(required for $C_{26}H_{32}O_9$: C, 63.9; H, 6.6; O, 29.5).

7: UV (MeOH) 276 nm (ϵ 7960); IR (KBr) 3470, 3340, 2940, 1764, 1748, 1729, 1708, 1685, 1641, 1452, 1372, 1307, 1265, 1252, 1171, 1150, 1118, 1018, 999, and 919 cm^{-1}; CD (c 0.54, MeOH) $[\theta]_{221}$ −9200°, $[\theta]_{275}$ −20900°, $[\theta]_{305}$ −3400°, $[\theta]_{317}$ −3700°, $[\theta]_{329}$ −2700°; ^1H NMR ($CDCl_3$) δ 1.22, 1.45, 1.48 × 2, 1.73, 1.94 (s, 3H × 6, H20 ABC, H21 ABC, H24 ABC, H26 ABC, H28 ABC, H30 ABC), 1.80 (cm, 1 H, H1A eq), 1.80 (s, ex, 1 H, H25), 2.28 (bd, J = 14 Hz, 1 H, H11 A or B), 2.38 (ddd, J = 14, 11, 8 Hz, 1 H, H1B ax), 2.54 (ddd, J = 19, 11, 8 Hz, 1 H, H2B ax), 2.73 (bdd, J = 19, 8 Hz, 1 H, H2A eq), 2.99 (bd, J = 14 Hz, 1 H, H11 A or B), 3.55 (s, 1 H, H14), 3.81 (s, 3 H, H34 ABC), 5.11, 5.49 (bs, 1 H × 2, H27 AB), 6.16 (s, ex, 1 H, H22).

Preliminary diffraction experiments indicated that the symmetry of the orthorhombic crystal lattice of the clear, white crystals of 7 (mp 260–262 °C) was $P_{2_12_12_1}$ with a = 11.866 (1), b = 13.530 (1), and c = 14.326 (2) Å with Z = 4 for a calculated density of 1.41 g/cm^3. Of the 1784 unique reflections measured with $2\theta \leq 114°$, 1698 (95%) were considered observed ($I \geq 3\sigma I$). These reflections were subsequently corrected for Lorentz and polarization effects but not absorption. Structure solution, using a multisolution tangent formula approach,[11] gave initial positions for 30 of the 35 nonhydrogen atoms. Fourier differences and least-squares refinements[12] minimizing $\Sigma w[|F_o| - |F_c|]^2$ with $w = (1/\sigma F_o)^2$ gave coordinates for the remaining atoms. The final unweighted R factor using anisotropic temperature parameters for the nonhydrogen atoms and fixed isotropic parameters for hydrogen atoms is 0.041. There are no significant peaks in the Fourier difference map, and all distances and angles are chemically reasonable. Tables II, III, and IV contain the fractional coordinates and temperature factors, bond distances, and bond angles respectively for terretonin (7).

Acknowledgment. We wish to thank Drs. B. Arison and W. C. Randall for obtaining ^1H NMR and CD measurements, respectively.

Registry No. 7, 71911-90-5.

Supplementary Material Available: Figure 2 containing the ^{13}C NMR spectrum of 7 (25 MHz, recorded in a 70/30 mixture of $CDCl_3$ and Me_2SO-d_6), Figure 3 containing the 300 MHz ^1H NMR spectrum of 7, and Tables II, III, and IV containing fractional coordinates and temperature parameters, bond distances, and bond angles of 7 from the X-ray experiments (7 pages). Ordering information is given on any current masthead page.

(11) P. Main, L. Lessinger, M. M. Woolfson, G. Germain, and J. P. Declercq, "MULTAN 74, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data", Universities, York, England, 1974.

(12) J. M. Stewart, J. G. Kruger, H. L. Ammon, D. Dickinson, and S. R. Hall, "The X-Ray System, Version of June, 1972", TR-192, Computer Science Center, University of Maryland, College Park, Md., 1972.

(13) Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the U.S. Department of Agriculture and does not imply its approval to the exclusion of other products that may also be suitable.

Nucleosides. 113. Synthesis of 6-(β-D-Ribofuranosyl)pyrimidines. A New Class of Pyrimidine *C*-Nucleosides[1,2]

Steve Y-K. Tam, Robert S. Klein,* Federico G. de las Heras, and Jack J. Fox

Laboratory of Organic Chemistry, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, Sloan-Kettering Division of Graduate School of Medical Sciences, Cornell University, New York, New York 10021

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The synthesis of several 6-(β-D-ribofuranosyl)pyrimidines, a new class of *C*-nucleosides, from ethyl 3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propynoate (1) is described. Reaction of 1 with guanidine readily afforded 2-amino-4-oxopyrimidine 3. The 2-thio-4-oxopyrimidine derivative 18 was prepared via enamine 16 obtained by the addition of pyrrolidine to 1. Hydrolysis of 16 to β-keto ester 17 and cyclization with thiourea afforded 18, which serves as the synthetic precursor of C-6 ribosyl-2-thiouracil 19, uracil 26, 4-thiouracil 29, and cytosine 31.

In a recent report[3] from our laboratory, we described the preparation of a functionalized *C*-glycosyl compound, ethyl 3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-propynoate (1) (Scheme I), and its utilization in the synthesis of pyrazole- and triazole-*C*-nucleosides via 1,3-dipolar cycloaddition reactions. In an earlier brief communication[4] we had already reported the use of 1 as the starting material for the synthesis of several 6-(β-D-ribofuranosyl)pyrimidines, a new class of pyrimidine *C*-nucleosides. In this paper, we describe details of this and subsequent work in the synthesis of other members in this series of C-6 ribosylated pyrimidines. These compounds are of potential biological interest as they are isomeric with the 5-(β-D-ribofuranosyl)pyrimidines represented by the naturally occurring ψ-uridine[5] and by ψ-isocytidine. The latter was synthesized in our laboratory[6] and shown to have good antileukemic activities.[7]

The key synthetic intermediate propynoate 1 can be obtained readily from 2,3-*O*-isopropylidene-5-*O*-trityl-*D*-ribofuranose by our previously published procedure.[3] Although the method also affords a minor amount of the α compound 2, large-scale separation of the isomers can be carried out readily by dry-column chromatography on silica gel. The C≡C triple bond of α,β-acetylenic esters is known[8] to be highly reactive toward nucleophilic reag-

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(2) Presented in part at the ACS National Meeting, Chicago, Illinois, on August 29, 1975; Abstract Carb. 057.

(3) F. G. de las Heras, S. Y-K. Tam, R. S. Klein, and J. J. Fox, *J. Org. Chem.*, 41, 84 (1976).

(4) S. Y-K. Tam, F. G. de las Heras, R. S. Klein, and J. J. Fox, *Tetrahedron Lett.*, 3271 (1975).

(5) For a review, see R. W. Chambers, *Prog. Nucleic Acid Res. Mol. Biol.*, 5, 349 (1966).

(6) C. K. Chu, I. Wempen, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, 41, 2793 (1976).

(7) J. H. Burchenal, K. Ciovacco, K. Kalaher, T. O'Toole, R. Kiefner, M. D. Dowling, C. K. Chu, K. A. Watanabe, I. Wempen, and J. J. Fox, *Cancer Res.*, 36, 1520 (1976).

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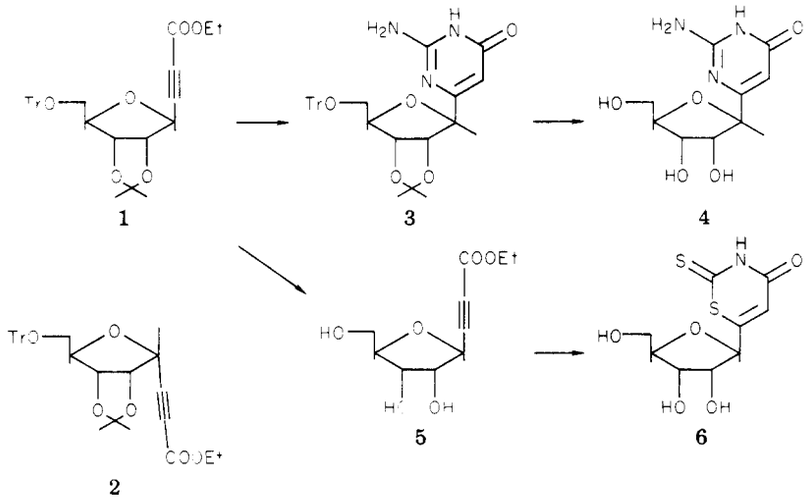
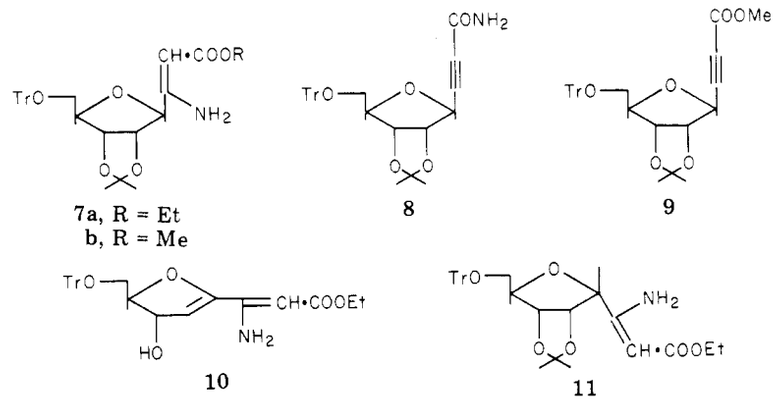
Scheme I



Scheme II



ents because of its conjugation to the activating ester group. It was thus envisaged that direct condensation of acetylenic ester **1** with a dinucleophile of the amidine type N=C—N would provide an entry into the pyrimidine ring system, through reactions at both the β position of the triple bond and the ester group. Several analogous cyclizations of this type have been reported.[9] In addition, successful condensations of guanidine with propynal[10] and ethynyl ketone[11] and, more recently, the preparation of uracil from propiolic acid with urea under strong acidic conditions[12] have all been described. In our case, condensation of the propynoate **1** with guanidine in the presence of sodium ethoxide at reflux temperature led to the formation of a large number of products. The ^1H NMR spectra of some of the products indicated a loss of the isopropylidene group from the structure. This complication was later found to be attributable to the presence of sodium ethoxide which abstracted H-1′ and initiated an elimination reaction (see below). Thus, the experiment was modified by using less than an equivalent amount of sodium ethoxide for the neutralization of guanidine hydrochloride and then allowing the free guanidine to react with **1** at room temperature. With these changes, a 55% yield of the desired product **3** could be readily obtained (Scheme I). Deblocking of **3** with methanolic hydrogen chloride afforded the free isocytosine *C*-nucleoside **4**. Proof that cyclization had indeed proceeded as anticipated was provided by comparing the UV spectrum of **4** to that of 6-methylisocytosine.

Cain and Warrener[13] have described the conversion of an α,β-acetylenic ester to 1,3-thiazine-2-thione derivatives by treatment with dithiocarbamic acid in the presence of mineralic acids and subsequent conversion of the thiazine intermediates to the corresponding 2-thiouracils by treatment with ammonia. Application of this procedure to **5** (obtained by treatment of **1** with ethanolic hydrogen chloride) afforded the crystalline 1,3-thiazine-2-thione **6** in 38% yield. Several attempts to convert the latter to the 2-thiouracil *C*-nucleoside **19** in the presence of ammonia, however, led only to decomposition products. Since an alternate approach to **19** was being developed simultaneously (vide infra), this route was not explored further.

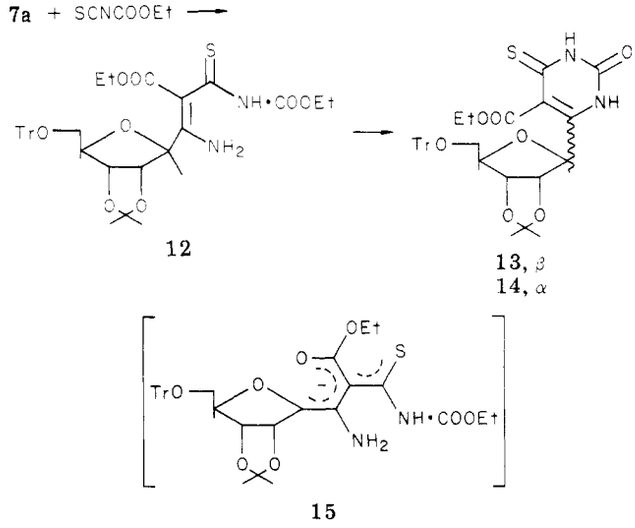
While the reactions of thioureas with α,β-acetylenic esters are known to give 1,3-thiazines[14-19] in the absence of base and benzalthiohydantoins[20] in their presence, the reactions with β-alkoxy acrylates,[21] enaminonitriles,[22] en-

(8) For a review, see E. Winterfeldt in "Newer Methods of Preparative Organic Chemistry", Vol. VI, W. Foerst, Ed., Verlag Chemie GmbH, 1971.
(9) For a review, see M. V. George, S. K. Khetan, and R. K. Gupta, *Adv. Heterocycl. Chem.*, **19**, 279 (1976).
(10) T. Tabuchi and G. Maemoto, Japanese Patent 180380 (1949); *Chem. Abstr.*, **46**, 4029 (1952).
(11) K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 953 (1946).
(12) (a) K. Harada and S. Suzuki, *Tetrahedron Lett.*, 2321 (1976); (b) R. J. De Pasquale, *J. Org. Chem.*, **42**, 2185 (1977).
(13) E. N. Cain and R. N. Warrener, *Aust. J. Chem.*, **23**, 51 (1970).
(14) H. Tanaka and A. Yokoyama, *Chem. Pharm. Bull.*, **10**, 19 (1962).
(15) E G Kataev, L. K. Konovalova, and E. G. Yarkova, *J. Org. Chem. USSR (Engl. Transl.)*, **5**, 610 (1969).
(16) J. W. Lown and J. C. N. Ma, *Can. J. Chem.*, **45**, 939 (1967).
(17) The rearrangement of 1,3-thiazine to 2-thiouracil proposed by Winterfeldt[18] has been disputed recently by Warrener and Cain.[19]
(18) E. Winterfeldt and J. M. Nelke, *Chem. Ber.*, **100**, 3671 (1967).
(19) R. N. Warrener and E. N. Cain, *Aust. J. Chem.*, **24**, 785 (1971).
(20) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Am. Chem. Soc.*, **86**, 107 (1964).

amino ketone, or enamino esters[23] have been reported to furnish the 2-pyrimidinethiones. The conversion of an α,β-acetylenic ester to β-alkoxy acrylate or enamino ester requires the addition of an alcohol or an amine, respectively. Such addition reactions to α,β-acetylenic ester usually take place under relatively mild conditions.[8] However, reaction of **1** with ethanol, either in the presence of a catalytic amount of triethylamine[24] or sodium ethoxide, gave erratic results even when performed in the cold. Addition of ethanol at higher temperature and without catalyst was equally unsuccessful and was further complicated by the concomitant loss of the trityl group. On the other hand, treatment of **1** with ethanolic ammonia in a sealed vessel at 105 °C for 4 h afforded an excellent yield of the enamino ester **7a** (Scheme II). When this reaction was performed at room temperature, a small amount (~ 30%) of the propynamide **8** was also obtained in addition to **7a**. It is interesting to note that treatment of the methyl ester derivative **9** with methanolic ammonia at 0 °C gave the propynamide **8** as the major product (77%), whereas the enamino ester **7b** was isolated only in 5% yield. The structures of **7a** and **7b** were established from their spectroscopic properties (IR, UV, and ^{1}H NMR), which are fully compatible with those of ethyl 3-aminocrotonate. The absorption at 1670 cm^{-1} in the IR spectrum was suggestive of hydrogen bonding of the NH_2 group with the ester carbonyl group.[25] Definite assignment of the geometric configuration of the olefinic double bond in **7a** and **7b**, however, could not be made on the basis of such data. As for **8**, the appearance of the amide (1675 cm^{-1}) and C≡C (2250 cm^{-1}) absorptions in the IR spectrum and the absence of the carboethoxy resonances in the ^{1}H NMR spectrum confirm the structure assigned.

The reaction of the enamino ester **7a** with thiourea in the presence of sodium ethoxide[23] did not afford the desired 2-thiouracil compound but instead gave a product which was later identified as **10** (Scheme II). Thus, the ^{1}H NMR spectrum of the product indicated loss of the isopropylidene signals and of one proton from the ribose moiety and showed the presence of one OH group (at δ 2.01). This, along with an observed paramagnetic shift of all other protons (as compared with the chemical shifts in the ^{1}H NMR of **7a**), suggested the presence of an unsaturation in the furanose ring. The assignment of structure **10** to this product is consistent with these data. The formation of **10** occurs at room temperature and undoubtedly results from abstraction by base of the H-1′ (in **7a**) rendered more acidic by the ester group in the vinylog system. As a further proof of the structure proposed, the α isomer of **7a** (**11**), which had been prepared by ammonia addition to the α-propynoate **2**, was allowed to react with sodium ethoxide alone to give **10** exclusively. Although **10** is the first isolated *C*-glycosyl compound containing a dihydrofuran moiety, several instances in *C*-nucleoside chemistry have been reported[26-28] where side reactions have

Scheme III

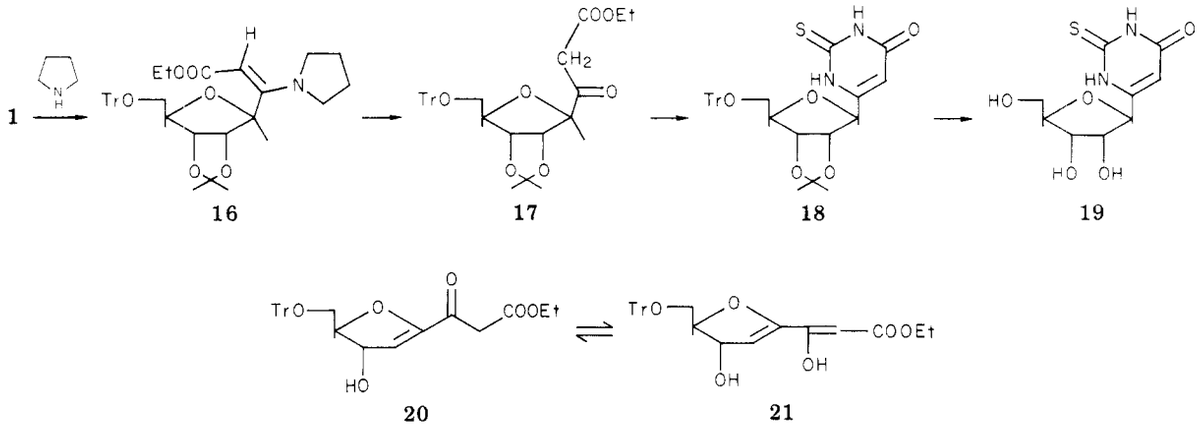


given furan derivatives which are likely to be secondary products derived from similar partially unsaturated intermediates. Further examples of this type of β elimination can be found in the chemistry of uronic acids and their derivatives.[29] It is interesting to note that the coupling constants, $J_{2'3'}$ and $J_{3'4'}$, of **10** (2.7 Hz) are similar to those in the 1′,2′-unsaturated nucleoside system, which has been recently prepared from base treatment of a 2,2′-anhydronucleoside.[30]

The unexpected lability of the isopropylidene blocking group in the above-mentioned reaction prompted us to investigate cyclization methods which could be performed under milder basic conditions. The reaction of an enamino ester with carbethoxy isothiocyanate[31-34] appeared eminently useful, because formation of the aminomethylenethioacylurethane intermediate **12** (Scheme III) would require only neutral conditions, and the subsequent cyclization to the 5-carbethoxy-4-thiouracil would be akin to the well-known Shaw synthesis of pyrimidines[35] which reportedly occurs under mild conditions. Indeed, reaction of **7a** with carbethoxy isothiocyanate readily afforded an intermediate presumed to be **12**, although definite assignment of the configuration at C-1′ could not be done by analysis of its ^{1}H NMR spectrum. Brief treatment of the intermediate **12** with sodium ethoxide gave an α,β mixture of the 5-carbethoxy-4-thiouracil derivatives which had very similar mobility on TLC. Partial separation of the two isomers by chromatography on silica gel afforded a pure sample of each. As expected, the ^{1}H NMR spectra indicated the presence of the carbethoxy group and the absence of the signal for the H-5 of thiouracil. Both isomers possessed UV absorption spectra similar to that of 4-thiouracil. The assignment of the configuration at C-1′ is based mainly on the ^{1}H NMR data. The β configuration was assigned to isomer **13**, which has a smaller δ value for H-1′ due to the shielding effect of the cis 2′-oxygen.[36] The

(21) (a) D. J. Brown, "The Pyrimidines", Wiley-Interscience, New York, 1962; (b) D. J. Brown, "The Pyrimidines", Suppl. I, Wiley-Interscience, New York, 1970.
(22) For a review, see E. C. Taylor and A. McKillop in "The Chemistry of Cyclic Enaminonitriles and *O*-Aminonitriles", Wiley-Interscience, New York, 1970.
(23) M. Polonovski, M. Pesson, and H. Schmitt, *Bull. Soc. Chim. Fr.*, 392 (1948); *Chem. Abstr.*, **42**, 5916 (1948).
(24) (a) A. W. McCulloch and A. G. McInnes, *Can. J. Chem.*, **52**, 3569 (1974); (b) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).
(25) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, 1958.
(26) T. Huynh-Dinh, A. Kolb, C. Gouyette, J. Igolen, and S. Tran-Dinh, *J. Org. Chem.*, **40**, 2825 (1975).
(27) H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **38**, 1836 (1973).
(28) H. P. Albrecht, D. B. Repke, and J. G. Moffatt, *J. Org. Chem.*, **39**, 2176 (1974).
(29) J. Kiss, *Adv. Carbohydr. Chem. Biochem.*, **29**, 229 (1974).
(30) M. J. Robins and E. M. Trip, *Tetrahedron Lett.*, 3369 (1974).
(31) For a review, see R. Esmail and F. Kurzer, *Synthesis*, 301 (1975).
(32) J. Goerdeler and H. Horn, *Chem. Ber.*, **96**, 1551 (1963).
(33) J. Goerdeler and D. Wieland, *Chem. Ber.*, **100**, 47 (1967).
(34) R. W. Lamon, *J. Heterocycl. Chem.*, **5**, 837 (1968).
(35) Reference 22a, p 87, and reference 22b, p 56.
(36) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. 2, W. W. Zorbach and R. S. Tipson, Eds., Wiley-Interscience, New York, 1973, p 333.

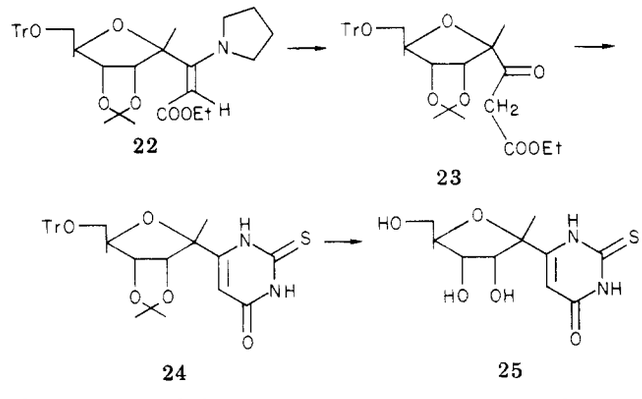
Scheme IV



isomerization is probably caused by abstraction of the H-1′ of **12** by base to form the highly delocalized anion **15**, which then affords an α,β mixture on reprotonation. In order to avoid anomerization of **12** so as to obtain β-isomer **13** exclusively, attempts were made to carry out the conversion in the presence of weak bases, such as ammonia or pyridine, or simply by heating. These attempts were uniformly unsuccessful, and mixtures of **13** and **14** were obtained in all cases. When the same conversion was attempted with the α isomer of **7a** (**11**), the same mixture of **13** and **14** was also obtained. ^{1}H NMR spectra of these mixtures all indicated that the α-compound **14** was the major product (**14**/**13** ~ 4). This instance of an isopropylidenated sugar which equilibrates to give preferentially a cis (endo) configuration is analogous to the isomerization at C-4′ of N^6-benzoyl-9-(6-deoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-ulofuranosyl)adenine[37] and to that of 1,2:5,6-di-*O*-isopropylidene-D-ribofuran-3-ulose[38] at C-4. As was pointed out recently,[39] such isomerizations might well be examples of kinetically favored protonation rather than thermodynamic equilibria.

Among all "3-carbon fragment"[21] precursors of pyridmines, β-keto esters are perhaps the most commonly employed. The synthesis of **17** was, therefore, investigated. Conceivably, this could be achieved by direct hydration[40] of the propynoate **1** or by hydrolysis of an enamino ester,[41] such as **7a** or **16**. It was found that **16** (Scheme IV) could be readily obtained by reaction of **1** with pyrrolidine at 0 °C without detectable formation of the corresponding propynamide. A tentative assignment of the geometric configuration of **16** was made on the basis of several reports of the general cis mode of addition of secondary amines to α,β-acetylenic esters.[42,24b] Of interest was the observation that the ^{1}H NMR spectrum of **16** displayed the signal of H-1′ at an unexpectedly low field with δ 6.34. This proton assignment was confirmed by double-irradiation experiments.[43] Elemental analysis and other spectroscopic

Scheme V

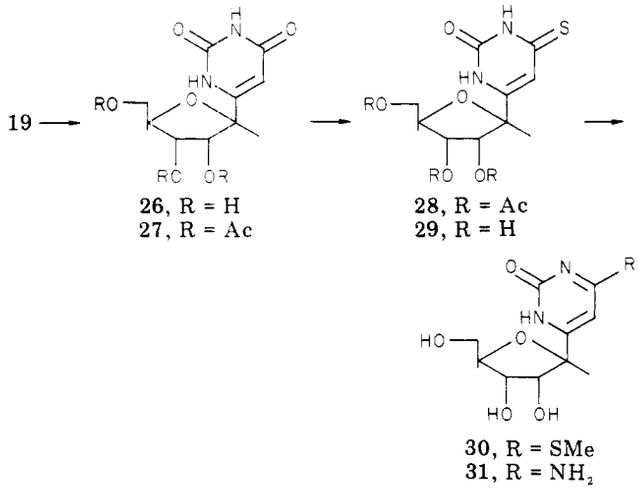


data confirmed the enamino ester structure. Hydrolysis of **16** was carried out in ethanol by treatment with wet Dowex-50 (H^+) resin and afforded the β-keto ester **17** as a syrup in excellent yield. The ^{1}H NMR spectrum of **17** displayed the geminal H-2 signals as an AB quartet which exchanged for deuterium upon addition of sodium deuteroxide which is consistent with the β-keto ester structure. In the IR spectrum, the presence of an absorption band at 1650 cm^{-1} distinct from the keto band at 1715 cm^{-1} and the ester band at 1746 cm^{-1} was ascribed to the ester carbonyl group hydrogen bonding to the enolic hydroxyl group.[25] This confirms the structure assigned to **17**. Cyclization of **17** with thiourea in the presence of sodium ethoxide at room temperature afforded the desired 2-thiouracil compound **18** in ~30–40% yield, together with an appreciable amount (40%) of side product **20** (and its enol form **21**). The identity of the tautomeric mixture of **20** and **21** was recognized because of the close resemblance of the ^{1}H NMR spectrum with that of **10** obtained earlier. It was found later that a preheating of the thiourea with sodium ethoxide *before* addition to the β-keto ester **17** increased the yield of **18** to 70%. Under these conditions, the mixture of **20** and **21** was obtained in less than 20% yield. Deblocking of **18** with methanolic hydrogen chloride gave the free 2-thiouracil *C*-nucleoside **19** in 90% yield. The UV data of **19** are in accord with that of a sample of 2-thiouracil.

In view of the well-known susceptibility of 5-(β-D-ribofuranosyl)pyrimidines (ψ-uridine type) to isomerization at C-1′,[5,6] a careful assignment of the configuration at C-1′ of all of the aforementioned compounds was of critical importance. The ^{1}H NMR spectra of **3**, **4**, **6**–**8**, and **16**–**19** indicate that they were all obtained in one pure form. Since all of them are synthetically related to common precursor **1**, which was conclusively assigned the β configuration,[3] it is reasonable to conclude that all have the

(37) R. S. Ranganathan, G. H. Jones, and J. G. Moffatt, *J. Org. Chem.*, **39**, 290 (1974).
(38) J. M. J. Tronchet and J. M. Bourgeois, *Carbohydr. Res.*, **29**, 373 (1973).
(39) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602 (1975).
(40) M. Miocque, N. M. Hung, and V. O. Yen, *Ann. Chim. (Paris)*, 8, 157 (1963).
(41) E. J. Stamhuis in "Enamines: Synthesis, Structure and Reactions", A. G. Cook, Ed., Marcel Dekker, New York, 1969, p 101.
(42) (a) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966); (b) K. Herbig, R. Huisgen, and H. Huber, *ibid.*, **99**, 2546 (1966).
(43) The H-1's of both isomers **16** and **22** have the same abnormally low chemical shift at δ 6.34. This may be due to the presence of a six-membered ring involving hydrogen bonding between the ester carbonyl group and H-1′.

Scheme VI



26, R = H
27, R = Ac

28, R = Ac
29, R = H

30, R = SMe
31, R = NH_2

β configuration. Complete inversion to the other isomer (i.e., from β to α) would be, of course, highly unlikely. To further confirm these assignments, we also prepared the α isomers (Scheme V) of compounds **7a** and **16–19** (viz., **11** and **22–25**, respectively), starting from the α-propynoate **2**, by procedures identical with those used for the β series. We have found that the β isomers can be differentiated from their α counterparts on the basis of their ^{1}H NMR data. Thus, inspection of the tabulated ^{1}H NMR data (Tables I and II) permits the following correlations. As with α and β nucleosides,[36] the chemical shifts of the H-1′ are consistently[43] further downfield for the α isomers (**2**, **11**, **14**, **23**, **24**, and **25**) than for the corresponding β isomers (**1**, **7a**, **13**, **17**, **18**, and **19**). It should be noted that this relationship has been observed also in the cases of the isomers of ψ-uridine,[44] pyrazomycin,[45] and some purine-like *C*-nucleosides.[26,46] Furthermore, 2,3-*O*-isopropylidenated α derivatives consistently exhibit values for $J_{3',4'} = 0$, while in the corresponding β-compounds $J_{3',4'} > 1.5$ Hz. This same phenomenon has been reported recently by Ohrui et al.[39] and ascribed to the greater predominance of the "O-endo" envelope conformation adopted by the α compounds. Finally, although the numerical difference in chemical shifts of the isopropylidene *gem*-dimethyl groups ($\Delta\delta$) for our *C*-nucleosides is not identical with that empirically determined by Imbach et al.[47] for 2′,3′-*O*-isopropylidenated *N*-nucleosides, the β compounds, nevertheless, all exhibit larger $\Delta\delta$ values than do their α isomers, which is consistent with the more general principles of this rule.[47]

With the configurational assignment confirmed, the β-2-thiouracil compound **19** was used as the starting material for preparation of other members of the series. Thus, treatment of **19** with chloroacetic acid followed by concentrated hydrochloric acid at reflux afforded a good yield of the uracil *C*-nucleoside **26** (Scheme VI). After acetylation, the triacetate **27** was heated with phosphorus pentasulfide in dioxane at 80 °C to give the 4-thiouracil compound **28** in 92% yield. Deblocking with methanolic hydrogen chloride followed by methylation with methyl iodide converted **28** to the 4-*S*-methyl *C*-nucleoside **30**. Finally, reaction of **30** with liquid ammonia in a sealed vessel at 70 °C afforded, after chromatography, a 40% yield of the cytosine compound **31**. The UV spectra of all of these new *C*-nucleosides are similar to those of their parent pyrimidines, which confirms the ring structure of the heterocyclic bases. The β configuration of **26**, **30**, and **31** at C-1′ is assigned on the basis of the established configuration of 2-thiouracil *C*-nucleoside precursor **19**. It is further confirmed by the existing similarity of the chemical shifts (Table I) of their H-1′ (4.36, 4.42, and 4.29 ppm, respectively) to those of the aforementioned β-*C*-nucleosides **4**, **6**, and **19** (4.25, 4.45, and 4.46 ppm, respectively).

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were obtained with a JEOL PFT-100 spectrometer with Me_4Si as the internal standard. Ultraviolet absorption spectra were obtained with a Cary recording spectrophotometer, Model 15. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Mich. Column chromatography was performed on Woelm silica gel (70-230 mesh). Thin layer chromatography was performed on 250 μ silica gel plates (Analtech, Inc.), and substances were visualized either by UV absorption or by spraying them with 20% ethanolic sulfuric acid and charring.

6-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-isocytosine (3). Guanidine hydrochloride (570 mg, 6 mmol) was stirred with sodium ethoxide (6 mmol) in ethanol (40 mL) for 1 h and then added slowly to a solution of compound **1** (3 g, 5.85 mmol) in ethanol (40 mL). After 7 h at room temperature, the reaction solution was neutralized by addition of 1 N HCl and was evaporated to dryness in vacuo. The residue was extracted with chloroform and washed successively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water. After being dried over sodium sulfate, the chloroform solution on evaporation afforded a solid residue which crystallized from ethanol to give 1.7 g (55%) of **3**, mp 224–225 °C dec.

Anal. Calcd for $C_{31}H_{31}O_5N_3$: C, 70.84; H, 5.94; N, 7.99. Found: C, 70.76; H, 5.90; N, 7.98.

6-(β-D-Ribofuranosyl)isocytosine (4). A suspension of compound **3** (140 mg) in methanol was treated with a saturated solution of HCl in methanol (0.6 mL) at room temperature. After 2 h, the reaction solution was evaporated to dryness in vacuo, and the residue was partitioned between methylene chloride and water. Evaporation of the aqueous layer afforded a solid which crystallized slowly from ethanol to give **4** as a hydrochloride salt (69 mg, yield 98.5%). This salt was neutralized with Amberlite IR 45 (OH^-) resin and then crystallized from isopropyl alcohol to give **4**: mp 233–236 °C dec; UV (H_2O) λ_{max} (pH 7) 286 nm (ϵ 7130), λ_{min} (pH 7) 246 (ϵ 1410), λ_{max} (pH 1) 261 (ϵ 7210), λ_{min} (pH 1) 238 (ϵ 3820), λ_{max} (pH 13) 276 (ϵ 6040), λ_{min} (pH 13) 250 (ϵ 1760). This spectral pattern is similar to that of 6-methylisocytosine.

Anal. Calcd for $C_9H_{13}O_5N_3$: C, 44.45; H, 5.39; N, 17.28. Found: C, 44.41; H, 5.30; N, 17.25.

Ethyl 3-(β-D-Ribofuranosyl)propynoate (5). A saturated solution of HCl in ethanol (10 mL) was added to a solution of **1** (1.7 g) in ethanol (20 mL), and the mixture was stirred at room temperature for 3 h. After removal of the solvent, the residue was partitioned between ether and water, and the aqueous layer was evaporated to give a syrupy product. Column chromatography with chloroform–methanol (10:1) as eluant afforded 670 mg (87%) of pure **5** as a light syrup.

Anal. Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.05; H, 6.01.

3,4-Dihydro-6-(β-D-ribofuranosyl)-4-oxo-3*H*-1,3-thiazine-2-thione (6). HCl (5 M, 2.4 mL, 12 mmol) was added to a stirred solution of ammonium dithiocarbamate (1.38 g, 12.6 mmol) in water (12 mL) at −5 °C. After 1 h, a solution of compound **5** (2.5 g, 9.3 mmol) in water (12 mL) was added, and the temperature of the reaction was allowed to warm up slowly to room temperature. After standing overnight, the reaction solution was

(44) (a) K. R. Darnall, L. B. Townsend, and R. K. Robins, *Proc. Natl. Acad. Sci. USA*, **57**, 548 (1967); (b) U. Lerch, M. G. Burdon, and J. G. Moffatt, *J. Org. Chem.*, **36**, 1507 (1971).

(45) (a) S. De Bernardo and M. Weigele, *J. Org. Chem.*, **41**, 287 (1976); (b) G. E. Gutowski, M. O. Chaney, N. D. Jones, R. L. Hamill, F. A. Davis, and R. D. Miller, *Biochem. Biophys. Res. Commun.*, **51**, 312 (1973).

(46) (a) S. Y-K. Tam, J. S. Hwang, F. G. de las Heras, R. S. Klein, and J. J. Fox, *J. Heterocycl. Chem.*, **13**, 1305 (1976); (b) F. G. de las Heras, C. K. Chu, S. Y-K. Tam, R. S. Klein, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, **13**, 175 (1976).

(47) J. L. Imbach and B. L. Kam, *J. Carbohydr. Nucleosides, Nucleotides*, **1**, 271 (1974).

evaporated to dryness, and the thick, syrupy residue was crystallized from ethanol to give 980 mg of **6** (38%): mp 174–175 °C; UV (H_2O) λ_{max} (pH 1) 313 nm (ε 13 450) and 248 (ε 16 210), λ_{min} (pH 1) 272 (ε 1690), λ_{max} (pH 13) 267 (ε 22 360) and 325 (ε 6240), λ_{min} (pH 13) 305 (ε 4840). This pattern is very similar to the spectrum of 6-(hydroxymethyl)-1,3-thiazine-2-thione.[18]

Anal. Calcd for $C_9H_{11}O_5NS_2$: C, 39.01; H, 3.99; N, 5.05; S, 23.13. Found: C, 39.06; H, 3.97; N, 5.00; S, 23.22.

Ethyl 3-Amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propenoate (7a). A mixture of compound **1** (4.0 g, 7.8 mmol) and a saturated solution of ethanolic ammonia (150 mL) was heated in a stainless steel bomb at 100 °C for 4 h. After evaporation of the solvent, the residue was crystallized from ethanol to give 4.0 g of **7a** (97%): mp 117–118 °C; UV λ_{max} (EtOH) 274 nm (ε 17 670); IR ν_{max} ($CHCl_3$) 3520 and 3380 (NH_2), 1670 (CO), 1615 cm^{-1} (C=C).

Anal. Calcd for $C_{32}H_{35}NO_6$: C, 72.57; H, 6.66; N, 2.64. Found: C, 72.62; H, 6.69; N, 2.69.

Methyl 3-Amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propenoate (7b) and 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)propynamide (8). To a cold (−5 °C) saturated solution of methanolic ammonia (40 mL) was added a solution of compound **9** (2.0 g, 4 mmol) in methanol (10 mL). The mixture was kept at −5 °C for 45 min. The cooling bath was then removed, and the solution was left at room temperature for another 45 min. After evaporation of the solvent, the residue was chromatographed on a silica gel column with petroleum ether–ethyl acetate (2:1) as eluant. This afforded 1.502 g of **8** (77%) as a syrup and 0.102 g of **7b** (4.9%).

For compound **7b**: mp 153–154 °C (MeOH); UV λ_{max} (EtOH) 274 nm (ε 16 780); IR ν_{max} (KBr) 3460 and 3320 (NH_2), 1670 (C=O), 1615 cm^{-1} (C=C).

Anal. Calcd for $C_{31}H_{33}NO_6$: C, 72.21; H, 6.45; N, 2.72. Found: C, 72.17; H, 6.48; N, 2.76.

For compound **8**: IR ν_{max} ($CHCl_3$) 3550 and 3450 (NH_2), 2250 (C=C), and 1675 cm^{-1} ($CONH_2$).

Anal. Calcd for $C_{30}H_{29}NO_5$: C, 74.52; H, 6.04; N, 2.90. Found: C, 74.33; H, 6.00; N, 2.78.

Ethyl 3-Amino-3-(2-deoxy-5-*O*-trityl-D-*erythro*-pent-1-enofuranosyl)propenoate (10). A solution of compound **7a** (1 g, 2 mmol) in ethanol (3 mL) containing 3 mmol of sodium ethoxide was heated at reflux for 0.5 h. After cooling, the reaction solution was diluted with chloroform and washed with dilute HCl, $NaHCO_3$, and water successively. The dried (Na_2SO_4) chloroform solution on evaporation afforded a syrup which was purified by silica gel column chromatography with chloroform–methanol (10:1) as eluant to give 420 mg of **10**, mp 62 °C.

A similar reaction of compound **11** and sodium ethoxide also gave compound **10** as the major product.

Anal. Calcd for $C_{29}H_{29}O_5N$: C, 73.87; H, 6.20; N, 2.97. Found: C, 73.94; H, 6.23; N, 2.61.

Ethyl 3-Amino-3-(2,3-*O*-isopropylidene-5-*O*-trityl-α-D-ribofuranosyl)propenoate (11). A mixture of compound **2** (2.7 g, 5.3 mmol) and a saturated solution of ethanolic ammonia (100 mL) was stored in a stainless steel bomb at 105 °C for 5.5 h. After evaporation of the solvent, the solid residue was crystallized from ethanol to give 2.5 g (89%) of **11**, mp 149–150 °C.

Anal. Calcd for $C_{32}H_{35}NO_6$: C, 72.57; H, 6.66; N, 2.64. Found: C, 72.53; H, 6.66; N, 2.59.

5-Ethoxycarbonyl-6-(2,3-*O*-isopropylidene-5-*O*-trityl-α,β-D-ribofuranosyl)-4-thiouracil (13 and 14). Potassium thiocyanate (0.4 g, 4 mmol) was heated with ethyl chloroformate (0.32 mL, 4 mmol) in acetone (10 mL) at reflux temperature for 15 min. After removal of the precipitated KCl by filtration, the filtrate was added to a solution of compound **7a** (1.1 g, 2 mmol) in acetone (10 mL), and the mixture was heated at reflux. After 45 min, the reaction solution was allowed to cool to room temperature and then poured slowly into ice water (200 mL). The precipitated yellowish solid was collected by filtration, dried, and weighed (1.09 g). Without purification, this solid was added to dioxane (20 mL) containing 7 mL of 1 N sodium hydroxide, and the mixture was stirred for 0.5 h. After neutralization with 1 N hydrochloric acid and evaporation of the solvent, the residue was extracted with chloroform, washed with $NaHCO_3$ solution and water, and dried. Evaporation of the chloroform solution gave a solid which was purified on a silica gel column with benzene–ethyl acetate (4:1) as eluant. This afforded 55 mg of pure **13**, 162 mg of a 2:1 mixture of **13** and **14**, and 563 mg of pure **14**. Thus, the total yield of **13** and **14** was 61%: UV λ_{max} (MeOH) 334 nm, λ_{max} (MeOH + 1N NaOH) 348 nm.

Anal. Calcd for $C_{34}H_{34}O_7N_2S$: C, 66.43; H, 5.57; N, 4.56; S, 5.22. Found: C, 66.15; H, 5.51; N, 4.49; S, 5.42.

Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-3-pyrrolidinopropenoate (16). A solution of pyrrolidine (2.14 g, 30 mmol) in ethanol (50 mL) was slowly added to a cold solution of compound **1** (14 g, 27 mmol) in ethanol (140 mL) at 0 °C. After 1.5 h, the reaction solution was evaporated to dryness in vacuo, and the solid residue was crystallized from ethanol to give 15 g (95%) of **16**: mp 118.5–120 °C; UV λ_{max} (EtOH) 297 nm; IR ν_{max} ($CHCl_3$) 1660, 1570 cm^{-1}.

Anal. Calcd for $C_{36}H_{41}O_6N$: C, 74.08; H, 7.08; N, 2.40. Found: C, 74.03; H, 7.16; N, 2.39.

Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-3-oxopropanoate (17). To a solution of compound **16** (8 g) in ethanol (200 mL) was added wet Dowex 50 (H^+) resin (20 mL) with efficient stirring. The progress of the reaction was followed by UV measurement on aliquots of the reaction mixture. As soon as the UV absorption at 297 nm reached zero, the reaction mixture was quickly filtered and evaporated to dryness in vacuo. The residue was extracted with ether, washed with $NaHCO_3$ solution and water, and dried. Removal of ether and purification of the residue by silica gel column chromatography (petroleum ether–EtOAc, 10:1) afforded 7.2 g (99%) of **17** as a syrup: IR ν_{max} ($CHCl_3$) 1746, 1715, 1650, 1600 cm^{-1}.

Anal. Calcd for $C_{32}H_{34}O_7$: C, 72.43; H, 6.46. Found: C, 72.19; H, 6.38.

6-(2,3-*O*-Isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)-2-thiouracil (18). A solution of thiourea (9 g, 0.12 mol) in ethanolic sodium ethoxide (80 mL, 0.06 mol) was heated to reflux for 0.5 h. After being cooled, this solution was added slowly to a solution of compound **17** (8 g, 0.015 mole) in ethanol (80 mL), and the mixture was stirred at room temperature for 3 days. After neutralization with 1 N HCl and evaporation of the solvent in vacuo, the solid residue was extracted with warm chloroform and then filtered. The filtrate was evaporated in vacuo, and the residue was purified by silica gel chromatography (benzene/ethyl acetate, 4:1) to give pure **18** (5.7 g, 70%), mp 119–120.5 °C.

Anal. Calcd for $C_{31}H_{30}O_5N_2S$: C, 68.62; H, 5.57; N, 5.16; S, 5.91. Found: C, 68.68; H, 5.60; N, 5.06; S, 5.84.

6-(β-D-Ribofuranosyl)-2-thiouracil (19). To a solution of compound **18** (2.8 g) in methanol (80 mL) was added a saturated solution of methanolic HCl (16 mL). After 45 min, the reaction solution was evaporated to dryness in vacuo. The residue was warmed with anhydrous ether, and the solid formed was collected by filtration and crystallized from ethanol to give 1.18 g of **19** (88%): mp 222–224 °C dec; UV (H_2O) λ_{max} (pH 3.58) 271 nm (ε 15 840), λ_{min} (pH 3.58) 241 (ε 3490), λ_{max} (pH 14) 260 (ε 11 730) and 290 (ε 6210), λ_{min} (pH 14) 280 (ε 6780). This spectral pattern is similar to that of 2-thiouracil.

Anal. Calcd for $C_9H_{12}O_5N_2S$: C, 41.53; H, 4.65; N, 10.76; S, 12.32. Found: C, 41.69; H, 4.69; N, 10.78; S, 12.38.

Ethyl 3-(2-Deoxy-5-*O*-trityl-D-*erythro*-pent-1-enofuranosyl)-3-oxopropanoate (20) and Its Enol Form 21. The tautomeric mixture of **20** and **21** was isolated as a minor product (382 mg) from the silica gel column chromatography described in the preparation of **18**. This same mixture could also be obtained as a major product from the reaction of compound **17** and sodium ethoxide.

Anal. Calcd for $C_{29}H_{28}O_6$: C, 73.71; H, 5.97. Found: C, 73.79; H, 6.13.

Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-α-D-ribofuranosyl)-3-pyrrolidinopropenoate (22). A solution of pyrrolidine (0.2 mL) in ethanol (2 mL) was added slowly to a cold solution of compound **2** (1 g) in ethanol (50 mL) at 0 °C. After 1 h, the reaction solution was evaporated to dryness in vacuo, and the solid residue was crystallized from ethanol to give 1.02 g (89.5%) of **22**, mp 96.5–98 °C.

Anal. Calcd for $C_{36}H_{41}O_6N$: C, 74.08; H, 7.08; N, 2.40. Found: C, 73.96; H, 7.09; N, 2.36.

Ethyl 3-(2,3-*O*-Isopropylidene-5-*O*-trityl-α-D-ribofuranosyl)-3-oxopropanoate (23). To a solution of compound **22** (512 mg) in acetone (7 mL) was added wet Dowex 50 (H^+) resin

Table I. 100 MHz Proton Chemical Shifts (δ)

compd no.	solvent[a]	H 1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	CMe_2 ($\Delta\delta$)	OTr	miscellaneous
1	B	4.76 (d)	4.84 (dd)	4.62 (dd)	4.33 (m)	3.29 (m)		1.30, 1.50 (0.20)	7.20–7.53	1.19 (t, 3, $CO_2CH_2CH_3$), 4.13 (q, 2, CO_2CH_2-CH_3)
2	B	5.18 (d)	4.96 (dd)	4.70 (d)	4.24 (m)	3.10 (dd)	3.43 (dd)	1.35, 1.56 (0.21)	7.27–7.38	1.30 (t, 3, $CO_2CH_2CH_3$), 4.24 (m, 3, $CO_2CH_2CH_3$, H-4′)
3	A	4.52 (d)	4.69 (dd)	4.42 (dd)	4.11 (m)	3.10 (m)		1.23, 1.45 (0.22)	7.28–7.37	5.74 (s, 1, H-5), 6.61 (bs, 2, NH_2), 10.72 (bs, 1, NH)
4	A	4.25 (d)	←	3.77 (m)	→	3.50 (m)				4.90 (m, 3, OH's), 5.74 (s, 1, H-5), 6.57 (bs, 2, NH_2), 10.4 bs, 1, NH)
5	A	4.69 (d)	←	3.71–4.05 (m)	→	3.46 (m)				1.23 (t, 3, $CO_2CH_2CH_3$), 4.19 (q, 2, CO_2CH_2-CH_3), 4.82, 5.07, and 5.42 (OH's)
6	A	4.45 (d)	←	3.88 (m)	→	3.46 (m)				6.64 (s, 1, H-5), 6.57, 7.07, and 7.59 (OH), 8.72 (NH)
7a	B	4.63 (m)		4.40 (m)	4.23 (m)	3.27 (dd)	3.46 (dd)	1.33, 1.54 (0.21)	7.25–7.48	1.26 (t, 3, $CO_2CH_2CH_3$), 4.12 (q, 2, CO_2CH_2-CH_3), 4.71 (s, 1, H-2), 6.71 (bs, 2, NH_2)
7b	B	4.64 (m)		4.40 (m)	4.24 (m)	3.27 (dd)	3.46 (dd)	1.32, 1.54 (0.22)	7.24–7.48	3.65 (s, 3, CO_2Me), 4.72 (s, 1, H-2), 6.66 (bs, 2, NH_2)
8	B	4.80 (d)	4.88 (dd)	4.67 (dd)	4.35 (m)	3.27 (m)		1.31, 1.51 (0.20)	7.24–7.53	5.23 and 5.94 (bs, 1, $CONH_2$)
9	B	4.75 (d)	4.83 (dd)	4.62 (dd)	4.33 (m)	3.28 (m)		1.30, 1.50 (0.20)	7.19–7.52	3.66 (s, 3, CO_2Me)
10	B		5.54 (d)	4.83 (t)	4.51 (m)	3.22 (m)			7.23–7.43	1.27 (t, 3, $CO_2CH_2CH_3$), 2.01 (bs, 1, OH), 4.14 (q, 2, $CO_2CH_2CH_3$), 5.12 (s, 1, H-2), 6.38 (bs, 2, NH_2)
11	B	4.75 (d)	4.89 (dd)	4.69 (d)	4.30 (m)	3.15 (dd)	3.37 (dd)	1.30, 1.47 (0.17)	7.24–7.40	1.26 (t, 3, $CO_2CH_2CH_3$), 4.13 (q, 2, $CO_2CH_2CH_3$), 4.58 (s, 1, H-2), 6.78 (bs, 2, NH_2)
13	B	4.90 (m)		4.70 (m)	~4.4 (m)	3.40 (m)		1.35, 1.55 (0.20)	7.26–7.38	1.37 (t, 2, $CO_2CH_2CH_3$), 4.25–4.46 (m, 3, CO_2-CH_2CH_3, H-4′), 8.78 and 9.37 (2 bs, 2, NH's)
14	B	5.40 (d)	5.22 (dd)	4.69 (d)	4.3 (m)	3.16 (dd)	3.52 (dd)	1.29, 1.43 (0.14)	7.25–7.39	1.18 (t, 3, $CO_2CH_2CH_3$), 4.03–4.39 (m, 3, $CO_2CH_2CH_3$, overlapped with H-4′), 8.99 and 10.15 (2 bs, 2, NH's)

16	B	6.34 (d)	4.85 (m)		~4.0 (m)	3.46 (m)		1.35, 1.59 (0.24)	7.22–7.48	1.21 (t, 3, $CO_2CH_2CH_3$), 1.78 and 3.38 (m, 4, pyrrolidine H's), 3.93–4.12 (m, 3, $CO_2CH_2CH_3$, H-4'), 4.61 (s, 1, H-2)
17	B	4.47–4.57 (m) (with H-3')	4.89 (dd)	4.47–4.57 (m) (with H-1')	4.26 (m)	3.25 (m)		1.33, 1.54 (0.21)	7.21–7.52	1.18 (t, 3, $CO_2CH_2CH_3$), 3.49 and 3.69 (2 d, 2, geminal coupling = 16.2 Hz, H-2's), 4.08 (q, 2, $CO_2CH_2CH_3$)
18	A	4.69 (d)	4.78 (d)	4.54 (dd)	4.10 (m)	3.17 (m)		1.27, 1.49 (0.22)	7.36	5.98 (s, 1, H-5), 12.44 (bs, 2, NH's)
19	A	4.46	←	3.91–4.01 (m)	→	3.59 (m)				5.07, 5.25, and 5.46 (OH's), 5.95 (s, 1, H-5), 11.94 and 12.41 (2 s, 2, NH's)
20	B		6.01 (d)	4.94 (m)	4.54 (m)	3.25 (m)			7.20–7.45	1.18 (t, 3, $CO_2CH_2CH_3$), 2.40 (bs, 1, OH), 3.68 (s, 2, H-2's), 4.12 (q, 2, $CO_2CH_2CH_3$)
21	B		5.82 (d)	4.84 (m)	4.54 (m)	3.21 (m)			7.20–7.45	1.30 (t, 3, $CO_2CH_2CH_3$), 2.10 (bs, 1, OH), 4.24 (q, 2, $CO_2CH_2CH_3$), 5.64 (s, 1, H-2), 11.69 (bs, 1, enol)
22	B	6.34 (d)	5.30 (dd)	4.61 (d)	4.32 (m)	3.13 (dd)	3.28 (dd)	1.28, 1.47 (0.19)	7.23–7.53	1.24 (t, 3, $CO_2CH_2CH_3$), 1.86 and 3.48 (m, 4, pyrrolidine H's), 4.07 (q, 2, $CO_2CH_2CH_3$), 4.55 (s, 1, H-2)
23	B	4.89 (d)	5.12 (dd)	4.67 (d)	4.38 (m)	3.11 (dd)	3.39 (dd)	1.28, 1.46 (0.18)	7.24–7.40	1.25 (t, 3, $CO_2CH_2CH_3$), 3.52 and 3.79 (2 d, 2, geminal coupling = 16.2 Hz, H-2's), 4.19 (q, 2, $CO_2CH_2CH_3$)
24	A	4.92 (d)	5.16 (dd)	4.71 (d)	4.34 (m)	3.16 (m)		1.25, 1.27 (0.02)	7.36–7.50	5.78 (s, 1, H-5), 12.40 (bs, 2, NH)
25	A	4.68 (dd)	4.30 (t)	4.02 (dd)	3.89 (m)	3.39 (dd)	3.63 (dd)			5.76 (d, 1, H-5, $J_{5,1'}$ = 0.6 Hz), 12.04 and 12.33 (2 b s, 2, NH's)
26	A	4.36 (d)	←	3.91 (m)	→	3.59 (m)				5.55 (s, 1, H-5)
27	B	4.72 (d)	←	5.18 (m)	→	4.40 (m)				2.13 (s, 9, OAc), 5.74 (s, 1, H-5), 9.58 and 9.65 (2 b s, 2, NH's)
28	B	4.72 (d)	←	5.18 (m)	→	4.40 (m)				2.15 and 2.18 (3 s, 9, OAc), 6.45 (s, 1, H-5), 9.64 and 10.23 (2 b s, 2, NH's)
30	A	4.42 (d)	←	3.90 (m)	→	3.60 (m)				2.44 (s, 3, SCH_3), 6.40 (s, 1, H-5), 11.16 (b s, 1, NH)
31	A	4.29 (d)	←	3.88 (m)	→	3.56 (m)				5.60 (s, 1, H-5), 7.08 (b s, 2, NH_2)

[a] A = Me_2SO-d_6; B = $CDCl_3$.

Table II. First-Order Coupling Constants (Hz)

compd no.	$J_{1'2'}$	$J_{2'3'}$	$J_{3'4'}$	$J_{4'5'a}$	$J_{4'5'b}$	$J_{5'a5'b}$
1	2.8	5.8	1.8	*a*	*a*	*a*
2	4.7	6.0	~0	3.1	3.0	10.2
3	3.0	6.4	4.3	*a*	*a*	*a*
4	3.0	*a*	*a*	*a*	*a*	*a*
5	6.4	*a*	*a*	*a*	*a*	*a*
6	6.4	*a*	*a*	*a*	*a*	*a*
7a	*a*	*a*	*a*	4.1	3.4	10.5
7b	*a*	*a*	*a*	*a*	*a*	*a*
8	2.8	5.8	1.5	*a*	*a*	*a*
9	2.9	5.8	1.5	*a*	*a*	*a*
10		2.7	2.7	*a*	*a*	*a*
11	4.6	5.8	~0	4.3	3.6	10.4
13	*a*	*a*	*a*	*a*	*a*	*a*
14	4.6	5.8	~0	2.5	2.0	10.4
16	4.5	*a*	*a*	*a*	*a*	*a*
17	4.1	6.4	*a*	*a*	*a*	*a*
18	3.6	5.0	4.5	*a*	*a*	*a*
19	4.0	*a*	*a*	*a*	*a*	*a*
20		2.7	*a*	*a*	*a*	*a*
21		2.7	*a*	*a*	*a*	*a*
22	4.4	6.1	~0	3.3	3.1	10.2
23	4.9	6.1	~0	3.6	3.6	10.1
24	4.6	6.0	~0	*a*	*a*	*a*
25	4.0	4.3	7.6	4.0	1.9	12.0
26	5.2	*a*	*a*	*a*	*a*	*a*
27	4.7	*a*	*a*	*a*	*a*	*a*
28	4.8	*a*	*a*	*a*	*a*	*a*
30	5.5	*a*	*a*	*a*	*a*	*a*
31	5.5	*a*	*a*	*a*	*a*	*a*

[a] Unresolved.

(2 mL) with efficient stirring. After 15 min, the reaction was worked up as described in the preparation of **17**. After silica gel column chromatography (petroleum ether–EtOAc, 10:1), compound **23** was obtained as a syrup (420 mg).

Anal. Calcd for $C_{32}H_{34}O_7$: C, 72.43; H, 6.46. Found: C, 72.24; H, 6.26.

6-(2,3-*O*-Isopropylidene-5-*O*-trityl-α-D-ribofuranosyl)-2-thiouracil (24) and 6-(α-D-Ribofuranosyl)-2-thiouracil (25). Compound **23** (4.0 g, 7.5 mmol) was reacted with thiourea (4.5 g, 60 mmol) and sodium ethoxide (30 mmol) in the same manner as described in the preparation of **18**. After silica gel column chromatography (benzene–EtOAc, 4:1), compound **24** was isolated as a solid (2.1 g), mp 118–120 °C (ether).

Compound **24** (100 mg) was dissolved in methanol (2 mL) containing 0.5 mL of saturated methanolic HCl. After 5 h, the reaction was worked up in the usual manner to give a solid which crystallized from isopropyl alcohol, giving 40 mg (83.5%) of **25**, mp 214–217 °C dec.

Anal. Calcd for $C_9H_{12}O_5N_2S$: C, 41.53; H, 4.65; N, 10.76; S, 12.32. Found: C, 41.69; H, 4.70; N, 10.50; S, 12.16.

6-(β-D-Ribofuranosyl)uracil (26). To a suspension of compound **19** (650 mg, 2.5 mmol) in water (7.5 mL) was added chloroacetic acid (256 mg, 2.7 mmol). After the mixture was heated to reflux for 2.5 h, concentrated HCl (2.5 mL) was added, and heating was continued for another hour. After being cooled and neutralized by addition of Amberlite IR 45 (OH^-) resin, the mixture was filtered and evaporated to dryness in vacuo. The solid residue was crystallized from methanol to give 505 mg (83%) of **26**: mp 205–207 °C; UV (H_2O) λ_{max} (pH 7) 262 nm (ε 18 680), λ_{min} (pH 7) 228 (ε 2100), λ_{max} (pH 13) 284 (ε 17 850), λ_{min} (pH 13) 243 (ε 3130), λ_{max} (pH 14) 279 (ε 15 650), λ_{min} (pH 14) 246 (ε 4150). This spectral pattern is similar to that of uracil.

Anal. Calcd for $C_9H_{12}O_6N_2$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.23; H, 5.01; N, 11.48.

6-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-thiouracil (28). A mixture of **26** (420 mg, 17 mmol), pyridine (4 mL), and acetic anhydride (4 mL) was stirred at room temperature for 2 h. After the usual workup, the crude product (**27**, 630 mg) was dissolved in dry dioxane (12 mL) and then treated with P_2S_5 (380 mg) in three fractions at 80 °C. After 15 h, the solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (petroleum ether–EtOAc, 1:2) to give pure **28** (608 mg, 92%) as a syrup: UV λ_{max} (MeOH) 332 nm, λ_{max} (1 N NaOH) 345, λ_{min} (1 N NaOH) 285.

Anal. Calcd for $C_{15}H_{18}N_2O_8S$: C, 46.63; H, 4.69; N, 7.24; S, 8.29. Found: C, 46.87; H, 4.74; N, 7.06; S, 8.20.

6-(β-D-Ribofuranosyl)-4-*S*-methyl-4-thiouracil (30). The triacetate **28** (350 mg, 0.9 mmol) was stirred in a 10% methanolic hydrogen chloride solution (10 mL) at room temperature for 1 h. After evaporation of the solvent in vacuo, the residue (crude **29**) was redissolved in methanol (10 mL), and the solution was neutralized with methanolic sodium methoxide. This was followed by addition of 0.7 mmol of sodium methoxide and 0.3 mL of methyl iodide. After 1 h, the reaction solution was neutralized with methanolic hydrogen chloride and evaporated to dryness in vacuo. The residue was purified on a silica gel column (CH_2Cl_2/MeOH, 4:1) to give pure **30** (113 mg, 55%): mp 192–194 °C; UV (H_2O) λ_{max} (pH 7) 302 nm (sh) and 270 (ε 13 350), λ_{min} (pH 7) 302 nm (sh) and 270 (ε 13 350), λ_{min} (pH 7) 240 (ε 1620), λ_{max} (pH 1) 330 (sh), 320 (ε 17 790), and 270 (ε 4220), λ_{min} (pH 1) 285 (ε 3900) and 245 (ε 1950).

Anal. Calcd for $C_{10}H_{14}N_2O_5S$: C, 43.80; H, 5.15; N, 10.22; S, 11.66. Found: C, 43.67; H, 5.14; N, 10.24; S, 11.56.

6-(β-D-Ribofuranosyl)cytosine (31). A solution of **30** (62 mg, 0.22 mmol) in saturated methanolic ammonia (10 mL) was heated in a stainless steel bomb at 70 °C for 3 days. After evaporation of the solvent, the residue was purified on a silica gel column (ethyl acetate/acetone/methanol/water, 6:1:1:1). The fractions containing **31** were combined and evaporated to dryness. The solid residue was redissolved in a small amount methanol and applied to a Dowex AG-50 (H^+) resin column. After elution with water, followed by 6% ammonium hydroxide solution, the fractions containing **31** were combined and evaporated to dryness to give pure **31** as an amorphous solid: mp >200 °C; UV λ_{max} (pH 7) 271 nm (ε 6800), λ_{min} (pH 7) 247 (ε 4380), λ_{max} (pH 1) 279 (ε 9770), λ_{min} (pH 1) 241 (ε 1740), λ_{max} (pH 13) 284 (ε 6690), λ_{min} (pH 13) 251 (ε 1660).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.45; H, 5.39; N, 17.28. Found: C, 44.54; H, 5.34; N, 17.35.

Registry No. **1**, 57016-91-8; **2**, 57016-93-0; **3**, 58109-11-8; **4**, 71948-50-0; **4** hydrochloride, 71912-01-1; **5**, 71912-02-2; **6**, 71912-03-3; **7a**, 58109-15-2; **7b**, 71912-04-4; **8**, 71912-05-5; **9**, 57016-90-7; **10**, 71912-06-6; **11**, 71912-07-7; **12**, 71948-47-5; **13**, 58109-13-0; **14**, 58109-12-9; **16**, 71962-36-2; **17**, 58109-17-4; **18**, 58109-14-1; **19**, 71912-08-8; **20**, 71912-09-9; **21**, 71912-10-2; **22**, 71962-37-3; **23**, 71912-11-3; **24**, 71912-12-4; **25**, 71912-13-5; **26**, 955-13-5; **27**, 71912-14-6; **28**, 71912-15-7; **29**, 71912-16-8; **30**, 71912-17-9; **31**, 71912-18-0; guanidine hydrochloride, 50-01-1; ammonium dithiocarbamate, 513-74-6; potassium thiocyanate, 333-20-0; ethyl chloroformate, 541-41-3; pyrrolidine, 123-75-1; thiourea, 62-56-6.