was washed with water, dried, and evaporated *in vacuo*. The product, 1.89 g of pale yellow oil, was crystallized from benzene–light petroleum mixtures to give 0.994 g of colorless crystals melting at 114–116.5°.

6-(*N*-Methyl)amino-2,3,4-trimethoxybenzocycloheptane (18). The carbamate 17 (820 mg 2.7 mmol) dissolved in 15 ml of dry tetrahydrofuran was slowly added dropwise to 1.3 g (34 mmol) of $LiAlH_4$ suspended in 15 ml of dry tetrahydrofuran cooled to 0°. The mixture was stirred 0.5 hr at 0° after which time it was refluxed for 2 hr. The reaction was terminated by adding 1.3 ml of water in 10 ml of tetrahydrofuran and made filterable with 5 ml of 12% NaOH. After filtering, drying, and evaporating 643 mg (91%) of yellow oil was obtained. The compound was isolated as the oxalate, mp 195–205°.

5-β-Cyano-6-oxo-2,3,4-trimethoxybenzocycloheptane (19). This compound was made as already described[12] from the ketone 12 in 98% crude yield. Recrystallization from ethanol gave a product melting at 107–110° (lit. mp 110.5–111.2°).

β-(6-Oxo-2,3,4-trimethoxybenzocycloheptan-5-yl)propionic Acid (20). Compound **20** was made from the hydrolysis of the cyano ketone **19** by methods already described[12] in nearly quantitative yield. The ir spectrum was as expected, mp 87–89° (lit. mp 88–90°).[13]

β-[5-(6-Hydroxy-2,3,4-trimethoxybenzocyclohepten-5-yl)]-propionic Acid δ-Lactone (21). This product was made from the keto acid **20** by previously described methods[12] in 59% yield of material melting at 105–107° (lit. mp 104–105°).

β-[5-(6-Hydroxy-2,3,4-trimethoxybenzocyclohepten-5-yl)]-propionic Acid δ-*N*-Methyllactam (22). The crude keto acid **20** (528 mg, 1.6 mmol) was added to 25 ml of ethanol which had been saturated with methylamine. The mixture was heated in a stainless steel bomb at 140° for 8 hr. The product remaining after the evaporation of the ethanol was purified by chromatography on a silica gel plate using chloroform as a solvent (R_f = 0.05–0.25). The product was removed from the plate and crystallized from light petroleum to give 230 mg (44%) of colorless microcrystals which melted at 104–106°. The ir spectrum was as expected.

Biological Evaluation. Male albino mice of the Swiss-Webster strain weighing 20–25 g were used. All injections were *via* the intravenous route (tail) in volumes not exceeding 0.01 ml/g of body weight. Testing protocol consisted of suspending or dissolving all compounds in water or 0.5% methylcellulose. Approximate 0.5 log-spaced doses were employed to characterize a "no effect" to 100% lethal response. Four animals were used at each dose level. Each animal was evaluated for significant activity at 5, 10, 15, 30, and 60 min postinjection and thereafter at 2, 4, and 24 hr. The statistical method, employed for the calculation of LD_{50} and MED_{50}, is that described by Weil.[14] The MED_{50} shown in Table I is based on the first pharmacological effect shown in the "effects" column; other effects (those shown after the comma) may or may not be observed at the MED_{50} dose. The MED_{50} is based on the pharmacological effect shown at the lowest dose which gave any clear effect.

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Puromycin Analogs.[1] Synthesis and Biological Activity of 5′-Deoxypuromycin and Its Aminonucleoside, 6-Dimethylamino-9-(3′-amino-3′,5′-dideoxy-β-D-ribofuranosyl)purine†

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The antibiotic puromycin derives its antimicrobial and antitumor activity from its ability to cause a premature release of growing polypeptide chains from ribosomes.[2] The aminonucleoside derived from puromycin is devoid of antibacterial activity but is three to four times as cytotoxic as the parent antibiotic against mammalian cells.[3] Consequently, an additional cytotoxic effect on the host may result from the release of aminonucleoside if hydrolytic or enzymatic removal of the amino acid moiety from administered puromycin occurs[4] (Figure 1). Recent studies demonstrate that the aminonucleoside is monodemethylated[5] and subsequently converted to the 5′-nucleotide.[6] It is not unreasonable to assume, therefore, that nucleotide formation is a prerequisite to cytotoxic activity. This same metabolic scheme may also account for the severe nephrotoxic manifestations, including renal lesions, resulting from administered puromycin aminonucleoside.

In an attempt to improve the selective toxicity of the antibiotic, an assessment of the requirement for the 5′-OH in both the antimicrobial activity of puromycin and in the cytotoxic activity of the aminonucleoside is desirable. Previous studies with carbocyclic analogs have been useful in defining the ribosomal binding requirements of the antibiotic.[7] However, the absence of a sugar moiety in these analogs precludes the assessment of the 5′-OH group's contribution to the cytotoxic effect. Thus, we have developed

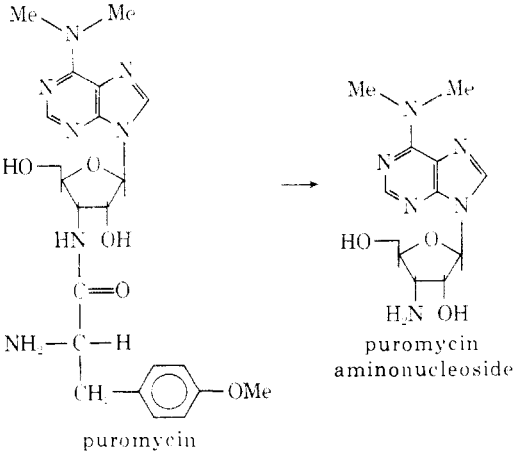

Figure 1.

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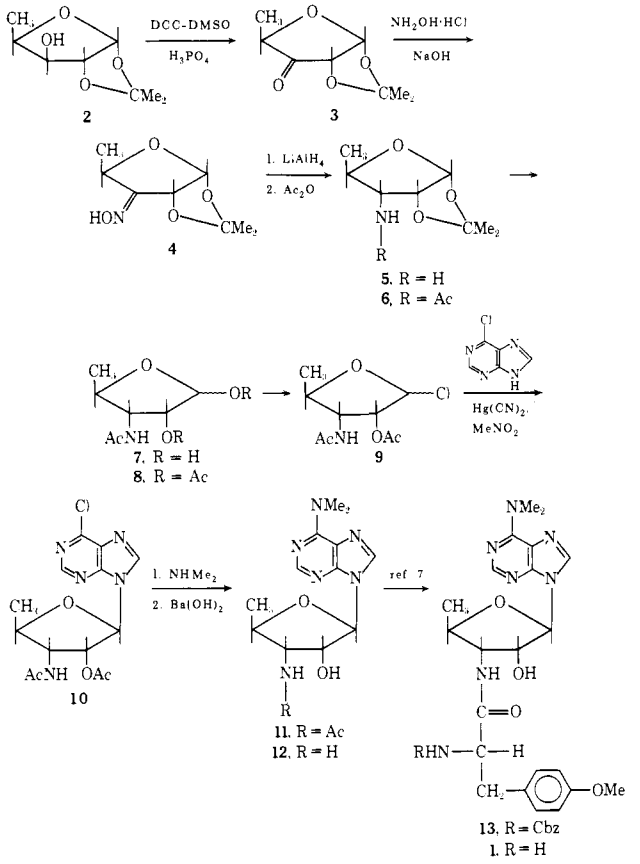
a synthesis of 5′-deoxypuromycin (1) and its aminonucleoside (12).

Chemistry. The synthesis of 5′-deoxypuromycin is outlined in Scheme I. Oxidation of 1,2-*O*-isopropylidene-5-deoxy-α-D-xylofuranose (2)[8] gave the keto sugar 3 which

Scheme I



was subsequently converted to the corresponding oxime 4.‡ Lithium aluminum hydride reduction of the oxime gave exclusively the previously identified 3-amino-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (5)[9] which was N-acetylated to 6. Selective removal of the isopropylidene group was accomplished with IR-120 Amberlite resin. The sugar 7 was isolated and identified as a crystalline material. However, direct conversion of the unpurified material to the diacetate 8 was accomplished with better overall yields. The anomeric configuration of 8 was identified as a 1α-2.2β mixture from the anomeric proton signals in the nmr spectrum: δ 6.42 (d, $J_{1,2}$ = 5.0 Hz, α anomer), 6.07 (s, β anomer). Conversion of 8 to the chloro sugar 9 followed by condensation with 6-chloropurine in the presence of mercuric cyanide gave the 6-chloropurine nucleoside 10. Treatment of 10 with aqueous dimethylamine gave the 6-dimethylaminopurine nucleoside in which the β anomer 11 was isolated as the major product, along with a small amount of the α-nucleoside. The anomeric configurations of the two isomeric nucleosides were firmly identified by their pmr spectra. There appears to be no exception to the observations that the signal from the anomeric proton of cis nucleosides occurs at lower field (usually *ca.* δ 0.5) than that of trans nucleosides.[10,11] In addition, the Karplus equation[12] predicts that the observed coupling constants of the anomeric proton and the C-2 proton of the sugar moieties ($J_{1',2'}$) can vary from 3.5 to 8.0 Hz for the α-nucleoside, and 0.0–8.0 Hz for the β-nucleoside. Thus, when both anomers are available, an assignment of the β configuration can be made if the coupling constant is found to be less than 3.5 Hz. The observed chemical shifts of δ 6.00 (J = 1.6 Hz) for the β-nucleoside 11 and δ 6.47 (J = 3.5 Hz) for the α-nucleoside are consistent with the predicted values. Both nucleosides underwent acyl migration in ethanolic HCl, confirming that no epimerization of the 2′-OH occurred during the glycosidation reaction.[10] Hydrolysis of 11 with barium hydroxide gave the 5′-deoxyaminonucleoside analog (12) of puromycin. The aminonucleoside was coupled with *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine using dicyclohexylcarbodiimide and *N*-hydroxysuccinimide by the method previously described.[7] Hydrogenolysis of the resulting carbobenzoxy-blocked nucleoside 13 gave the desired 5′-deoxypuromycin (1).

‡During the course of this work the preparation of 4 from the ruthenium tetroxide oxidation product of 2 was reported.[9]

Table I. Inhibition of L-[^{14}C]Polyphenylalanine Formation[a]

Compd	M	% inhibition Poly(U)	% inhibition Poly(UC) (1:1)
1	10^{-3}	91.9	100
	10^{-4}	40.9	100
	10^{-5}	2.0	55
Puromycin	10^{-3}	98.1	100
	10^{-4}	53.7	100
	10^{-5}	6.2	71

[a] Assay conditions are those previously described.[13] All counts were corrected by blanks and all values represent an average of triplicate determinations. The average deviation of such replicates are < ±4%.

Results and Discussion

Minimum inhibitory concentrations by a twofold serial dilution assay for 1 and puromycin, respectively, are as follows (mM): *Staphylococcus aureus* (NRRL B-313), 0.027 and 0.054; *Escherichia coli* (NRRL B-210), 0.031 and 0.062. Examination of Table I reveals that 1 inhibits the formation of polyphenylalanine in the *E. coli* cell free system to the same degree exhibited by puromycin. The degree of inhibition exerted by both compounds varied with the composition of template used (Table I). Similar observations have been reported for puromycin[13] and other antibiotics.[13-15] The greater activity of 1 relative to puromycin in the antimicrobial systems may be due to higher intracellular concentrations of 1; however, this possibility has not been examined.

Since puromycin aminonucleoside is highly cytotoxic to mammalian cells including tumor cells,[3] the role of the 5′-OH group was evaluated by growing P-388 mouse lymphoid leukemia cells in the presence of either puromycin aminonucleoside or 5′-deoxypuromycin aminonucleoside (12). The puromycin aminonucleoside exhibited an LD_{50} concentration of 8.1 × 10^{-6} M, whereas 12 had no effect on cell growth even at 40 times this concentration.

We conclude from these data that the 5′-OH moiety can be removed from the puromycin molecule without detriment to its ability to inhibit protein biosynthesis at the ribosomal level. In addition, the inactivity of 5′-deoxypuromycin aminonucleoside (12) in mammalian cell cultures demonstrates an involvement of the 5′-OH group in cytotoxicity at the aminonucleoside level. Since the same cytotoxic metabolite is most likely responsible for the nephrotic syndrome, the administration of 5′-deoxypuromycin could not release a toxic metabolite upon enzymatic or

hydrolytic removal of the amino acid moiety. Metabolic and nephrotoxicity studies are now in progress.

Experimental Section

Melting points were determined on a Mel-Temp and are corrected. Optical rotations were measured at ambient temperatures with a Perkin-Elmer 141 automatic polarimeter, nmr with a Varian A-60D spectrometer, ir with a Perkin-Elmer 237B spectrophotometer, and uv with a Cary 14 recording spectrophotometer. Analytical results were determined by M-H-W Laboratories, Garden City, Mich., and are within ±0.4% of the calculated values.

1,2-*O*-Isopropylidine-5-deoxy-α-D-*erythro*-pentofuran-3-ulose Oxime (4). A solution of 5.62 g (57.0 mmol) of crystalline H_3PO_4 in DMSO (62 ml) was added to a stirring solution of 20.0 g (115 mmol) of 2,[8] 71.0 g (344 mmol) of DCC, and 4.60 ml (57.0 mmol) of pyridine in DMSO (240 ml). The mixture was stirred at 20–25° for 45 min and at ambient temperature for 18 hr. Ethyl acetate (600 ml) was added, followed by a slow addition of 29.0 g (299 mmol) of oxalic acid dihydrate in MeOH (58 ml). The mixture was stirred for 30 min and mixed with a saturated NaCl solution (1200 ml). The mixture was filtered, and the filter cake was washed with EtOAc (100 ml). The filtrate layers were separated, and the water layer was extracted with EtOAc (230 ml) and CH_2Cl_2 (2 × 230 ml). The organic layers were combined and washed with 3% sodium bicarbonate in saturated NaCl solution (600 ml) and saturated NaCl (2 × 600 ml). The aqueous layers were extracted with CH_2Cl_2 (450 ml), and the organic layers were combined, dried (Drierite), and evaporated *in vacuo* at 40°. A small amount of solid was removed from the oily product by addition of EtOAc (30 ml) followed by filtration. The filtrate was concentrated *in vacuo* to a light orange oil, 19.4 g. Distillation of the oil gave 13.5 g of ketone 3 as a light yellow oil, bp 49–57° (0.50 mm). This product was shown by nmr to contain 5% DMSO.

To 12.3 g (7.14 mmol) of 3 and 16.0 g (231 mmol) of hydroxylamine hydrochloride in water (44 ml) was added 43.3 ml of 10% NaOH. The mixture was stirred at 65° for 2 hr and then extracted with CH_2Cl_2 (3 × 80 ml). The combined organic extracts were washed with saturated NaCl solution (120 ml), dried (Drierite), and concentrated *in vacuo* to a syrup. Trituration with petroleum ether (bp 60–70°) gave the white solid oxime 4, 11.7 g, mp 85–87°. An analytical sample was prepared by crystallization from petroleum ether and gave white needles, mp 89° (lit. mp 90.5–91°).[9] *Anal.* ($C_8H_{13}NO_4$) C, H, N.

3-Acetamido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (6). To a solution of 8.61 g (49.7 mmol) of 3-amino-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-ribofuranose (5; prepared from 4 as described in ref 9) in pyridine (75 ml) was added 14 ml (149 mmol) of Ac_2O. The mixture was stirred at ambient temperature for 17 hr and the volatile materials were removed *in vacuo* at 40°. The orange syrup product was dissolved in $CHCl_3$ (400 ml) and washed with 5% HCl (250 ml), saturated $NaHCO_3$ (250 ml), and saturated NaCl (250 ml), respectively. The $CHCl_3$ layer was dried (Drierite) and evaporated *in vacuo* to an orange syrup. Petroleum ether (bp 30–60°) was added, and the mixture was evaporated *in vacuo* to a light yellow solid, 8.89 g. Crystallization from Et_2O gave the analytical product 6 as white crystals: 7.88 g (74%); mp 106–107°; $[\alpha]^{22}D$ +169° (*c* 2.12, MeOH). *Anal.* ($C_{10}H_{17}NO_4$) C, H, N.

3-Acetamido-3,5-dideoxy-D-ribose (7). To a solution of 4.50 g (20.9 mmol) of 6 in H_2O (150 ml) at 60° was added 58 ml (110 mequiv) of IR-120 acidic resin (Amberlite, Mallinckrodt) in water (100 ml), and the mixture was stirred at 60° for 1 hr. The resin was removed by filtration, and the filtrate was evaporated *in vacuo* to a yellow solid, 3.43 g (this material could be used in subsequent reactions without loss of yields). Crystallization from EtOAc gave an analytical sample of 7 as white crystals, mp 119–121°. *Anal.* ($C_7H_{13}NO_4$) C, H, N.

1,2-*O*-Diacetyl-3-acetamido-3,5-dideoxy-D-ribofuranose (8). A solution of 736 mg of crude 7 and 2.19 ml (23.2 mmol) of Ac_2O in pyridine (13 ml) was stirred at ambient temperature for 18 hr. The volatile materials were removed *in vacuo* at 40°. The oily residue was dissolved in $CHCl_3$ (50 ml) and washed with 5% HCl (20 ml), saturated $NaHCO_3$ (20 ml), and saturated NaCl (20 ml). The organic layer was dried (Drierite) and evaporated to a light yellow oil, 0.982 g. Crystallization from Et_2O gave 8 as white crystals: 0.817 g (68%) from 6; mp 101–103°; nmr ($CDCl_3$) δ 6.42 (d, 0.31, $J_{1,2}$ = 5.0 Hz, α anomer), 6.07 (s, 0.69, β anomer). *Anal.* ($C_{11}H_{17}NO_6$) C, H, N.

6-Dimethylamino-9-(3′-acetamido-3′,5′-dideoxy-β-D-ribofuranosyl)purine (11). The $Hg(CN)_2$–$MeNO_2$ nucleoside condensation method of Yomaoka, *et al.*,[16] was used. A solution of 2.00 g (7.72 mmol) of 8 and 2 ml of acetyl chloride in anhydrous Et_2O (80 ml) saturated with HCl gas was allowed to stand at 0° for 72 hr. The solution was evaporated to a white gummy foam which was immediately dissolved in azeotropically dried $MeNO_2$ (90 ml). To this solution was added 3.56 g (23.0 mmol) of 6-chloropurine, 2.90 g (11.5 mmol) of $Hg(CN)_2$, and 2.0 g of Drierite, and the mixture was heated under reflux for 2 hr. The reaction mixture was filtered hot, and the filter cake was extracted (twice with hot $MeNO_2$ and refiltered. The combined filtrates were evaporated under aspirator vacuum (HCN ▲) at 50° and then at 1 mm at 45°. The remaining tan foam was extracted with $CHCl_3$ (3 × 100 ml) and the extracts were combined, washed with 30% KI in half-saturated NaCl (100 ml) and saturated NaCl (100 ml), and dried (Drierite). Evaporation of the dried organic layer gave the 6-chloropurine nucleoside 10 as a light yellow foam which would not crystallize; yield 2.03 g. This material was not further purified and was dissolved in 40% aqueous dimethylamine (32 ml) and allowed to stand at ambient temperature for 30 min. The volatile materials were removed under aspirator vacuum at 30°. The orange residue was mixed with saturated NaCl (100 ml) and extracted with CH_2Cl_2 (3 × 150 ml). The organic extracts were combined, dried (Drierite), and evaporated *in vacuo* to 1.24 g of a light yellow solid which contained a mixture of α- and β-nucleosides.

The β-nucleoside 11 crystallized from EtOAc (65 ml) as a white solid: yield 927 mg (37.5% from 8); mp 205–206°; uv_{max} (nm) (pH 1) 267, (pH 7) 274, (pH 13) 275; nmr (CD_3OD) δ 8.18 (s) and 8.07 (s) (H-2 and H-8), 6.00 (d, 1, *J* = 1.6 Hz, H-1′), 4.60 (dd, 1, $J_{1',2'}$ = 1.6 Hz, $J_{2',3'}$ = 5.2 Hz, H-2′), 4.29 (dd, 1, $J_{2',3'}$ = 5.2 Hz, $J_{3',4'}$ = 10.7 Hz, H-3′), 3.48 (s, 6, NMe_2), 2.05 (s, 3, $NCOCH_3$), 1.43 (d, 3, $J_{4',5'}$ = 5.5 Hz, 5′-CH_3); $[\alpha]^{22}D$ −11.0° (*c* 0.99, MeOH). *Anal.* ($C_{14}H_{20}N_6O_3$) C, H, N.

Concentration of the above EtOAc filtrate to 15 ml and cooling yielded a solid mixture of the α- and β-nucleosides (162 mg). This mixture was separated on a preparative silica gel plate (Brinkman, F-254) by developing three times with 10% MeOH in $CHCl_3$. An additional 85 mg of the β-nucleoside was removed from the plate by extraction of the band at R_f 0.61 (total yield 40.9%). The α-nucleoside was obtained from the band at R_f 0.49; yield 51.3 mg (12.1%). The α-nucleoside was crystallized from MeOH and gave an analytical sample as the monohydrate, softens at 155°, melts at 177.5–180°; uv_{max} (nm) (pH 1) 267, (pH 7) 275, (pH 13) 275; nmr (CD_3OD) δ 8.17 and 8.10 (2 s, 2 × 1, H-2 and H-8), 6.47 (d, 1, *J* = 3.5 Hz, H-1′), 3.50 (s, 6, NMe_2), 2.02 (s, 3, amide), 1.33 (d, 3, *J* = 5.5 Hz, 5′-CH_3). *Anal.* ($C_{14}H_{22}N_6O_4$) C, H, N.

6-Dimethylamino-9-(3′-amino-3′,5′-dideoxy-β-D-ribofuranosyl)purine (12). A solution of 925 mg (2.89 mmol) of 11 and 44 ml of 0.5 *N* $Ba(OH)_2$ was heated at 85° for 3.5 hr. Absolute EtOH (45 ml) was added to the cooled reaction mixture and the solution was neutralized with excess Dry Ice. The solid was removed by filtration and washed with EtOH (20 ml). The filtrate was evaporated *in vacuo* to a white solid. The solid was mixed with hot EtOH (40 ml) and filtered. The filter cake was washed with hot EtOH (40 ml), and the filtrate was evaporated to a white solid. This process was repeated, and the white solid residue was dissolved in EtOAc (50 ml). Refrigeration of the EtOAc solution gave 12 as a white powder which was removed by filtration: yield 369 mg; mp 200–201°. The filtrate was evaporated and the solid residue (321 mg) was treated with 15 ml 0.5 *N* $Ba(OH)_2$ using the same work-up as above. An additional 228 mg of 12 was obtained. The two fractions of product were combined and recrystallized from EtOAc and gave pure 12: yield 542 mg (67.4%); mp 204–205°. *Anal.* ($C_{12}H_{18}N_6O_2$) C, H, N.

6-Dimethylamino-9-[3′-(benzyloxycarbonyl-*p*-methoxyphenyl-L-alanylamino)-3′,5′-dideoxy-β-D-ribofuranosyl]purine (13). A mixture of 200 mg (0.719 mmol) of 12, 249 mg (0.755 mmol) of *N*-benzyloxycarbonyl-*p*-methoxyphenyl-L-alanine,[17] 86.8 mg (0.755 mmol) of *N*-hydroxysuccinimide, and dry DMF (9 ml) was stirred at ambient temperature and 156 mg (0.755 mmol) of DCC was added. The stirring was continued for 17 hr, the mixture was then cooled in an ice bath and filtered, and the filtrate was evaporated at 1 mm at 40° to a white gummy solid. The solid was mixed with DMF–H_2O (3:1; 7 ml), chilled, and filtered. The filtrate was concentrated *in vacuo* to a gummy solid. The solid was dissolved in EtOAc–BuOH (2:1, 50 ml) and washed with one-tenth saturated NaCl (15 ml), half-saturated $NaHCO_3$ (3 × 15 ml), one-tenth saturated NaCl (15 ml), and 3% saturated NaCl, respectively (attempts to wash with H_2O caused emulsions). The organic layer was dried (Drierite) and evaporated *in vacuo* and

the BuOH was azeotroped with cyclohexane. The pure product, **13**, was obtained as a white powder: yield 409 mg (96.5%); mp 191–192°. *Anal.* ($C_{30}H_{35}N_7O_6$) C, H, N.

5′-Deoxypuromycin (1). A solution of 350 mg (0.595 mmol) of **13**, 175 mg 10% Pd/C, and HOAc (30 ml) was shaken under 1 atm of hydrogen until the theoretical amount of hydrogen was absorbed (15 min). Fresh hydrogen was added to the system and the mixture was shaken for an additional 10 min. The catalyst was removed by filtration through Celite and the HOAc was removed *in vacuo* at 30°. The oily residue was dissolved in MeOH and passed through an IRA 400 (OH^-) resin (30 ml) column. The first 50 ml of effluent was evaporated *in vacuo* to an oil which crystallized from 95% EtOH (2.5 ml). Pure 1 was obtained as a white powder: yield 182 mg (67.4%); softens at 104°, melts at 112–120°; $[\alpha]^{22}D$ +17.0° (c 1.01, MeOH); uv_{max} (nm) (pH 1) 267 (ε 19,700), (pH 7) 275 (ε 19,500), 215 (ε 22,700), (pH 13) 275 (ε 20,100). *Anal.* ($C_{22}H_{29}N_7O_4$) C, H, N.

Biological Testing. The assay procedures for the antimicrobial testing and the *in vitro* protein synthesis measurements have been described previously.[7,13]

P-388 *in Vitro* **Assay.** Tenfold dilutions of puromycin aminonucleoside or **12** were tested in duplicate sets of tubes inoculated with 240,000 P-388 cells in 4 ml of Fischer's medium with 10% horse serum. The tubes were plugged with silicone stoppers and incubated for 72 hr at 37° at a 30° angle without agitation. Cell growth was determined by cell count with a hemocytometer, per cent inhibition calculated from the corresponding controls correcting all counts of inoculum.

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Effect of Trifluoromethoxy, Chlorodifluoromethoxy, and Trifluoromethyl on the Antimalarial Activity of 5-Benzyl- and 5-Phenyl-2,4-diaminopyrimidines

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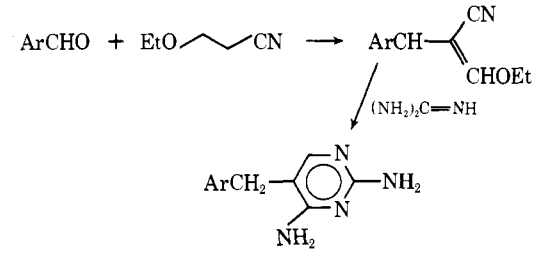
Halogens are prominent for their pharmacophoric behavior[1] in many classes of antimalarial agents. Recent drug syntheses have noted that dramatic improvements in drug efficacy may occur when these simple halogens are replaced by CF_3[2] groups. The significance of this functionality to the antimalarial activity of benzyl- and phenyl-2,4-diaminopyrimidines appears to have escaped synthetic and biological attention. Considering the relevance of this class of drugs, as exemplified by pyrimethamine [5-(*p*-chlorophenyl)-2,4-diamino-6-ethylpyrimidine], to the treatment of various malarial infections, synthesis of benzyl- and phenyl-2,4-diaminopyrimidines substituted with CF_3 groups warranted study. In addition, this paper details the introduction of two related perhalomethyl functions into this class of diaminopyrimidines, namely, the CF_3O- and the CF_2ClO- groups. The rationale for their inclusion in this study is based on the fact that the magnitude and the direction of their group electronic character is diametrically opposed to CF_3, being more akin to the simple halogens.

Chemistry. The synthetic strategy employed to obtain trifluoromethyl- and perhalomethoxybenzyldiaminopyrimidines used for our study was detailed by Stenbuck and Baltzly.[3] Although the yields were low, the sequential base condensation of aromatic aldehyde with ethoxypropionitrile and guanidine occurred without undue complication.



One exception to this preparative method was encountered with 4-(α,α,α-trifluoro)tolualdehyde. Since the trifluoromethylbenzaldehydes **1**, **3**, and **4** are amenable to these series of reactions, it would appear that the normal condensations are only impeded by para-positioned electron-withdrawing groups.

The perhalomethylarylaldehydes required for the synthesis of the target compounds *via* the indicated scheme are listed in Table I.

A halogen–metal interchange between commercially available trifluoromethyl- and trifluoromethoxybromobenzenes and BuLi followed by reaction with DMF was used to prepare the trifluoromethyl- and trifluoromethoxybenzaldehydes **1–5**. Several of these aldehydes have previously been reported; however, the reaction sequence detailed in the Experimental Section appears to offer procedural advantages.

The unavailability of the appropriate trifluoromethoxybromobenzene precluded synthesis of **9** *via* method A. The reaction sequence shown in Scheme I was employed for the synthesis of the benzaldehyde **9**. Conversion of *m*-anisic acid to *m*-(α,α,α-trichloro)anisoyl chloride was realized after the method Yagupol'skii[4] detailed for preparation of the para isomer.

Initial attempts to effect the fluorine–chlorine metathesis with SbF_3 yielded a mixture containing predominately two fairly close boiling components. One of these was identified as **8a** by hydrolysis to the known 3-(α,α,α-trifluoro)anisic acid.[5] The proportion of **8a** in the mixture could be increased by employing higher exchange reaction temperatures or preferably by using SbF_3–$SbCl_5$ for the metathesis. The proton spectrum of the other component was almost superimposable with that of **8a**. This, in con-