Chemical Synthesis of 2′-Deoxy-5-(trifluoromethyl)uridine and the α Anomer[1]

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5-(Trifluoromethyl)uracil, as the bis(trimethylsilyl) derivative, was condensed with the 3,5-bis(*p*-nitrobenzoate) of 2-deoxyribofuranosyl chloride. Reaction occurred in benzene solution at room temperature in the presence of mercuric acetate. The resultant α,β-nucleoside, upon fractional crystallization, afforded the β anomer; the α anomer could be isolated only by chromatography. Mild deacylation of the anomers with methanolic diisopropylamine gave 2′-deoxy-5-(trifluoromethyl)uridine and its α anomer. When 2-deoxy-3,5-di-*p*-toluoylribofuranosyl chloride was used in the condensation, the resultant β-nucleoside could then, too, be crystallized from the anomeric mixture, but could not successfully be deacylated without basic decomposition of the trifluoromethyl group.

Reported biological properties[2,3] of 2′-deoxy-5-(trifluoromethyl)uridine[4] (**β-14**) have created intense interest in large-scale testing of this new nucleoside to define further antitumor activity. So far the compound has been prepared[2] only by an enzymatic transfer process, but such a method is obviously awkward and inconvenient for large quantities. Any projected chemical synthesis of this molecule must be planned around certain inherent problems, among them the known base sensitivity[2,5] of the CF_3 group, the acid sensitivity of the N-glycosidic bond in a deoxyribonucleoside, and the expected formation of an α anomer along with the desired β anomer if a 2-deoxyribose derivative is condensed with a heterocyclic base. We have investigated both the Hilbert–Johnson synthesis[6,7] of nucleosides and a recent procedure,[8] communicated in preliminary form, for the condensation under mild conditions of bis(trimethylsilyl)uracil derivatives with acylated chloro sugars. A successful synthesis of **β-14** was achieved by the latter method.

Thymidine syntheses were first conducted as model experiments. (See Scheme I.) The Hilbert–Johnson reaction of 5-methyl-2,4-dimethoxypyrimidine (**3**) with 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-ribofuranosyl chloride (**7**), in agreement with the finding of Šorm and co-workers,[7] formed predominantly the α-nucleoside **α-9**. (Anomeric configuration and composition of nucleosides were inferred from analysis of the nmr spectra, see below.) The α:β ratios of the crude product **9** were 7:1 and 3:1 when acetonitrile and benzene, respectively, were used as reaction solvents; in each case, **α-9**[7] was preferentially crystallized from the mixture. In contrast, when the chloro sugar **7** was treated with bis(trimethylsilyl)thymine[8] (**5**) in benzene solution at 25° with mercuric acetate as acid acceptor, an α:β ratio of 1:2 was observed in the crude nucleoside, and di-*p*-toluoylthymidine[9] (**β-11**) could be crystallized, as reported by Wittenburg[8] (the labile trimethylsilyl groups are lost during isolation).

Similarly, Hilbert–Johnson reaction of the chloro sugar **7** with 2,4-dimethoxy-5-trifluoromethylpyrimidine[5,10] (**4**) in acetonitrile afforded crude nucleoside **10** with an α:β ratio of 5:1; unreacted **4** and some 5-(trifluoromethyl)uracil (**2**) were also present in the crude **10**. A reversal of the ratios resulted with the use of bis(trimethylsilyl)-5-(trifluoromethyl)uracil (**6**). This silyl ether (attachment is assumed to be at O rather than N) was prepared from the reaction of 5-trifluoromethyluracil with hexamethyldisilazane and a catalytic amount of trimethylchlorosilane, essentially as described[8] for the thymine derivative **5**. Reaction of **6** with the chloro sugar **7** in benzene at room temperature in the presence of mercuric acetate afforded crude nucleoside **12** with an α:β ratio of 1:2, from which the desired β anomer **β-12** could be crystallized. However, the synthesis of trifluorothymidine **β-14** could not be completed by the deacylation of **β-12**. Not only was the CF_3 group highly sensitive to base, but the toluoyl esters seemed unusually resistant to saponification. For instance, thymidine could be obtained in 70% yield from **β-11** upon boiling with methanolic diisopropylamine[15] for 2 hr. When, however, the tri-

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(2) C. Heidelberger, D. G. Parsons, and D. C. Remy, *J. Med. Chem.*, **7**, 1 (1964).

(3) H. Gottschling and C. Heidelberger, *J. Mol. Biol.*, **7**, 541 (1963).

(4) Professor Heidelberger has suggested "trifluorothymidine" as a convenient trivial name.

(5) T. Y. Shen, H. M. Lewis, and W. V. Ruyle, *J. Org. Chem.*, **30**, 835 (1965).

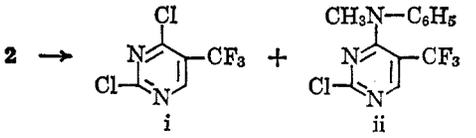
(6) M. Prystaš and F. Šorm, *Collection Czech. Chem. Commun.*, **29**, 131 (1964), and leading references.

(7) M. Prystaš, J. Farkaš, and F. Šorm, *ibid.*, **28**, 3140 (1963).

(8) E. Wittenburg, *Z. Chem.*, **4**, 303 (1964); *Chem. Abstr.*, **61**, 14763*h* (1964).

(9) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *J. Am. Chem. Soc.*, **81**, 4112 (1959).

(10) A side reaction in the treatment of 5-(trifluoromethyl)uracil (**2**) with phosphorus oxychloride and dimethylaniline was the formation of 2-chloro-4-(N-methylanilino)-5-(trifluoromethyl)pyrimidine (ii), along with



the desired 2,4-dichloro compound i,[5] which is used to form **4** (amination at C-4 was assumed by analogy with known examples,[11] where this position is favored). The distillation residue from i was sublimed at 110° (2 mm) to form 12% (based on **2**) of ii: mp 82–84°; nmr data in chloroform-*d*, τ 1.58 s (C-6 H), 2.69 d (C_6H_5), and 6.47 s (N–CH_3); infrared bands between 8.5 and 9.0 μ (Nujol mull) could be assigned to the CF_3 group. (*Anal.* Calcd for $C_{12}H_9ClF_3N_3$: C, 50.1; H, 3.15; Cl, 12.3; N, 14.6. Found: C, 49.5; H, 3.03; Cl, 12.4; N, 14.3.) Products like ii have been observed in the reaction of 5-nitro-6-styryluracil[12] and 5-nitro-6-methyluracil[13] with the same reagents. The dimethylaniline, which was free of the monomethylamine, was probably quaternized by reaction with the 4-chloro group in i; a nitro group at C-5 activates the 4-chlorine, and the 5-CF_3 group would be expected to have the same effect. Loss of an N-methyl from the quaternary salt must have occurred, as was suggested[14] in a similar reaction of purine derivatives.

(11) E. C. Taylor and M. J. Thompson, *J. Org. Chem.*, **26**, 5224 (1961); H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *ibid.*, **27**, 181 (1962).

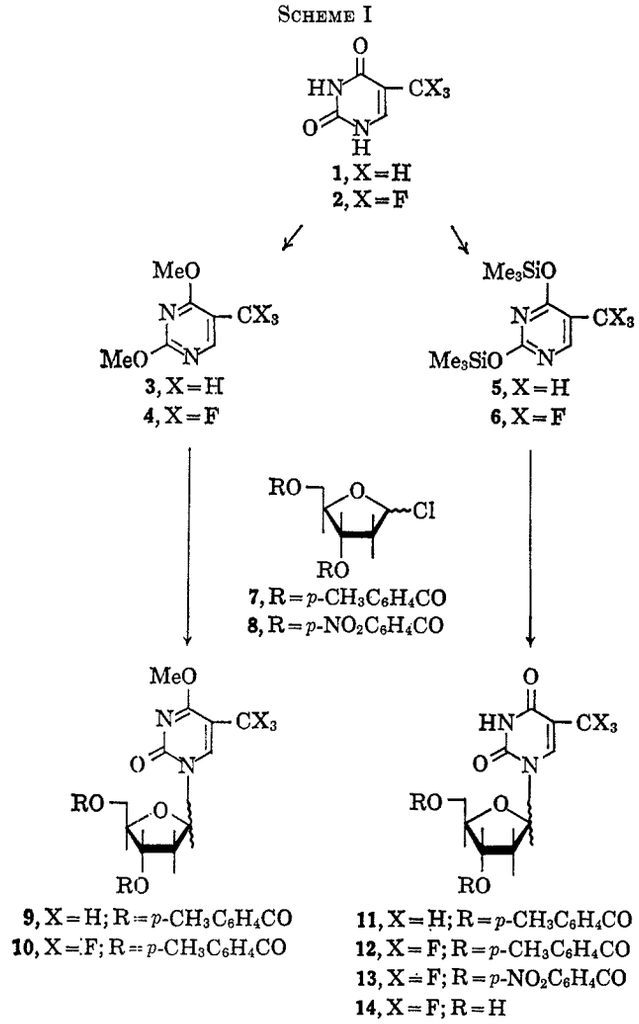
(12) W. C. J. Ross, *J. Chem. Soc.*, 1128 (1948).

(13) J. R. Marshall and J. Walker, *ibid.*, 1004 (1951).

(14) R. K. Robins and B. E. Christensen, *J. Am. Chem. Soc.*, **74**, 3624 (1952).

(15) L. Goldman, J. W. Marsico, and M. J. Weiss, *J. Med. Chem.*, **6**, 410 (1963); L. Goldman and J. W. Marsico, *ibid.*, **6**, 413 (1963).

SCHEME I



fluorothymidine di-*p*-toluate β-**12** was thus boiled for 18 hr, most of the nucleoside remained as the diester, and there was only 20% of a water-soluble nucleoside fraction free of blocking groups. Paper chromatography of the deacylated material revealed the presence of two components, one with the flow rate and ultraviolet maximum (260 mμ) of authentic β-**14**, the other with an ultraviolet maximum at 278 mμ which we tentatively attributed to the 5-carbomethoxyuracil analog of β-**14**. Boiling β-**12** with methanolic sodium methoxide gave similar results, whereas methanolic ammonia in a steel bomb at 100° apparently formed entirely the 5-carbomethoxynucleoside. That the toluate esters in **12** were even less reactive than those in the thymidine diester **11** may be attributed to the increased acidity[2,3] of the uracil N-3–H in the trifluoromethyl series relative to the thymine series of compounds. With **12**, dissociation to the anionic species is probably complete in the presence of methoxide, for instance, and approach of base to the ester carbonyls in the same molecule is consequently less favored than in **11**.

A more easily saponified aroyl ester for protection of the sugar hydroxyls was therefore sought. *p*-Nitrobenzoate seemed a logical choice, and use of 2-deoxy-3,5-bis-*O*-(*p*-nitrobenzoyl)-D-ribofuranosyl chloride[16] (**8**) in the condensation reaction with **6** led finally to a successful synthesis of β-**14**. As before, benzene at room temperature was the solvent, with mercuric acetate as acid acceptor. As the reaction proceeded, the benzene solution became supersaturated in nucleoside **13**, both anomers of which slowly precipitated on standing. The optimum reaction period was 15–18 hr. If the time was reduced to 3–5 hr, only low yields of **13** were obtained.[17] The decreased solubility of the α- and β-nucleosides as the bis-*p*-nitrobenzoates α-**13** and β-**13** significantly affected isolation of the product. The α:β ratio in crude **13** was 1:2, and fortunately the β anomer could be separated by a slow crystallization of this derivative of the desired trifluorothymidine β-**14**. The mother liquor contained the anomers α-**13** and β-**13** in a nearly even ratio, and further separation by crystallization techniques was not possible. The α anomer α-**13** was isolated as an amorphous powder by preparative thin layer chromatography.

Methanolysis of the *p*-nitrobenzoate esters from either anomer was successfully accomplished by boiling α-**13** or β-**13** briefly with methanolic diisopropylamine[15] until completely dissolved. The free nucleoside was then obtained with the CF_3 group intact, but was at least partly a salt of diisopropylamine because of the increased acidity of the heterocyclic N-3–H in β-**14** (or α-**14**) relative to thymidine. Conversion to the uracil free base was completed by regeneration with an ion-exchange resin (H) in aqueous solution. Trifluorothymidine[4] β-**14** was thus obtained from the bis-*p*-nitrobenzoate β-**13** in quantitative yield, and the extinction of the ultraviolet maximum indicated essentially complete purity. Absence of any shift in the maximum toward longer wavelengths showed no methanolysis of the CF_3 group to COOMe had occurred during the mild methanolysis of the ester groups in β-**13**. Slow conversion in aqueous base of the CF_3 group in trifluorothymidine β-**14** to the sodium carboxylate was studied by observing the slow shift of the ultraviolet maxima from 260 to 272 mμ. The shift was linear with time. Similar observations were made by Shen and co-workers[5] with the β-D-arabinoside of trifluoromethyluracil. Trifluoromethyluracil itself (**2**) seems considerably less stable[2] to base than its nucleosides.

The crystalline α anomer α-**14** of trifluorothymidine was obtained from the amorphous diester α-**13**. Comparison of optical rotations with both the blocked and unblocked pairs of anomers showed that α,β-**13** and α,β-**14** provided two additional examples of the exceptional properties[18] of pyrimidine deoxyribosides with respect to Hudson's rules. Thin layer chromatographic resolution of α-**14** and β-**14** permitted either anomer to be declared free of the other; good confirmation of this fact was obtained from nmr studies (see below).

The identity of the di-*p*-toluate β-**12** as a derivative of trifluorothymidine β-**14** was proven by comparison with an authentic sample. This was obtained by acylation of β-**14** with *p*-toluoylchloride in pyridine. Direct isolation of β-**12** was possible only when exactly

(16) R. K. Ness, D. L. MacDonald, and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 2895 (1961).

(17) When the condensation did not go to completion, a by-product was then 1-*O*-acetyl-3,5-bis-*O*-(*p*-nitrobenzoyl)-2-deoxy-β-D-ribofuranose, *cf.* Experimental Section.

(18) T. R. Emerson and T. L. V. Ulbricht, *Chem. Ind.* (London), 2129 (1964).

2 molar equiv of *p*-toluoyl chloride was used. When excess toluoyl chloride was used, the product was largely a tri-*p*-toluoyl derivative, as evidenced by spectral and chromatographic data. Integration of the nmr spectrum showed there were about 2.8 toluoyl groups relative to the sugar moiety. In the infrared, there was an additional "active" carbonyl band at about 5.65 μ, which was not present in **β-12**, and which suggested acylation of the heterocycle. On a thin layer chromatogram, the major spot was one which traveled faster than the small amount of **β-12** present. Stability to dilute methanolic hydrochloric acid suggested the third toluoyl group was attached to the uracil ring at N-3. Similar acylation of the uracil ring was observed by Fox and co-workers[19] with uridine, thymidine, and uracil xyloside.

Nmr Studies.[20]—The nmr spectra of the nucleosides described above were used as a convenient means of determining the anomeric configuration of pure isomers and, upon integration, the anomeric composition of mixtures. Most useful was the general fact that the signal from the 5-substituent of the uracil ring was shifted farther downfield in an α-nucleoside than in the corresponding β anomer, as shown in Table I. This could be established, since the configuration of at least one member of each anomeric pair, except **α,β-10**, was known by other means; the generality was assumed to hold for **10**.

TABLE I

CHEMICAL SHIFT OF 5-CX_3[a]

Compd	X	α	β
9	H	8.11[b]	8.34[b]
11	H	8.16[b]	8.39[b]
10	F	62.4[c]	63.2[c]
12	F	62.8[c]	63.2[c]
13	F	63.5[c]	64.0[c]
14	F	64.0[c]	64.6[c]

[a] See ref 20. [b] Proton shifts in τ units. [c] ^{19}F shifts in parts per million.

With the unblocked pair, **α-14** and **β-14**, mixtures of these anomers could also be analyzed by measuring the signals from the C-6 proton on the uracil ring, where the chemical shifts were τ 1.55 (α) and 1.23 (β); these signals were obscured in the *p*-nitrobenzoyl esters. The patterns described by Lemieux[21] for the anomeric proton at C-1′ in thymidine and its anomer, and in the corresponding di-*p*-toluates (**α-** and **β-11**), were a triplet for the β anomers and a quartet for the α anomers. Similar patterns were observed with the nucleosides we obtained in this work, and in purine deoxyribosides we have previously reported;[22] these are useful criteria in assigning anomeric configuration of pure anomers. In **β-14**, **β-9**, and **β-11**, the patterns for the anomeric protons were actually quartets and appeared to constitute exceptions to what we thought might be a general rule, but the quartets were unevenly spaced with the center members close together, and in **β-14** the appearance was indeed that of a rough triplet. Any unevenness in spacing of the quartet for α anomers, on the other hand, tended toward separation rather than overlapping of the two center peaks. Whenever both members of an anomeric pair were available for comparison, the configuration could so far be assigned by the resemblance of the C-1 proton signal to a quartet (α anomers) or to a triplet (β anomers). Usually one anomer was sufficient for the assignment.

Experimental Section[23]

Bis(trimethylsilyl)-5-(trifluoromethyl)uracil (6).—A mixture of 15.5 g (86.0 mmoles) of **2**,[2,24,25] 50 ml of hexamethyldisilazane, and 1 ml of chlorotrimethylsilane, protected from moisture, was refluxed (bath temperature 150–170°) for 1 hr, while ammonium chloride (which precipitated almost immediately) sublimed and was allowed to collect in the condenser. The resultant clear solution was cooled and concentrated at 1 mm (bath temperature not above 50–60°). The residual oily **6** could be distilled, but was more conveniently used without distillation because of high sensitivity to atmospheric moisture. Weights were 120–170% of theory, owing to the presence of unremoved starting materials and by-products. Any cloudiness in the oil was suggestive of some hydrolysis to 5-(trifluoromethyl)uracil.

3′,5′-Bis-*O*-(*p*-nitrobenzoyl)-2′-deoxy-5-(trifluoromethyl)uridine (β-13).—A solution of 12.5 g (27.8 mmoles) of chloro sugar[16] **8** in 750 ml of benzene (dried over calcium hydride) was treated with a solution of 15.0 g of residual oily **6** (166% of theory from 5.00 g, 27.8 mmoles, of **2**) in 25 ml of dried benzene. To the clear solution (any cloudiness suggests hydrolysis of **6**) was added 9.0 g of mercuric acetate (Mallinkrodt analytical reagent, 98.0–100.1%). The suspension was stirred for 18 hr at 25°, and then was poured through a filter slowly so that the mixture did not accumulate in the funnel. The filter cake was washed with 200 ml of benzene; the small amount of **α,β-13** remaining with these inorganics could not be recovered (if the reaction mixture stood for several days, or was filtered rapidly, considerable amounts of **α,β-13** precipitated and were lost on the filter). The filtrate was supersaturated in **α,β-13** and partial precipitation occurred. The mixture was concentrated and the residual glass was powdered and triturated with 300 ml of aqueous 30% potassium iodide, then with two 300-ml portions of water. The glass was dissolved in 250 ml of acetone, clarified by filtration through Celite, and concentrated to form 21 g (127% yield, soluble mercuric salts were still present) of **α,β-13** as a foamed glass. Both anomers were observed on tlc;[26] the α:β ratio was 1:2 by ^{19}F nmr spectroscopy.

This crude product was dissolved in 80 ml of 2-heptanone, and methanol (*ca.* 180 ml) was added just to incipient cloudiness. Crystals began to form within 1–2 hr. After 6 days at 25° the mixture had deposited 6.18 g of **β-13**, mp 140–144°, containing a faint trace of **α-13** by tlc.[26] This was dissolved in 20 ml of warm 2-heptanone by adding 20 ml of acetone, the acetone was re-

(19) (a) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.*, **81**, 178 (1959); (b) J. F. Codington, R. Fecher, and J. J. Fox, *ibid.*, **82**, 2794 (1960).

(20) Varian A-60 and HR-60 nmr spectrometers were used. Proton chemical shifts (τ) at 60 Mc/s were measured from 4% tetramethylsilane as internal reference in acetone-d_6 solutions, except as noted with **β-12**; ^{19}F shifts at 56.4 Mc/s were measured (parts per million) in acetone-d_6 solutions with $CFCl_3$ as external reference. Proton shifts were measured to multiplet centers, with an accuracy of ±0.05 ppm. Shifts of ^{19}F signals were accurate only to ±1.0 ppm, but separation of the ^{19}F signals could be observed with an accuracy of ±0.1 ppm. Signals are recorded as singlets (s), doublets (d), triplets (t), quartets (q), quintets (p), and multiplets (m). The N–H signals in **α-14** and **β-14** were lost on exchange with D_2O.

(21) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961); R. U. Lemieux, *ibid.*, **39**, 116 (1961).

(22) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **27**, 3949 (1962); *J. Med. Chem.*, **6**, 684 (1963).

(23) Melting points were observed on a Fisher-Johns hot stage and are corrected. Optical rotations were measured on 1% solutions in 1-dm tubes with a Rudolph photoelectric polarimeter. Ultraviolet spectra were determined with a Cary Model 11 recording spectrophotometer. Concentration of solutions was carried out *in vacuo*.

(24) M. P. Mertes and S. E. Saheb, *J. Pharm. Sci.*, **52**, 508 (1963).

(25) The authors are grateful to Dr. Harry B. Wood, Jr., of the Cancer Chemotherapy National Service Center for supplying the 5-(trifluoromethyl)uracil used, and for a reference sample of enzymatically prepared trifluorothymidine **β-14**.

(26) Thin layer chromatography (tlc) was carried out with silica gel HF on glass plates (5 × 20 cm) in ethyl acetate–methanol–water–*n*-heptane (10:6:5:3), upper phase. Spots were detected under ultraviolet light. The α anomers moved a little slower than, and separate from, the β anomers. Absolute R_f values varied considerably from plate to plate, but relative values were reproducible.

moved *in vacuo*, the heptanone solution was filtered through Celite, and the Celite was washed with 5 ml of heptanone. The filtrate was diluted with 60 ml of methanol. After 18 hr at 0–5°, 5.44 g (33%) was obtained: mp 142–144°; $[\alpha]^{22}D$ +5.6 ± 1.0° (dimethylformamide); R_f[26] 0.64; nmr data, τ 1.80 s (p-C_6H_4–), 3.72 t (C-1′ H), 4.25 q (C-3′ H), 5.1–5.3 broad (C 4′ H), 5.20 s (C-5′ H), and 7.10 q (C-2′ H); 64.0 s (–CF_3) ppm.

Anal. Calcd for $C_{24}H_{17}F_3N_4O_{11}$: C, 48.5; H, 2.88; F, 9.59; N, 9.44. Found: C, 48.2; H, 3.32; F, 9.64; N, 9.23.

The mother liquor from the initial crystallization of β-**13** was concentrated to form a residual glass (14.5 g). Further separation could not be accomplished by crystallization techniques. Excessive weight indicated some soluble mercuric salts were also present. The amount of α,β-**13** present was determined by deacylation (by the procedure for β-**14**, below) and measurement of the ultraviolet extinction of the crude α,β-**14**; in this way the over-all yield of nucleoside from the condensation was estimated at 86%.

1-[3,5-Bis-*O*-(*p*-nitrobenzoyl)-2-deoxy-α-D-ribofuranosyl]-5-(trifluoromethyl)uracil (α-**13**).—A 2.8-g portion of the above residual glassy **13** (14.5 g, α:β ratio 1:1) was subjected to chromatography[26] on 14 glass plates (20 × 20 cm) containing 2-mm layers of silica gel. Crude α-**13** (1.3 g) was eluted with acetone. A second pass with seven plates afforded 0.75 g (23% yield) of α-**13** of 90% purity, by nmr, containing a little β-**13**. Chromatographically homogeneous α-**13**, R_f 0.75, could be obtained by a third chromatographic separation, or by taking more selective cuts of absorbent from the second pass. The amorphous powder could not be crystallized: $[\alpha]^{23}D$ −40.2 ± 1.4° (dimethylformamide); nmr data, τ 1.70 s and 1.79 s (p-C_6H_4–), 3.56 q (C-1′ H), 4.12 d (C-3′ H), 4.62 t (C-4′ H), 5.31 d (C-5′ H), and 6.5–7.4 m (C-2′ H); 63.5 s (–CF_3) ppm.

Anal. Found: C, 48.6; H, 3.20; F, 9.24; N, 9.22.

2′-Deoxy-5-(trifluoromethyl)uridine (β-**14**).—A suspension of 4.00 g (6.75 mmoles) of β-**13** in 250 ml of methanol was treated with 10 ml of diisopropylamine and refluxed until β-**13** had dissolved (*ca.* 18 min), and the solution was concentrated. The dry residue was partitioned between 50 ml of chloroform and 50 ml of water. The chloroform layer was washed with 20 ml of water, and the combined aqueous layers were concentrated. A low ultraviolet extinction (ε 7200 and 262 mμ; pH 1) and the presence of isopropyl signals in the nmr spectrum (two singlets at τ 8.73 and 8.85) indicated the dry residue contained diisopropylamine, probably as a salt with the relatively acidic[2,3] heterocyclic N–H in **14**. A solution in 75 ml of water was treated with 8 ml (volume of resin) of Dowex 50 (H), prewashed with water and methanol. The resin was removed on a filter and washed with 25 ml of methanol and 50 ml of water. The combined filtrate was evaporated *in vacuo* to form 1.99 g (100%), mp 171–175°, $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 9580), chromatographically homogeneous by tlc,[26] R_f 0.64, identical with that of a sample prepared by the enzymatic process.[2,25] Reprecipitation by concentrating an ethyl acetate solution afforded 1.18 g (58% yield) in two crops: mp 177–179° (lit.[2] 186–189°); $[\alpha]^{20}D$ +46.9 ± 1.4° (water); $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 10,200) [lit.[2] 260 mμ (ε 9960)]; $\lambda_{max}^{pH\ 7}$ 262 mμ (ε 9800); $\lambda_{max}^{pH\ 11}$ 260 mμ (ε 6930) [lit.[2] (ε 6590)]; nmr data, τ −0.60 (NH), 1.23 s (C-6 H slightly split by CF_3), 3.73 t (C-1′ H), and 7.62 t (C-2′ H); 64.6 (CF_3) ppm. The mixture melting point with the enzymatically prepared sample (mp 181–184°) was also 181–184°.

Anal. Calcd for $C_{10}H_{11}F_3N_2O_5$: C, 40.5; H, 3.74; F, 19.2; N, 9.45. Found: C, 40.4; H, 3.68; F, 19.1; N, 9.46.

1-(2-Deoxy-α-D-ribofuranosyl)-5-(trifluoromethyl)uracil (α-**14**).—The same procedure was used to deacylate 0.75 g of α-**13**. The product was crystallized from acetone–chloroform to give 0.14 g of chromatographically homogeneous[26] α-**13**: R_f 0.56; mp 175–178°; $[\alpha]^{21}D$ −17.4 ± 1.0° (water); $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 9830); $\lambda_{max}^{ph\ 7}$ 262 mμ (ε 9320); $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 6730); nmr data, τ −0.40 (NH), 1.55 (C-6 H, weakly split by CF_3), 3.78 q (C-1′ H), and 7.0–7.8 m (C-2′ H); 64.0 s (CF_3) ppm.

An additional 0.04 g (total yield 0.18 g, 48%) was recovered from the mother liquor by preparative tlc.

Anal. Found: C, 40.8; H, 3.81; F, 19.0; N, 9.34.

2′-Deoxy-3′,5′-di-*O*-*p*-toluyl-5-(trifluoromethyl)uridine (β-**12**).

A. From Direct Condensation.—A solution of 25.0 g (60.3 mmoles) of chloro sugar **7**[27] and residual oily silyl derivative **6** (obtained from 10.8 g, 60.0 mmoles, of **2**) in 600 ml of dry benzene was treated with 5.0 g of mercuric acetate, stirred at 25° for 3 days, and filtered through Celite. The filtrate was concentrated and the residue was dissolved in 700 ml of chloroform. The solution was washed with 200 ml of aqueous 30% potassium iodide solution (there was mechanical loss in breaking an emulsion), with 200 ml of water, and was concentrated to form 29.0 g (91%) of crude residual glass. A 2:1 ratio of β-**12** to α-**12** was disclosed in the ^{19}F magnetic resonance spectrum. Crystallization from chloroform–carbon tetrachloride separated 10.0 g (31%) of β-**12**, mp 172–175°, containing a few per cent α-**12** by ^{19}F resonance, $[\alpha]^{21}D$ −38.9 ± 1.5° (chloroform). Further purification by recrystallization from chloroform–carbon tetrachloride, then from methanol, was rather tedious and afforded 10% of β-**12**: mp 196–197°; $[\alpha]^{21}D$ −40.6° ± 1.1°; nmr data in chloroform-*d*, τ 0.38 (NH), 1.93 (C-6 H, weakly split by –CH_3), 2.0–2.9 two quartets (2 p-C_6H_4 groups), 3.70 q (C-1′ H), 4.41 crude d (C-3′ H), 5.2–5.5 m (C-4′ H and C-5′), 6.9–7.8 m (C-2′ H), and 7.62 s ($ArCH_3$); 63.2 ppm.

Anal. Calcd for $C_{26}H_{22}F_3N_2O_7$: C, 58.8; H, 4.18; F, 10.7; N, 5.28. Found: C, 58.8; H, 4.42; F, 10.9; N, 5.52.

B. From β-**14.**—Acylation of a sample of β-**14** in pyridine with a stoichiometric quantity of p-toluoyl chloride, as in the dibenzoylation of thymidine,[19a] afforded β-**12**, mp 195–196° after purification by recrystallization (always tedious with this compound) and preparative thin layer chromatography on silica gel in chloroform–ethyl acetate (1:1), R_f 0.9.

The mixture melting point with product from **A** was also 195–196°; the infrared spectra of the two samples were identical.

1-*O*-Acetyl-3,5-bis-*O*-(*p*-nitrobenzoyl)-2-deoxy-β-D-ribofuranose.—In one intended preparation of β-**13**, the mercuric acetate used had become contaminated with atmospheric moisture, and the condensation was prevented by hydrolysis of the silyl derivative **6**. Consequently, the chloro sugar **8** was converted largely to the 1-acetate, mp 85–87°, assigned as the β anomer from the triplet pattern for the C-1 proton in the nmr spectrum: τ 1.72 and 1.76 (two p-C_6H_4 groups), 3.54 t (C-1 H), 4.25 m (C-3 H), 5.36 ms (C-4 H, C-5 H), 7.26 q (C-2 H), and 8.03 s (–$OCOCH_3$); infrared data, 5.78 (ester C=O), 6.53 and 7.40 (NO_2), 7.87 (benzoate COC), 8.10, (acetate COC), 9.08 (benzoate), and 13.9 (benzoate) μ.

Anal. Calcd for $C_{22}H_{18}N_2O_{11}$: C, 54.3; H, 3.73; N, 5.76; mol wt, 486. Found: C, 54.1; H, 4.27; N, 5.60; mol wt, 493 (with a vapor-pressure osmometer).

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