified product were combined and recrystallized from H_2O (20 ml) to give analytically pure material: yield 400 mg (28%); mp 90°; $[\alpha]^{25}D$ −56.3 ± 0.3 (*c* 1.03, EtOH); tlc (9:1 $CHCl_3$–MeOH); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 1, 214 (13.3), 251 broad (3.5), 296 (21.5); pH 7, 216 (11.7), 251 broad (3.6), 296 (21.6); pH 13, 220 (10.1), 249 broad (4.1), 296 (21.8). *Anal.* ($C_{11}H_{13}FN_4O_4S$) C, H, N.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-2-fluoro-*N*-hydroxyadenine (9).—A solution (3 ml, 0.5 *N*) of $HONH_2$ in EtOH was added to a solution of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine[17] (**6**, 800 mg, 1.9 mmol) in EtOH (10 ml, dried over Linde 3A sieve), and the solution was stirred under N_2 at 5° for 10 min before a second addition of 0.5 *N* $HONH_2$ in EtOH (4 ml). The reaction mixture was stirred for an additional hour before it was evaporated to dryness *in vacuo* (10–15 mm/25°). The residue was triturated with EtOAc (10 ml), filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was triturated with C_6H_6 (4 × 50 ml) and the combined C_6H_6 extracts was evaporated to dryness *in vacuo* to give the crude product, which was purified by tlc (EtOAc). The partially purified product was rechromatographed (95:5 $CHCl_3$–MeOH). The pure product was eluted from the silica gel with EtOAc. Evaporation of the EtOAc solution to dryness *in vacuo* gave the pure product as a glass which was dried *in vacuo* (0.05 mm/77°): yield 262 mg (32%); $[\alpha]^{25}D$ −23.3 ± 1.2 (*c* 0.6, $CHCl_3$); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 1, 269 (13.5), 274 (sh), pH 7, 267 (15.7), 274 (sh); pH 13, 292 (12.2). *Anal.* ($C_{16}H_{18}FN_5O_8$) C, H, N.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-*N*-amino-2-fluoroadenine (10).—After the addition of 1 *N* ethanolic NH_2NH_2 (4.9 ml) to a solution of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine[17] (**6**, 1.4 g, 3.3 mmol) in EtOH (40 ml, dried over Linde 3A sieve), the reaction mixture was stirred at 5° for 30 min before it was evaporated to dryness *in vacuo* (10–15 mm/25°). The residue was triturated with C_6H_6 (30 ml), the solids were removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was absorbed on a previously packed column (2.6 × 35 cm, containing 90 g of silica gel wet packed with $CHCl_3$). The column was eluted with 95:5 $CHCl_3$–MeOH and the pure product was isolated as a glass: yield 806 mg (58%); $[\alpha]^{25}D$ −29.8 ± 0.6 (*c* 0.96, $CHCl_3$); λ_{max} um ($\epsilon \times 10^{-3}$), pH 1, 262 (14.6), 267 (sh); pH 7, 265 (16.8), 273 (sh); pH 13, 268 (sh), 274 (12.2), 282 (sh). *Anal.* ($C_{16}H_{19}FN_6O_7$) C, H, N.

2-Fluoro-*N*-methyladenosine (11). A.—A solution of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine[17] (**6**, 730 mg, 1.8 mmol) in EtOH (8 ml, dried over Linde 3A sieve) containing 2 mmol of $MeNH_2$ (2 ml of 1 *N* $MeNH_2$ in dry EtOH) was refrigerated overnight before it was evaporated to dryness *in vacuo* (10–15 mm/25°). The residue was triturated with C_6H_6 (30 ml), filtered through dry Celite, and the filtrate evaporated to dryness to give **7** as a tlc (2:1 EtOAc–C_6H_6)homogeneous glass in quantitative yield. Compound **7** was dissolved in EtOH (100 ml, dried over Linde 3A sieve) and the solution saturated with dry NH_3 at 5°. After refrigeration for 3 days, the reaction solution was evaporated to dryness and the residue was triturated with Et_2O (2 × 30 ml). The solid that formed was collected by filtration and recrystallized from EtOAc with Norit treatment. A second recrystallization from EtOAc gave the pure product: yield 295 mg (55%); mp 137° (Mettler FP1); tlc (4:1 $CHCl_3$–MeOH); $[\alpha]^{25}D$ −62.3 ± 0.6 (*c* 1.0, EtOH); λ_{max} um ($\epsilon \times 10^{-3}$), pH 1, 260 (sh), 267 (17.1), 275 (15.0); pH 7, 13, 260 (sh), 267 (19.1), 275 (15.3). *Anal.* ($C_{11}H_{14}FN_5O_4$) C, H, N.

B.—2-Amino-6-chloro-9-β-D-ribofuranosylpurine[21] (**1**, 7 g, 23.2 mmol) in 48% aq $MeNH_2$ (100 ml) was heated in a glass-lined bomb at 100–120° for 18 hr. The reaction mixture was evaporated to dryness and the residue was partitioned between H_2O and $CHCl_3$. The aq layer was washed with $CHCl_3$ and evaporated to dryness *in vacuo*. After two evaporations from EtOH solution, the crude product was extracted with boiling EtOAc. The solution was filtered through dry Celite and the filtrate was

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evaporated to dryness *in vacuo*. The residue was redissolved in boiling EtOH, treated with Norit and filtered, and the filtrate was seeded and refrigerated until crystallization was complete. The product, 2-amino-*N*-methyladenosine (**3**), was collected in several crops to give a total yield of 1.1 g (16%): mp 146–148°; λ_{max} nm, pH 1, 255, 290; pH 7, 218, 260 (sh), 278; pH 13, 260 (sh), 280. Tlc (4:1 $CHCl_3$–MeOH) showed a trace of 2-methylamino-*N*-methyladenosine as the only contaminant and indicated the material was suitable for use in the next step.

Aqueous $NaNO_2$ (520 mg, 7.5 mmol/0.8 ml) was added dropwise with stirring to a solution of 2-amino-*N*-methyladenosine (**3**, 1.3 g, 4.4 mmol) in 48% HBF_4 (10 ml) maintained at −20 to −10°. After the nitrite addition was complete, the reaction mixture was stirred at −10° for 20 min before H_2O-saturated *n*-BuOH (25 ml) was added. The resulting slurry was neutralized (pH 5–6) with 50% NaOH keeping the temperature below −5°. The neutral mixture was diluted with H_2O-saturated *n*-BuOH (50 ml) and the aq layer was separated and extracted with five 50-ml portions of H_2O-saturated *n*-BuOH. The combined *n*-BuOH solutions was washed with four 30-ml portions of *n*-BuOH-saturated H_2O before it was evaporated to dryness *in vacuo*. The residue was triturated with EtOH (5 ml) and filtered and the filtrate absorbed on a previously prepared column (1.9 × 35 cm, containing 40 g of silica gel wet packed with $CHCl_3$). The column was eluted with 9:1 $CHCl_3$–MeOH to give a glassy product which appeared by tlc to be homogeneous: yield 450 mg (34%). Both the uv and pmr spectra indicated, however, that the product was a mixture of **11** and an unidentified ribonucleoside.

2-Fluoro-*N*,*N*-dimethyladenosine (**12**).—Me_2NH_2 (135 mg, 3 mmol in abs EtOH) was added with stirring to a suspension of 2,6-difluoro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine[17] (**6**, 1 g, 2.4 mmol) in EtOH (20 ml, dried over Linde 3A sieve) at 5°, and the reaction mixture was stirred until complete solution was effected. After refrigeration for several hours (until the uv spectrum indicated mono replacement was complete), the reaction solution was evaporated to dryness *in vacuo* (10–15 mm, 25°). The residue was triturated with C_6H_6, the insoluble solid was removed by filtration, and the filtrate was evaporated to dryness *in vacuo* to give **8** as a white glass (tlc 1:1 $CHCl_3$–EtOAc). A solution of **8** in sieve-dried EtOH (50–75 ml) was saturated with dry NH_3 at 5°. After refrigeration for 3 days, the reaction solution was evaporated to dryness *in vacuo* and the residue was triturated with Et_2O containing sufficient EtOH to give a filterable solid. The solid was collected by filtration, washed with Et_2O, and dried *in vacuo* to give the crude product. Recrystallization from EtOH gave the pure material: yield 415 mg (53%); mp 170°; $[\alpha]^{25}D$ −67.2 ± 0.4 (*c* 0.99, EtOH); tlc (9:1 $CHCl_3$–MeOH); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 1, 274 (19.6); pH 7, 13, 274 (21.3). *Anal.* ($C_{12}H_{16}FN_5O_4$) C, H, N.

***N*-Amino-2-fluoroadenosine** (**14**).—A solution of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*N*-amino-2-fluoroadenine (**10**, 820 mg, 1.9 mmol) in EtOH–NH_3 (350 ml EtOH, dried over Linde 3A sieve, saturated at 5°) was refrigerated for 3 days before it was evaporated to dryness *in vacuo* [10–15 mm (25°)]. The residue was triturated with $CHCl_3$ and the insoluble residue was triturated with hot EtOH (25 ml). The resulting mixture was chilled until crystallization was complete and the homogeneous pigmented product (yield 57%) was collected by filtration. After two recrystallizations from EtOH with Norit treatment (which resulted in decomposition of most of the material) the pure colorless product was isolated: yield 6.6 mg (1.1%); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 1, 262 (13.9), 268 (sh); pH 7, 266 (16.1), 272 (sh); pH 13, 267 (sh), 273 (13.1), 282 (sh). *Anal.* ($C_{10}H_{13}FN_6O_4$) C, H, N.

9-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2-chloro-*N*-methyladenine.—A solution of 9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloropurine[22] (2.5 g, 4 mmol) in 20% aq $MeNH_2$ (30 ml) was allowed to stir at room temperature for 1 hr. The solid that formed was collected by filtration, washed with H_2O, and dried to give the crude product in 57% yield. The crude product was dissolved in $CHCl_3$ (3 ml) and the solution was absorbed on a previously prepared column (2.4 cm × 35 cm containing 90 g of silica gel). The column was eluted with 3:1 $CHCl_3$–EtOAc. The pure product was isolated as a glass: yield 800 mg (33%); tlc (1:1 C_6H_6–EtOAc); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 1, 243 (32.7), 283 (26.5); pH 7, 242 (37.6), 279 (27.5); pH 13, 217 (38.6), 273 (22.8). *Anal.* ($C_{32}H_{26}ClN_5O_7 \cdot 0.25H_2O$) C, H, N.

Acknowledgment.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute for the spectral and most of the microanalytical data reported, to Mrs. Martha Thorpe for her help in the interpretation of the pmr spectra, and to Mrs. Margaret H. Vail for the cytotoxicity data reported.

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