Studies on Organic Fluorine Compounds. Part 35.[1] Trifluoromethylation of Pyrimidine- and Purine-nucleosides with Trifluoromethyl–Copper Complex

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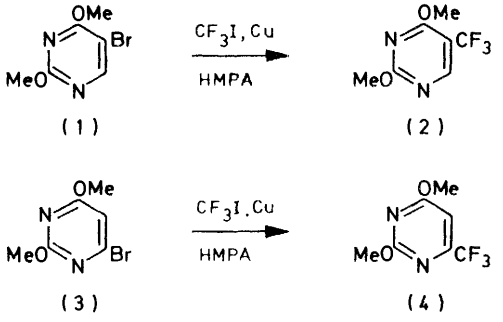
Halogenated nucleoside derivatives were trifluoromethylated using a solution of a trifluoromethyl–copper complex, which was prepared by shaking trifluoromethyl iodide and copper powder in hexamethylphosphoric triamide and filtering off the excess of copper powder. The following trifluoromethylated nucleosides were obtained in moderate to good yields: 5-trifluoromethyl-uridine, -deoxyuridine, -cytidine, -deoxycytidine, and -arabinosylcytosine; 8-trifluoromethyl-adenosine, -deoxyadenosine, and -inosine; and 6-trifluoromethylribofuranosylpurine. This procedure offers simple synthesis of many trifluoromethyl compounds.

SOME nucleic acid derivatives containing fluorine substituents show interesting biological activity. For example, 5-fluorouracil derivatives are used as antitumour agents and 5-(trifluoromethyl)deoxyuridine, which was synthesized by Heidelberger,[2] shows marked anti-viral activity.[3] We have published two preliminary reports on fluoro-nucleic acid derivatives: one on the synthesis of 8-fluoroadenosines [4] and the other on the synthesis of 5-(trifluoromethyl)uridines.[1b] We now report the trifluoromethylation of pyrimidine and purine nucleosides with trifluoromethyl iodide–copper complex. Ref. 1*b* was the first report of a method for the introduction of a trifluoromethyl group to nucleosides with carbon–carbon bond formation; previous methods for the synthesis of trifluoromethylated nucleic acids or bases involved ring-closure [5] or conversion of a carboxy-group into a trifluoromethyl group with sulphur tetrafluoride.[6] The trifluoromethylation of aryl halides with trifluoromethyl iodide in the presence of copper powder has been reported by us.[7]

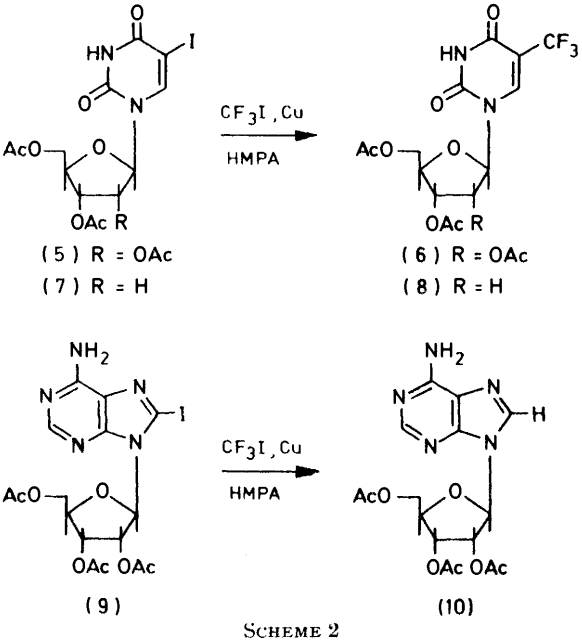
In the present work, many types of trifluoromethylated nucleosides have been synthesized by simple application



SCHEME 1

or modification of the foregoing method.[7] We first examined the trifluoromethylation of 5- or 6-bromo-2,4-dimethoxypyrimidine and found that hexamethylphosphoric triamide (HMPA) was the best solvent. Thus, 5-bromo-2,4-dimethoxypyrimidine (1) [8] was shaken with trifluoromethyl iodide and copper powder in a stainless steel tube at 110 °C for 40 h. Steam-distillation of the reaction mixture and extraction of the distillate gave the 5-trifluoromethyl compound (2) in 42% yield. Reaction of 6-bromo-2,5-dimethoxypyrimidine (3) [9] gave the 6-trifluoromethyl compound (4) in 31% yield (Scheme 1).

We then tried to apply this method to halogenonucleosides. The first objectives were 5-(trifluoromethyl)uridine derivatives, which are known to have antiviral activity. Treatment of 5-iodouridine tri-*O*-acetate (5), derived from 5-iodouridine,[10] in the same

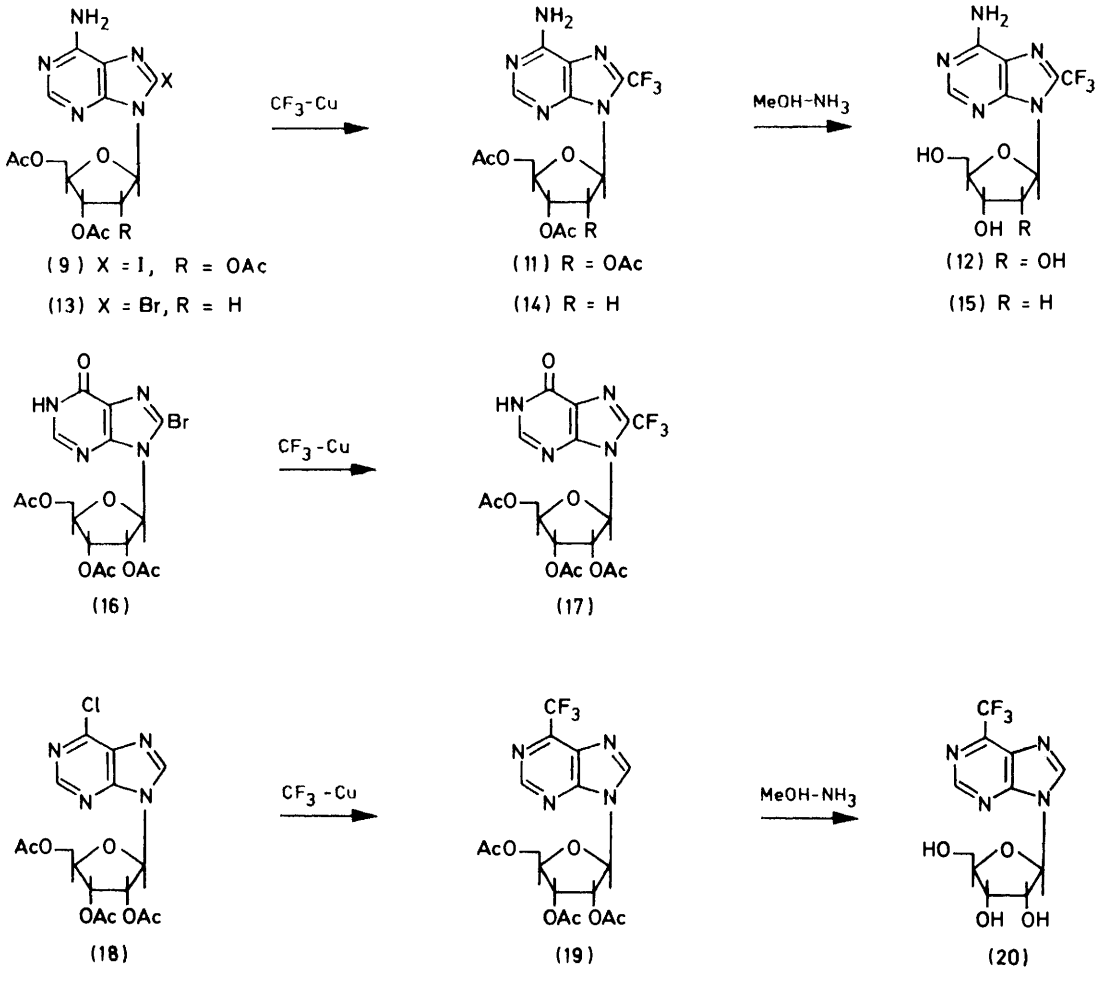


SCHEME 2

manner as for the pyrimidine, gave 38% of the trifluoromethyl compound (6). Similarly 3′,5′-di-*O*-acetyl-5-iododeoxyuridine (7), synthesized from 5-iododeoxyuridine, gave the corresponding trifluoromethyl compound (8) in 54% yield (Scheme 2).

We next investigated the trifluoromethylation of purine nucleosides. Although 8-(trifluoromethyl)-guanosine has been synthesized by ring-formation with trifluoroacetic acid derivatives,[11] no example of introduction of a trifluoromethyl group to a purine nucleoside itself is known. We first attempted the trifluoromethylation of 2′,3′,5′-tri-*O*-acetyl-8-iodoadenosine (9).[12]

However, similar treatment of (9) as for (1) gave the dehalogenated product 2′,3′,5′-tri-*O*-acetyladenosine (10) as the main product, possibly owing to reduction with metallic copper (Scheme 2). Therefore, we investigated the effect of filtering off the copper powder and using the filtrate for the trifluoromethylation. Although (iv) A lower temperature can be used for the trifluoromethylation than that for the synthesis of the trifluoromethyl copper complex. (v) Trifluoromethylation of thermally unstable compounds is possible. (vi) The CF_3–Cu complex solution can be applied more widely than previous methods. In fact, the trifluoromethylation of (9)



SCHEME 3

McLoughlin *et al.* reported that perfluoroalkyl copper derivatives with long chains were stable to water and heat,[13] trifluoromethyl–copper is very sensitive to humidity. Accordingly, after trifluoromethyl iodide and copper powder had been shaken in HMPA at 120 °C for 2.5 h, the mixture was filtered under dry nitrogen, and the filtrate was used for the trifluoromethylation [equation (1)].[14]

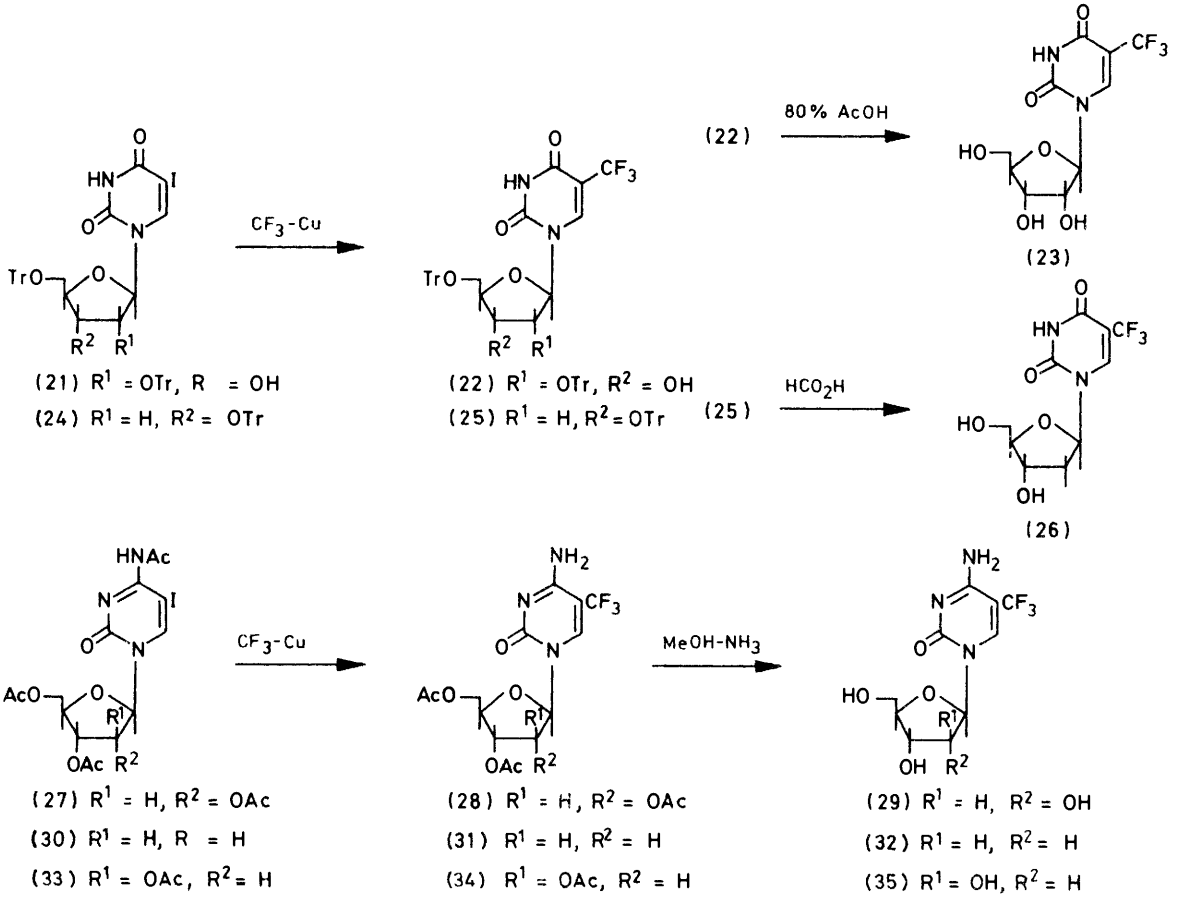
$$CF_3I + Cu \xrightarrow{HMPA} \xrightarrow{filter} CF_3\text{–}Cu\ (soln.) \xrightarrow{R\text{–}X} R\text{–}CF_3 \quad (1)$$

The characteristics of this modification are as follows. (i) The absence of metallic copper eliminates the possibility of the reductive dehalogenation occurring. (ii) The trifluoromethylation can be carried out in glass apparatus. (iii) The reaction can be followed easily by g.l.c. or t.l.c. by this two-stage method gave 2′,3′,5′-tri-*O*-acetyl-8-(trifluoromethyl)adenosine (11) in 46% yield. Deacylation of (11) with methanolic ammonia gave 8-(trifluoromethyl)adenosine (12). Similarly, 3′,5′-di-*O*-acetyl-8-bromo-deoxyadenosine (13)[15] gave the corresponding trifluoromethyl compound (14) in 64% yield, which was deacylated to 8-(trifluoromethyl)deoxyadenosine (15) (Scheme 3). Further, 2′,3′,5′-tri-*O*-acetyl-8-bromoinosine (16)[15] gave the trifluoromethyl derivative (17) in 42% yield. These results show that the two-stage method using the CF_3–Cu solution is superior to the previous method,[7] which could not be applied to 8-halogenopurine nucleosides. Among the modified purine nucleosides, 6-substituted purines are biologically interesting, like 6-mercaptopurine, as anti-leukaemia agents. Therefore, we applied this trifluoromethylation to 2′,3′,5′-tri-*O*-acetyl-6-chloropurineriboside (18)[16] and

obtained the corresponding trifluoromethyl compound (19) in 29% yield. Deacylation of (19) gave 6-(trifluoromethyl)purineriboside (20) in 50% yield.

As mentioned before, 5-(trifluoromethyl)pyrimidine nucleosides are known to have interesting biological activity. However, deacylation of (trifluoromethyl)uridine derivatives, *e.g.* (6) or (8), under basic conditions is known to cause hydrolysis of the trifluoromethyl group to a carboxy-group.[2] We therefore studied the possibility of application of the modified method to pyrimidine nucleoside protected with a much more labile group hydrolysable under acidic conditions to obtain trifluoromethyl-pyrimidine nucleosides unprotected in the sugar part. Thus, treatment of 2',5'-di-*O*-trityl-5-iodouridine (21) with the CF_3–Cu solution at 45 °C for 12 h gave the trifluoromethyl compound (22) which was detritylated by heating it in refluxing 80% acetic acid for 10 min to give 5-(trifluoromethyl)uridine (23) in 68% yield. Similar treatment of 3',5'-di-*O*-trityl-5-iododeoxyuridine (24) with the CF_3–Cu solution gave the corresponding trifluoromethyl derivative (25) in 89% yield. While treatment of (25) with hot 80% acetic acid caused fission of the glycoside bond, hydrolysis in 98% formic acid at 0 °C for 1 min [17] gave 5-(trifluoromethyl)-deoxyuridine (26) in 40% yield.

Thus, biologically active (trifluoromethyl)uridine derivatives could be synthesized in good yield, and we then tried to synthesize 5-(trifluoromethyl)cytidine derivatives, whose characteristics are not known but which were expected to show some biological activity. N^4,2',3',5'-Tetra-acetyl-5-iodocytidine (27), which was synthesized by iodination of the tetra-acetylcytidine, was treated with the CF_3–Cu solution to give 2',3',5'-tri-*O*-acetyl-5-(trifluoromethyl)cytidine (28) in 59% yield.



SCHEME 4 Tr = Ph_3C

One acetyl group seemed to be cleaved during the work-up. Deacylation of (28) with methanolic ammonia gave 5-(trifluoromethyl)cytidine (29) in 80% yield. Similarly, N^4,3',5'-triacetyl-5-iododeoxycytidine (30) gave 5-(trifluoromethyl)deoxycytidine (32) *via* the diacetyl compound (31). We also applied this method to introduce a trifluoromethyl group into an arabinosylcytosine, which is known to be an anti-tumour agent. Thus, treatment of N^4-2',3',5'-tetra-acetyl-5-iodoarabinosylcytosine (33) with the CF_3–Cu solution gave tetra-acetyl-5-(trifluoromethyl)arabinosylcytosine in 11% yield and 2',3',5'-tri-*O*-acetyl-5-(trifluoromethyl)arabinosylcytosine (34) in 39% yield. Deacylation of (34) gave 5-(trifluoromethyl)-arabinosylcytosine (35) in 76% yield (Scheme 4).

In conclusion, modification of our original method of trifluoromethylation by using the filtered CF_3–Cu

solution led to a milder and more selective method for trifluoromethylation of halogenated nucleoside derivatives which can be applied to a wide range of halogeno-compounds. However, in view of the reported carcinogenicity of HMPA, care should be taken in its use.

Antitumour effects against L 1210

Compound	Dosage mg/kg/day × 5	% of control
(8)	100	132
(11)	100	99
(12)	30	93
(17)	100	94
(20)	200	56 (toxic)
(29)	250	112
(32)	150	119
(35)	60	100

Biological tests of the anti-leukaemia activity of the trifluoromethyl compounds we have synthesized are shown in the Table. Unfortunately, significant results were not obtained. Other biological activities are now being examined.

EXPERIMENTAL

2,4-Dimethoxy-5-(trifluoromethyl)pyrimidine (2).—5-Bromo-2,4-dimethoxypyrimidine (1) (1.0 g) was shaken with trifluoromethyl iodide (9.6 g) and copper powder (6 g) in hexamethylphosphoric triamide (HMPA) (30 ml) at 110 °C for 40 h in a stainless steel tube. After steam-distillation, the distillate was extracted with ether. The solvent was then evaporated off and the residue purified by column chromatography and preparative t.l.c. (each on silica gel with pentane–CH_2Cl_2, 2 : 1, as eluant). Sublimation gave crystals of the *pyrimidine* (2) (405 mg, 42% yield); m.p. 54—56 °C; $\nu_{max.}$ (KBr) 1 320 and 1 140 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 257 nm (log ε 3.71) [256 (3.73) with acid, 257 (3.74) with alkali]; δ_H ($CDCl_3$) 8.38 (1 H, s, 6-H), 4.03, and 4.00 (6 H, s, OMe × 2); δ_F* ($CDCl_3$) −0.13 (s, CF_3); *m/e* 208 (M^+) and 189 (M^+ − F) (Found: M^+, 208.046 6. $C_7H_7F_3N_2O_2$ requires M^+ 208.045 9).

2,4-Dimethoxy-6-(trifluoromethyl)pyrimidine (4).—6-Bromo-2,4-dimethoxypyrimidine (3) (347 mg) was shaken with trifluoromethyl iodide (4.8 g) and copper powder (3 g) in HMPA (15 ml) at 125 °C for 40 h in a stainless steel tube. Work-up as for (2) gave crystals of the *pyrimidine* (4) (103 mg, 31% yield); m.p. 50—51 °C; $\nu_{max.}$ (KBr) 1 190 and 1 155 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 265 nm (log ε 3.76) [265 (3.77) with acid, 265 (3.77) with alkali]; δ_H ($CDCl_3$) 6.60 (1 H, s, 5-H) and 3.97 (6 H, s, OMe × 2); δ_F($CDCl_3$) +8.4 (s, CF_3); *m/e* 208 (M^+), 189 (M^+ − F), and 69 (CF_3) (Found: M^+ 208.046 6. $C_7H_7F_3N_2O_2$ requires M^+ 208.045 9).

2′,3′,5′-Tri-O-acetyl-5-(trifluoromethyl)uridine (6).—2′,3′,5′-Tri-*O*-acetyl-5-iodouridine (5) (1.0 g) was shaken with trifluoromethyl iodide (7.2 g) and copper powder (3 g) in HMPA (20 ml) at 110 °C for 40 h in a stainless steel tube. The mixture was then treated with ice–water and extracted with diethyl ether–ethyl acetate. After removal of the solvent, the residue was purified by column chromatography (silica gel; $CHCl_3$–EtOH, 30 : 1) and preparative t.l.c. (silica gel; $CHCl_3$–EtOH, 20 : 1) to give the *uridine* (6) as an amorphous powder (330 mg, 38% yield); $\nu_{max.}$ [258 (3.96) with acid, 260 (3.81) with alkali]; δ_H($CDCl_3$) (KBr) 1 140 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 258 nm (log ε 3.96) 10.08br (1 H, s, NH), 8.09 (1 H, s, 6-H), 6.08 (1 H, d, 1′-H), 5.41 (2 H, m, 2′- and 3′-H), 4.41 (3 H, m, 4′- and 5′-H), and 2.12 (9 H, s, OAc × 3); δ_F($CDCl_3$) +0.8 (s, CF_3); *m/e* 378 (M^+ − $OCOCH_3$), 259 (sugar), and 181 (base unit + 2 H) (Found: M^+ − $OCOCH_3$), 378.070 6. $C_{14}H_{13}F_3N_2O_7$ requires M − $OCOCH_3$ 378.067 5).

3′,5′-Di-O-acetyl-5-(trifluoromethyl)-2′-deoxyuridine (8).—3′,5′-Di-*O*-acetyl-5-iodo-2′-deoxyuridine (7) (1.0 g) was shaken with trifluoromethyl iodide (7.2 g) and copper powder (3 g) in HMPA (20 ml) at 110 °C for 40 h in a stainless steel tube. Work-up as for (6) gave the *deoxyuridine* (8) as an amorphous powder (468 mg, 54% yield); $\nu_{max.}$ (KBr) 1 135 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 260 nm (log ε 3.98) [260 (4.01) with acid, 260 (3.81) with alkali]; δ_H [$(CD_3)_2SO$] 12.00br (1 H, s, NH), 8.16 (1 H, s, 6-H), 6.12 (1 H, d, 1′-H), 5.24 (1 H, m, 3′-H), 4.30 (3 H, m, 4′- and 5′-H), 2.48 (2 H, m, 2′-H), 2.08 and 2.04 (6 H, s, OAc × 2); δ_F [$(CD_3)_2SO$] +0.8 (s, CF_3); *m/e* (M^+), 201 (sugar), 181 (base unit + 2 H), and 69 (CF_3) (Found: C, 44.2; H, 3.9; N, 7.2. $C_{14}H_{15}F_3N_2O_7$ requires C, 44.2; H, 4.0; N, 7.3%).

General Procedure for Trifluoromethylation of Nucleoside Derivatives with Trifluoromethyl–Copper Complex Solution.—Trifluoromethyl iodide (8.4 g) and copper powder † (5 g) in HMPA (20 ml) were shaken in a stainless steel tube at 120 °C for 2.5 h and the excess of copper powder was removed by filtration through Celite in a glove box with exclusion of air. To the dark green solution of the trifluoromethyl–copper complex, the halogenated nucleoside derivative was added and the mixture stirred under argon. The mixture was treated with ice–water and extracted with ethyl acetate. After removal of the solvent, the residue was purified by column chromatography on silica gel with dichloromethane–ethanol (35 : 1) as eluant. The following preparations, give the amounts of trifluoromethyl iodide, copper, HMPA, and starting material, reaction time, reaction temperature, product (g), m.p. (appearance, solvent), and physical data for the products.

8-(Trifluoromethyl)adenosine (12).—Trifluoromethyl iodide (9.6 g), copper (5 g), HMPA (20 ml), and 2′,3′,5′-tri-*O*-acetyl-8-iodoadenosine (9) (1.0 g), after 12 h at room temperature, gave *2′,3′,5′-tri-O-acetyl-8-(trifluoromethyl)adenosine* (11) (407 mg, 46% yield); m.p. 198—199 °C (crystalline, EtOH), $\nu_{max.}$ (KBr) 1 170, 1 140 cm^{-1} (CF): $\lambda_{max.}$ (MeOH) 265 nm (log ε 4.08) [261.5 (4.19) with acid, 263 (4.08) with alkali]; δ_H($CDCl_3$) 8.44 (1 H, s, 2-H), 6.46 (1 H, dd, 2′-H), 6.28br (2 H, s, 6-NH_2), 6.11 (1 H, d, 1′-H), 5.94 (1 H, dd, 3′-H), 4.48 (1 H, d, 4′-H), 4.48 (2 H, m, 5′-H), 2.17, 2.09, and 2.07 (9 H, s, OAc × 3); δ_F($CDCl_3$) −1.2 (s, CF_3); *m/e* 461 (M^+), 259 (sugar), and 204 (base unit + 2 H) (Found: C, 44.2; H, 4.0; F, 12.4; N, 15.5. $C_{17}H_{18}F_3N_5O_7$ requires C, 44.2; H, 3.9; F, 12.0; N, 15.2%). Deacetylation of (11) (300 mg) with methanolic ammonia at 5 °C overnight gave crystals of the *adenosine* (12) (from EtOH) (148 mg, 68% yield); m.p. 198—200 °C; $\nu_{max.}$ (KBr) 1 160 and 1 120 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 264 nm (log ε 4.07) [262 (4.18) with acid, 267 (4.08) with alkali]; δ_H [$(CD_3)_2SO$] 8.24 (1 H, s, 2-H), 7.92br (2 H, s, 6-NH_2), 5.81 (1 H, d, 1′-H), 5.52 (2 H, m, OH × 2), 5.24 (1 H, m, OH), 5.04 (1 H, dd, 2′-H), 4.23 (1 H, m, 3′-H), 4.04 (1 H, m, 4′-H), 3.62, and 3.49 (2 H, m, 5′-H); δ_F [$(CD_3)_2SO$] −4.4 (s, CF_3); *m/e* 335 (M^+), 204

* In p.p.m. to high field of internal $PhCF_3$ for all δ_F in the report.

† Copper powder precipitated from aqueous copper(II) sulphate by adding zinc powder (R. Q. Brewster and T. Groening, *Org. Synth.*, 1948, Coll. Vol. II, p. 445).

(base unit + 2 H), and 203 (base unit + H) (Found: C, 39.2; H, 3.6; F, 17.6; N, 20.9. $C_{11}H_{12}F_3N_5O_4$ requires C, 38.9; H, 3.6; F, 17.3; N, 20.8%).

8-(*Trifluoromethyl*)-2′-*deoxyadenosine* (15).—Trifluoromethyl iodide (8.4 g), copper (5 g), HMPA (20 ml), and 3′,5′-di-*O*-acetyl-8-bromo-2′-deoxyadenosine (13) (900 mg), after 24 h at 45 °C, gave 3′,5′-*di*-O-*acetyl*-8-(*trifluoromethyl*)-2′-*deoxyadenosine* (14) (565 mg, 64% yield); m.p. 126 °C (crystalline, EtOH), $\nu_{max.}$ (KBr) 1 145 (CF) cm^{-1}; $\lambda_{max.}$ (MeOH) 264 nm (log ε 4.06) [262 (4.19) with acid, 264 (4.09) with alkali]; $\delta_H(CDCl_3)$ 8.32 (1 H, s, 2-H), 6.40 (1 H, t, 1′-H), 6.30br (2 H, s, NH_2), 5.58 (1 H, m, 3′-H), 4.36 (3 H, m, 4′- and 5′-H), 3.72 (1 H, m, 2′-H), 2.44 (1 H, m, 2′-H), 2.12, and 2.02 (6 H, s, OAc × 2); $\delta_F(CDCl_3)$ −1.4 (s, CF_3); *m/e* 403 (M^+), 204 (base unit + 2 H), and 203 (base unit + H) (Found: C, 44.6; H, 4.3; F, 14.1; N, 17.6. $C_{15}H_{16}F_3N_5O_5$ requires C, 44.65; H, 4.0; F, 14.1; N, 17.4%). Compound (14) (450 mg) was deacetylated with methanolic ammonia at 5 °C overnight. After removal of the solvent, column chromatography of the residue on silica gel with dichloromethane–methanol (10 : 1) as eluant and recrystallization from ethanol–cyclohexane gave crystals of the *deoxyadenosine* (15) (300 mg, 84% yield); m.p. 153—155 °C; $\nu_{max.}$ (KBr) 1 145 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 266 nm (log ε 4.11) [263 (4.20) with acid, 266 (4.11) with alkali]; δ_H-[$(CD_3)_2SO$] 8.24 (1 H, s, 2-H), 7.68br (2 H, s, NH_2), 6.30 (1 H, t, 1′-H), 5.38br (1 H, s, OH), 4.50 (1 H, m, 3′-H), 3.96 (1 H, m, 4′-H), 3.66 (2 H, m, 5′-H), 3.50 (1 H, m, OH), 3.16 (1 H, m, 2′-H), and 2.24 (1 H, m, 2′-H); δ_F [$(CD_3)_2SO$] −3.2 (s, CF_3); *m/e* 203 (base unit + H) and 117 (sugar) (Found: C, 41.2; H, 3.7; F, 18.1; N, 22.0. $C_{11}H_{12}F_3N_5O_3$ requires C, 41.4; H, 3.8; F, 17.9; N, 21.9%).

2′,3′,5′-*Tri*-O-*acetyl*-8-(*trifluoromethyl*)*inosine* (17).—Trifluoromethyl iodide (9.6 g), copper (5 g), HMPA (20 ml), 2′,3′,5′-tri-*O*-acetyl-8-bromoinosine (16) (1.0 g), after 24 h at 45 °C, gave the *inosine* (17) (amorphous) (410 mg, 42% yield); $\nu_{max.}$ (KBr) 1 140 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 253 nm (log ε 3.99) [252 (4.00) with acid, 276 (3.99) with alkali]; $\delta_H(CDCl_3)$ 12.99br (1 H, s, NH), 8.59 (1 H, s, 2-H), 6.35 (1 H, dd, 2′-H), 6.15 (1 H, d, 1′-H), 5.81 (1 H, m, 3′-H), 4.50 (3 H, m, 4′- and 5′-H), 2.19, and 2.11 (9 H, s, OAc × 3); δ_F(CD-Cl_3) −1.6 (s, CF_3); *m/e* 426 (M^+), 259 (sugar), 205 (base unit + 2 H), 204 (base unit + H), and 69 (CF_3).

9-(β-D-*Ribofuranosyl*)-6-(*trifluoromethyl*)*purine* (20).—Trifluoromethyl iodide (8.4 g), copper (4.5 g), HMPA (20 ml), and 2′,3′,5′-tri-*O*-acetyl-6-chloro-9-(β-D-ribofuranosyl)-purine (18) (810 mg), after 60 h at 60 °C, and silica gel column chromatography (benzene–acetone 6 : 1), gave 2′,3′,5′-*tri*-O-*acetyl*-6-(*trifluoromethyl*)-9-(β-D-*ribofuranosyl*)-*purine* (19) (253 mg, 29% yield); $\nu_{max.}$ (CCl_4) 1 160 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 271.5 nm (unchanged with acid or alkali); $\delta_H(CDCl_3)$ 9.08 (1 H, s, 2-H), 8.46 (1 H, s, 8-H), 6.30 (1 H, d, 1′-H), 5.96 (1 H, dd, 2′-H), 5.64 (1 H, dd, 3′-H), 4.46 (3 H, m, 4′- and 5′-H), 2.16, 2.10, and 2.08 (8 H, s, OAc × 3); $\delta_F(CDCl_3)$ +4 (s, CF_3); *m/e* 386 ($M^+ - CH_3CO_2H$, 259 (sugar), 189 base unit + 2H), and 170 (base unit + 2H − F) (Found: $M^+ - CH_3COOH$, 386.081 0. $C_{15}H_{13}F_3N_4O_5$ requires $M^+ - CH_3COOH$ 386.083 7). Deacetylation of (19) (780 mg) with methanolic ammonia at 5 °C overnight gave crystals of the *purine* (20) (from Pr^iOH–Pr^i_2O) (286 mg, 50% yield); m.p. 176 °C; $\nu_{max.}$ (KBr) 1 120 and 1 140 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 271 nm (log ε 4.08) [271 (4.08) with acid, 258 (4.08) with alkali]; δ_H[$(CD_3)_2SO$] 9.13 (1 H, s, 2-H), 9.08 (1 H, s, 8-H), 6.12 (1 H, d, 1′-H), 5.58 (1 H, d, OH), 5.26 (1 H, d, OH), 5.08 (1 H, t, OH), 4.62 (1 H, m, 2′-H), 4.24 (1 H, m, 3′-H), 4.02 (1 H, m, 4′-H), and 3.68 (2 H, m, 5′-H); δ_F [$(CD_3)_2SO$] + 0.9 (s, CF_3); *m/e* 290 (M^+ − 30), 231 (M^+ − 89), 217 (base unit + 30), 189 (base unit + 2), and 188 (base unit + 1) (Found: C, 41.6; H, 3.5; F, 17.6; N, 17.4. $C_{11}H_{11}F_3N_4O_4$ requires C, 41.2; H, 3.5; F, 17.8; N, 17.6%).

5-(*Trifluoromethyl*)*uridine* (23).—Trifluoromethyl iodide (9.6 g), copper (5 g), HMPA (25 ml), and 2′,5′-di-*O*-trityl-5-iodouridine (21) (2 g), after 12 h at 45 °C, and silica gel column chromatography (benzene–acetone, 15 : 1), gave 5-(*trifluoromethyl*)-2′,5′-*di*-O-*trityluridine* (22) (1.15 g, 62% yield); m.p. 231—232 °C (crystalline, EtOH); $\nu_{max.}$ (KBr) 1 120 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 262 nm (log ε 3.92) [262 (3.92) with acid, 260 (3.86) with alkali]; $\delta_H(CDCl_3)$ 11.9br (1 H, s, NH), 7.56 (1 H, s, 6-H), 7.16 (30 H, m, OTr × 2), 6.16 (1 H, d, 1′-H), 4.28 (1 H, dd, 2′-H), 4.08 (1 H, m, 3′-OH) 3.93 (1 H, m, 3′-H), 3.50 (1 H, m, 4′-H), and 3.00 (2 H, m, 5′-H); $\delta_F(CDCl_3)$ +0.4 (s, CF_3); *m/e* 243 (Ph_3C) and 180 (base unit + 1). A solution of (22) (400 mg) in 80% acetic acid (30 ml) was refluxed for 10 min. After removal of the solvent, the residue was washed with cold benzene and dissolved in a small amount of ethanol, and the solution filtered. To the filtrate diethyl ether–hexane was added dropwise until it became slightly turbid. The turbid solution was kept in a refrigerator, and crystals of the *uridine* (23) precipitated (106 mg, 68% yield); m.p. 184—185 °C; $\nu_{max.}$ (KBr) 1 125 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 262 nm (log ε 3.99) [262 (4.00) with acid, 260 (3.83) with alkali]; δ_H[$(CD_3)_2CO$] 8.88 (1 H, s, 6-H), 5.88 (1 H, d, 1′-H), 4.60br (1 H, s, NH), 4.32 (2 H, d, 5′-H), 4.60 (1 H, m, 4′-H), 3.88 (3 H, m, 2′- and 3′-H), and 2.84br (3 H, s, OH × 3); δ_F [$(CD_3)_2CO$] −0.14 (s, CF_3); *m/e* 294 (M^+ − F), 209 (base unit + 30), 181 (base unit + 2), and 133 (sugar) (Found: C, 38.3; H, 3.5; F, 18.1; N, 9.0. $C_{10}H_{11}F_3N_2O_6$ requires C, 38.5; H, 3.6; F, 18.3; N, 9.0%).

5-(*Trifluoromethyl*)-2′-*deoxyuridine* (26).—Trifluoromethyl iodide (9.6 g), copper (5 g), HMPA (25 ml), and 3′,5′-di-*O*-trityl-5-iodo-2′-deoxyuridine (24) (1.43 g), after 12 h at 45 °C and silica gel column chromatography (benzene–acetone, 20 : 1) gave a product which was dissolved in boiling diethyl ether and filtered. Hexane was added dropwise to the filtrate until it became slightly turbid. The turbid solution was kept in a refrigerator, and 5-(*trifluoromethyl*)-3′,5′-*di*-O-*trityl*-2′-*deoxyuridine* (25) crystallized out (1.19 g, 89% yield); m.p. 130—132 °C; $\nu_{max.}$ (KBr) 1 140 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 262 nm (log ε 4.04) [262 (4.06) with acid, 260 (3.95) with alkali]; $\delta_H(CDCl_3)$ 8.84br (1 H, s, NH), 8.13 (1 H, s, 6-H), 7.12 (30 H, m, OTr × 2), 6.22 (1 H, m, 1′-H), 4.14 (1 H, m, 3′-H), 3.60 (1 H, m, 4′-H), 3.26, 2.80 (2 H, m, 5′-H), and 2.00 (2 H, m, 2′-H); $\delta_F(CDCl_3)$ +0.4 (s, CF_3); *m/e* 243 (Ph_3C), 180 (base + 1) (Found: C, 73.8; H, 5.2; F, 7.2; N, 3.7. $C_{46}H_{39}F_3N_2O_5$ requires C, 73.8; H, 5.0; F, 7.3; N, 3.6%). Compound (25) (200 mg) was stirred with ice-cold 98% formic acid (10 ml) for 1 min. The acid was distilled off at room temperature *in vacuo*, the last traces being removed by distillation with dioxan (2 × 2-ml portions). The residue was extracted with warm water (6 ml) and the aqueous filtrate was evaporated to dryness under reduced pressure. The residue was extracted with boiling diethyl ether, and hexane was added dropwise to the extract until it became slightly turbid. The turbid solution was kept in a refrigerator, and the *deoxyuridine* (26) crystallized out (30 mg, 40% yield); m.p. 182—183 °C; $\nu_{max.}$ (KBr) 1 125 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 262 nm (log ε 3.97) [262 (3.97) with acid, 260 (3.81) with alkali]; δ_H(CD_3)$_2$CO] 8.76 (1 H, s, 6-H), 6.20 (1 H, m, 1′-H) 4.46 (2H, m, 3′-H),

4.16br (1 H, s, NH), 3.96 (1 H, m, 4'-H), 3.80 (2 H, d, 5'-H), 2.80br (2 H, s, OH + 2), and 2.34 (2 H, m, 2'-H); δ_F [$(CD_3)_2$-CO] −0.14 (s, CF_3); *m/e* 180 (base unit + 1) and 117 (sugar) (Found: C, 40.3; H, 3.7; F, 19.6; N, 9.3. $C_{10}H_{11}F_3N_2O_5$ requires C, 40.5; H, 3.7; F, 19.3; N, 9.5%).

N^4,2',3',5'-O-*Tetra-acetyl-5-iodocytidine* (27).—N^4,2',3',4'-*O*-Tetra-acetylcytidine (1.3 g) and silver trifluoroacetate (1.4 g) were stirred in dry dichloromethane (50 ml) at 0 °C. A solution of iodine (2.5 g) in dry dichloromethane (15 ml) was added dropwise to this suspension at 0 °C which was then stirred for 5 h at room temperature. Saturated aqueous sodium hydrogencarbonate (200 ml) was added, and the mixture filtered through Celite. The organic layer was washed with cold water saturated with sodium thiosulphate and then with water. After removal of the solvent, the residue was chromatographed on a silica gel column (CH_2Cl_2–EtOH, 30 : 1) to give the *cytidine* (27) as an amorphous powder (930 mg, 55% yield); $\lambda_{max.}$ (MeOH) 319 nm (log ε 3.75) [308 (3.88) with acid, 297 (3.80) with alkali]; $\delta_H(CDCl_3)$ 8.12 (1 H, s, 6-H), 7.52br (1 H, s, NH), 6.03 (1 H, d, 1'-H) 5.40 (1 H, m, 2'-H), 5.32 (1 H, m, 3'-H), 4.40 (3 H, m, 4'- and 5'-H), 2.60 (3 H, s, NAc), 2.14, 2.12, and 2.09 (9 H, s, OAc × 3); *m/e* 478 (M^+ − $OCOCH_3$), 280 (base unit + 2 H), and 237 (base unit + 2 H − $COCH_3$).

5-(*Trifluoromethyl*)*cytidine* (29). Trifluoromethyl iodide (9.6 g), copper (5 g), HMPA (25 ml), and N^4,2',3',5'-*O*-tetra-acetyl-5-iodocytidine (27) (1.5 g), after 12 h at 45 °C, and column chromatography on silica gel (CH_2Cl_2–EtOH, 40 : 1), gave 2',3',5'-*tri*-O-*acetyl*-5-(*trifluoromethyl*)*cytidine* (28) (715 mg, 59% yield); m.p. 137—138 °C (crystalline; EtOH); $\nu_{max.}$ (KBr) 1 120 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 260 nm (log ε 3.83) [227 (4.06) with acid, 275 (3.85) with alkali]; $\delta_H(CDCl_3)$ 8.48br (1 H, s, NH), 8.04 (1 H, s, 6-H), 6.02 (1 H, d, 1'-H), 5.68br (1 H, s, NH), 5.36 (2 H, m, 2'- and 3'-H), 4.36 (3 H, m, 4'- and 5'-H), 2.08 and 2.04 (9 H, s, OAc × 3); $\delta_F(CDCl_3)$ −0.96 (s, CF_3); *m/e* 259 (sugar), 208 (base unit + 30), and 180 (base unit + 2).

Deacetylation of (28) (250 mg) with methanolic ammonia at 5 °C overnight gave the crystalline *cytidine* (29) (from EtOH) (142 mg, 80% yield); m.p. 216—218 °C; $\nu_{max.}$ (KBr) 1 120 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 270 nm (log ε 3.85 [283 (4.11) with acid, 274 (3.87) with alkali]; $\delta_H[(CD_3)_2SO]$ 8.84 (1 H, s, 6-H), 7.72br, 7.16br (2 H, s, NH_2), 5.76 (1 H, m, 1'-H), 5.48 (1 H, d, OH), 5.28 (1 H, t, OH), 5.00 (1 H, d, OH), 3.96 (3 H, m, 4'- and 5'-H), 3.70 (1 H, m, 2'-H), and 3.52 (1 H, m, 3'-H); $\delta_F[(CD_3)_2SO]$ −4 (s, CF_3); *m/e* 208 (base unit + 30), 180 (base unit + 2), and 179 (base unit + 1) (Found: C, 38.7; H, 3.9; F, 18.5; N, 13.8. $C_{10}H_{12}F_3N_3O_5$ requires C, 38.6; H, 3.9; F, 18.3; N, 13.5%).

N^4,3',5'-O-*Triacetyl-5-iodo-2'-deoxycytidine* (30).—N^4,3',5'-*O*-Triacetyl-2'-deoxycytidine (3.2 g) was iodinated with silver trifluoroacetate (4.4 g) and iodine (7.6 g) as for (27). Purification of the crude product through a silica gel column (CH_2Cl_2–EtOH, 30 : 1) gave the *deoxycytidine* (30) as an amorphous powder (2.7 g, 62% yield); $\lambda_{max.}$ (MeOH) 319 nm (log ε 3.74) [307 (3.88) with acid, 295 (3.78) with alkali]; $\delta_H(CDCl_3)$ 8.12 (1 H, s, 6-H), 7.76br (1 H, s, NH), 6.18 (1 H, t, 1'-H), 5.18 (1 H, m, 3'-H), 4.36 (3 H, s, 4'- and 5'-H), 2.74 (1 H, m, 2'-H), 2.60 (3 H, s, NAc) 2.12 (1 H, m, 2'-H), 2.12 (6 H, s, OAc × 2); *m/e* 479 (M^+), 280 (base unit + 2 H), 201 (sugar), and 153 (base unit + 1 − 1).

5-(*Trifluoromethyl*)-2'-*deoxycyitidine* (32).—Trifluoromethyl iodide (9.6 g), copper (5 g), HMPA (25 ml), and N^4,3'-5'-*O*-triacetyl-5-iodo-2'-deoxycytidine (30) (1.0 g), after 12 h at 45 °C, and column chromatography on silica gel (CH_2Cl_2–EtOH, 30 : 1), gave 3',5'-*di*-O-*acetyl*-5-(*trifluoromethyl*)-2'-*deoxycytidine* (31) (490 mg, 62% yield); m.p. 75—76 °C (crystalline, EtOH); $\nu_{max.}$ (KBr) 1 130 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 267 nm (log ε 3.85) [280 (4.09) with acid, 275 (3.87) with alkali]; $\delta_H(CDCl_3)$ 8.54br (1 H, s, NH), 8.08 (1 H, s, 6-H), 6.18 (1 H, t, 1'-H), 5.72br (1 H, s, NH), 5.19 (1 H, m, 3'-H), 4.36 (3 H, s, 4'- and 5'-H), 2.74 (1 H, m, 2'-H), 2.24 (1 H, m, 2'-H), 2.12 and 2.08 (9 H, s, OAc × 2); $\delta_F(CDCl_3)$ −0.68 (s, CF_3); *m/e* 379 (M^+), 201 (sugar), 180 (base unit + 2), and 179 (base unit + 1) (Found: C, 44.1; H, 4.2; F, 15.0; N, 11.3. $C_{14}H_{16}F_3N_3O_6$ requires C, 44.3; H, 4.3; F, 14.9; N, 11.1%). Deacetylation of (31) (316 mg) with methanolic ammonia at 5 °C overnight gave crystals of the *deoxycytidine* (32) (from EtOH) (153 mg, 69% yield); decomp. 205—208 °C; $\nu_{max.}$ (KBr) 1 110 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 270 nm (log ε 3.85) [283 (4.11) with acid, 274 (3.87) with alkali]; $\delta_H(CD_3)_2SO$ 8.60 (1 H, s, 6-H), 7.64br (1 H, s, NH), 7.04br (1 H, s, NH), 6.04 (1 H, t, 1'-H), 5.19 (1 H, d, OH), 5.06 (1 H, d, OH), 4.20 (1 H, m, 3'-H), 3.82 (1 H, m, 4'-H) 3.62 (2 H, m, 5'-H), and 2.16 (2 H, m, 2'-H); $\delta_F[(CD_3)_2SO]$ −0.72 (s, CF_3); *m/e* 295 (M^+), 206 (M^+ − 89), 180 (base unit + 2), and 179 (base unit + 1), (Found: C, 40.7; H, 4.2; F, 19.2; N, 14.1. $C_{10}H_{12}F_3N_3O_4$ requires C, 40.7; H, 4.2; F, 19.3; N, 14.2%).

N^4,2',3',5'-O-*Tetra-acetyl-5-iodoarabinosylcytosine* (33).—N^4,2',3',5'-*O*-Tetra-acetylarabinosylcytosine (2.9 g) was iodinated with silver trifluoroacetate (3.1 g) and iodine (5.4 g) as for (27). Purification of the crude product through a silica gel column (CH_2Cl_2–EtOH 30 : 1) gave the *cytosine* (33) as an amorphous powder (1.3 g, 34% yield); $\lambda_{max.}$ (MeOH) 318 nm (log ε 3.68) [302 (3.82) with acid, 295 (3.81) with alkali]; $\delta_H(CDCl_3)$ 8.06 (1 H, s, 6-H), 7.80br (1 H, s, NH), 6.28 (1 H, d, 1'-H), 5.48 (1 H, m, 2'-H), 5.04 (1 H, m, 3'-H), 4.40 (2 H, m, 5'-H), 4.24 (1 H, m, 4'-H), 2.60 (3 H, s, NAc), 2.18 (6 H, s, OAc × 2), and 2.02 (3 H, s, OAc); *m/e* 537 (M^+), 280 (base unit + 2 H), and 259 (sugar).

5-(*Trifluoromethyl*)*arabinosylcytosine* (36).—Trifluoromethyl iodide (9.6 g), copper (5 g), HMPA (25 ml), and N^4,2',3',5'-*O*-tetra-acetyl-5-iodoarabinosylcytosine (33) (1.03 g), were heated at 45 °C for 12 h as in the general procedure. After removal of solvent from the extract, column chromatography (silica gel; CH_2Cl_2–EtOH 40 : 1) and preparative t.l.c. (silica gel; CH_2Cl_2–EtOH, 25 : 1) of the residue gave N^4,2',3',5'-O-*tetra-acetyl*-5-(*trifluoromethyl*)-*arabinosylcytosine* (98 mg, 11% yield) as an amorphous powder and crystals of 2',3',5'-*tri*-O-*acetyl*-5-(*trifluoromethyl*)-*arabinosylcytosine* (34) (from EtOH) (326 mg, 39% yield); m.p. 190—191 °C; $\nu_{max.}$ (KBr) 1 120 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 263 nm (log ε 3.90) [278 (4.10) with acid, 277 (3.93) with alkali]; $\delta_H(CDCl_3)$ 8.72br (1 H, s, NH), 8.02 (1 H, s, 6-H), 6.33 (1 H, d, 1'-H), 5.72br (1 H, s, NH), 5.44 (1 H, dd, 2'-H), 5.08 (1 H, m, 3'-H), 4.42 (2 H, d, 5'-H), 4.24 (1 H, m, 4'-H), and 2.12, 2.00 (9 H, s, OAc × 3); $\delta_F(CDCl_3)$ −1.00 (s, CF_3); *m/e* 259 (sugar), 308 (base unit + 30), 180 (base unit + 2 H), and 179 (base unit + H) (Found: C, 44.0; H, 4.1; F, 13.1; N, 9.5. $C_{16}H_{18}F_3N_3O_8$ requires C, 43.9; H, 4.15; F, 13.0; N, 9.6%). The presence of compound (34) was detected by ^{19}F n.m.r. spectroscopy, but it was deacetylated to (34) during attempted purification. Deacetylation of (34) (130 mg) with methanolic ammonia at 5 °C overnight gave crystals of the *cytosine* (35) (from EtOH) (70 mg, 75.7% yield); decomp. 239—240 °C; $\nu_{max.}$ (KBr) 1 120 cm^{-1} (CF); $\lambda_{max.}$ (MeOH) 271 nm (3.86) [283 (4.11) with acid, 278 (3.91) with alkali]; $\delta_H[(CD_3)_2SO]$ 8.16 (1 H, s, 6-H), 7.72br (1 H, s, NH), 7.08br (1 H, s, NH), 6.04 (1 H, d, 1'-H), 5.54 (1 H, d,

OH), 5.44 (1 H, d, OH), 5.10 (1 H, d, OH), 3.92 (2 H, m, 2′-H, 3′-H), 3.76 (1H, m, 4′-H), and 3.58 (2H, m, 5′-H); δ_F[$(CD_3)_2SO$] −0.6 (s, CF_3); *m/e* 208 (base unit + 30), 180 (base unit + 2 H), and 179 (base unit + H) (Found: C, 38.3; H, 4.0; F, 18.2; N, 13.3. $C_{10}H_{12}F_3N_3O_5$ requires C, 38.6; H, 3.9; F, 18.3; N, 13.5%).

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