Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71. Found: C, 63.72; H, 10.68.

2-Methyl-1,2,4-butanetriol (27): colorless oil; ^1H NMR (CD_3COCD_3) δ 1.15 (s, 3 H, CH_3), 1.73 (t, 2 H, CH_2, J = 6 Hz), 3.4 (s, 2 H, CH_2OH), 3.75 (t, 2 H, CH_2OH, J = 6 Hz), 3.95 (br s, 3 H, OH); MS, m/e 89 ($M^+ - CH_2OH$), 87, 75, 71, 69, 57, 31.

Anal. Calcd for $C_5H_{12}O_3$: C, 49.98; H, 10.07. Found: C, 49.93; H, 10.04.

1,3,4-Hexanetriol (28): colorless oil; ^1H NMR (CD_3COCD_3) δ 1 (t, 3 H, CH_3, J = 6 Hz), 1.25–1.85 (m, 4 H, CH_2), 3.1–3.9 (m, 2 H, CHOH), 3.7 (t, 2 H, CH_2OH, J = 6 Hz), 4.55 (br s, 3 H, OH); MS, m/e 103 ($M^+ - CH_2OH$), 71, 43, 31, 30.

Anal. Calcd for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.68; H, 10.49.

1,2,4-Pentanetriol (29): colorless oil; VPC (70 °C) gave an erythro/threo diastereomeric ratio of 95:5. Erythro isomer: t_R = 2.40; ^1H NMR (D_2O) δ 1.2 (d, 3 H, CH_3), 1.65 (t, 2 H, CH_2), 3.4–4.3 (complex pattern, 4 H, CH_2OH, CHOH). Threo isomer: t_R = 2.51; MS, m/e 89 ($M^+ - CH_2OH$), 87, 71, 69, 31, 30.

Anal. Calcd for $C_5H_{12}O_3$: C, 49.98; H, 10.07. Found: C, 49.93; H, 10.04.

2-Methylpentane-1,2,4-triol (30): colorless oil; VPC (90 °C) gave an erythro/threo diastereomeric ratio of 94:6. Erythro isomer: t_R = 4.27; ^1H NMR (CD_3COCD_3) δ 1.15 (d, 3 H, CH_3, J = 6 Hz), 1.2 (s, 3 H, CH_3), 1.4–1.6 (m, 2 H, CH_2), 2.2 (br s, 3 H, OH), 3.4 (d, 2 H, CH_2OH), 3.8–4.4 (m, 1 H, CHOH). Threo isomer: t_R = 4.41; MS, m/e 103 ($M^+ - CH_2OH$), 85, 75, 59, 57.

Anal. Calcd for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.67; H, 10.48.

Acknowledgment. We are grateful to the National Research Council (Centro di Studio per la Fisica delle Macromolecole) for financial support.

Registry No. *cis*-1, 83134-75-2; *trans*-1, 83134-76-3; 2, 83134-77-4; *cis*-3, 83134-78-5; *trans*-3, 83134-79-6; 4, 78947-98-5; 5 (isomer 1), 83134-80-9; 5 (isomer 2), 83134-81-0; *cis*-6, 83134-82-1; *trans*-6, 83134-83-2; 7, 78947-95-2; 8, 78947-94-1; *cis*-9, 82770-18-1; *trans*-9, 82770-17-0; *cis*-10, 83134-84-3; *trans*-10, 83134-85-4; *erythro*-11, 83134-86-5; *threo*-11, 83134-87-6; 12, 4798-68-9; *erythro*-13, 53837-93-7; *threo*-13, 53837-92-6; 14, 872-30-0; *cis*-15, 26828-72-8; *trans*-15, 26828-73-9; *erythro*-16, 29428-56-6; *threo*-16, 29428-57-7; 17, 59954-67-5; 18, 67663-02-9; *erythro*-19, 83134-88-7; *threo*-19, 83134-89-8; *erythro*-20, 83134-90-1; *threo*-20, 83134-91-2; *erythro*-21, 83134-92-3; *threo*-21, 64446-63-5; 22, 36283-98-4; *erythro*-23, 83134-93-4; *threo*-23, 83134-94-5; 24, 25245-58-3; *dl*-25, 13302-87-9; *meso*-25, 2630-65-1; *erythro*-26, 83134-95-6; *threo*-26, 83134-96-7; 27, 62875-07-4; 28, 83134-97-8; *erythro*-29, 83212-31-1; *threo*-29, 83212-32-2; *erythro*-30, 83134-98-9; *threo*-30, 83134-99-0; 31, 83135-00-6; 32, 83135-01-7; 1-hexen-3-ol, 4798-03-2; (*E*)-2-octen-4-ol, 20125-81-9; 2-methyl-1-hepten-3-ol, 13019-19-7; 2-methyl-2-propen-1-ol, 513-42-8; 2-cyclohexen-1-ol, 822-67-3; linalool, 78-70-6; 3-methyl-3-buten-1-ol, 763-32-6; (*Z*)-3-hexen-1-ol, 928-96-1; 4-penten-2-ol, 625-31-0; 4-methyl-4-penten-2-ol, 2004-67-3.

Synthetic Studies of the Thieno[3,2-*d*]pyrimidine *C*-Nucleoside Isostere of Inosine[1]

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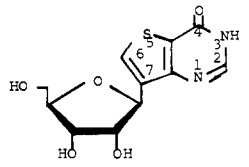
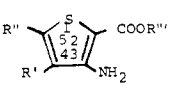
Received May 3, 1982

Synthesis of the thieno[3,2-*d*]pyrimidine *C*-nucleoside isostere of inosine 1β was achieved via a two-step ring closure of C-4 ribosylated methyl 3-aminothiophene-2-carboxylate 11β or, more efficiently, by reaction of 3-aminothiophene-2-carboxamide 14β with triethyl orthoformate. Intermediates 11β and 14β were obtained from common synthetic precursor 3 by reaction with methyl 2-mercaptoacetate or 2-mercaptoacetamide, respectively, and cyclization in base. The corresponding derivatives in the α series were made by identical procedures to confirm all structural assignments.

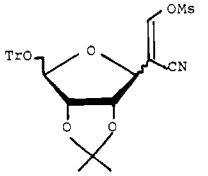
As part of an ongoing program concerned with the synthesis and biological evaluaton of *C*-nucleoside analogues of the natural purine nucleosides, we reported recently the synthesis of several pyrrolo[3,2-*d*]pyrimidine (9-deazapurine) *C*-nucleosides.[2,3] We report here the synthesis of 7-β-D-ribofuranosylthieno[3,2-*d*]pyrimidin-4-(3*H*)-one (1β), the first member of a structurally related, new class of *C*-nucleosides and an isostere of inosine and of formycin B.[4]



1β



2



3

The synthesis of a thieno[3,2-*d*]pyrimidine system was first reported by Gompper et al.[5] A more systematic investigation of this class of heterocycles by several investigators[6-8] was made possible by the development of a practical and versatile approach to their most common synthetic precursors, the 3-amino-2-carbalkoxythiophenes 2 by reaction of α,β-dichloropropionitriles with 2-mercaptoacetate esters in base.[9] Continued interest in these thienopyrimidines has been generated mainly by the wide spectrum of pharmacological activity discovered for

(1) This investigation was supported by funds from the National Cancer Institute, DHHS (Grants CA-08748, -18856, and -24634) and from the American Cancer Society (Grant CH-169).

(2) Lim, M.-I.; Klein, R. S.; Fox, J. J. *Tetrahedron Lett.* **1980**, *21*, 1013.

(3) Lim, M.-I.; Klein, R. S. *Tetrahedron Lett.* **1981**, *22*, 25.

(4) Presented in part at the 180th National Meeting of the American Chemical Society, Aug, 1980, San Francisco, CA, Aug 24–29, 1980, American Chemical Society, Washington, DC, 1980, Abstr MEDI 87.

(5) Gompper, R.; Kutter, E.; Töpfl, W. *Liebigs Ann. Chem.* **1962**, *659*, 90.

(6) (a) Robba, M.; Lecomte, J. M.; Cuguon de Sevricourt, M. *Bull. Soc. Chim. Fr.* **1970**, 3630. (b) *Tetrahedron* **1971**, *27*, 487. (c) *C. R. Hebd. Seances Acad. Sci., Ser. C* **1968**, *267*, 697.

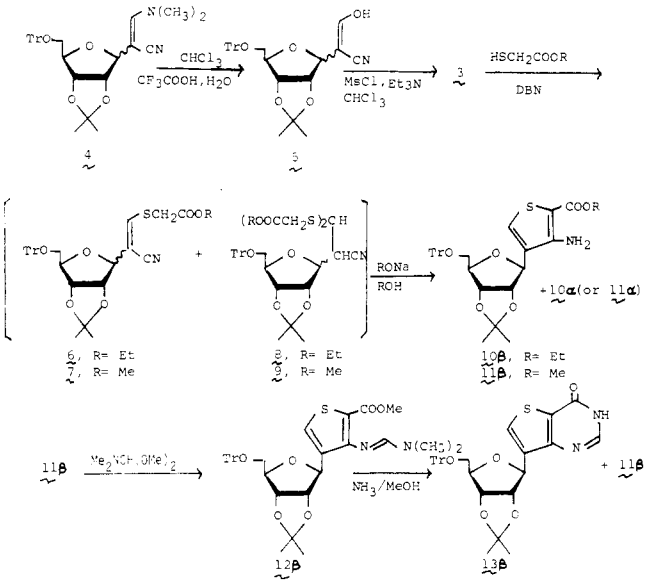
(7) (a) Ried, W.; Giesse, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 136. (b) *Liebigs Ann. Chem.* **1968**, *713*, 143. (c) Ried, W.; Kahr, E. *Ibid.* **1968**, *716*, 219.

(8) Gronowitz, S.; Fortea-Laguna, J.; Ross, S.; Sjoberget, B.; Stjernstrom, N. E. *Acta. Pharm. Suec.* **1968**, *5*, 563.

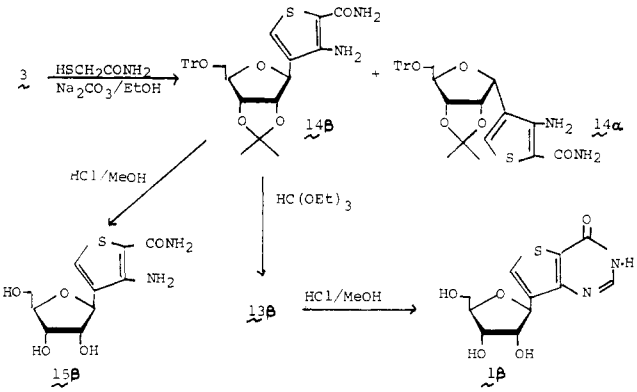
(9) Fiesselmann, H. *Angew. Chem.* **1959**, *71*, 377. German Patent 1 055 007; *Chem. Abstr.* **1961**, *55*, P6497c. British Patent 837 086, Farbwerke Hoechst Akt.-Ges. vorm. Meister Lucius and Brüning; *Chem. Abstr.* **1960**, *54*, P24798e.

0022-3263/82/1947-4633$01.25/0

Scheme I



Scheme II



many of their derivatives.[10]

A synthetic equivalent to the prerequisite α,β-dichloropropionitrile of Fiesselmann's approach[9] to a ribosylated 3-amino-2-carbalkoxythiophene **2** (R′ = D-ribofuranosyl) is represented by enol mesylate ribofuranosyl derivative **3**,[2] readily obtained from 3-(dimethylamino)-acrylonitrile **4**[11] by mild acid hydrolysis,[2,3] followed by O-mesylation of the 2-formylacetonitrile intermediate **5**[2] (Scheme I).

In a preliminary study, we observed that treatment of **3** with ethyl 2-mercaptoacetate in chloroform at 0 °C with an equivalent amount of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) afforded a complex mixture of products. After partial separation by silica gel column chromatography, several isomers of **6**, together with two isomeric diadducts **8**,[12] could be identified. Treatment of this mixture with sodium ethoxide in ethanol at room temperature afforded two major products only. These were readily separable by column chromatography and identified as methyl 3-amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)thiophene-2-carboxylate (**10**β) and its α-isomer **10**α. These were obtained in moderate overall yields (from **4**) but with an unfavorable ratio of $\alpha/\beta > 7$. Modification of this procedure by utilization of methyl 2-mercaptoacetate under identical conditions afforded (after treatment of the initial mixture of products with sodium methoxide in methanol) the corresponding crystalline methyl 3-aminothiophene-2-carboxylate *C*-nucleoside (**11**β) and its α isomer (**11**α) in an improved ratio of $\alpha/\beta \simeq 3{:}2$ (33% overall yield from **4**).

Our initial approach to the cyclization of the second (fused pyrimidine) ring was based on a procedure we had utilized successfully for the synthesis of 9-deazainosine.[2] Thus, treatment of **11**β with DMF–dimethyl acetal[13] afforded the expected dimethylaminomethylenimine derivative **12**β. Because of its relative instability, this intermediate was used immediately after workup. Cyclization of **12**β with saturated methanolic ammonia (70 °C, 3 days) gave the blocked inosine analogue **13**β (47% yield) but, unlike the case of the 9-deazainosine, led also to ammonolysis of the enamine N=C bond and partial recovery of **11**β (20%). Alternative approaches to **13**β were therefore sought. Of particular interest were a number of general procedures reported for cyclization of 3-amino-2-carbalkoxythiophene derivatives to the corresponding thieno[3,2-*d*]pyrimidines (e.g., boiling formamide;[7,9] treatment of the *N*-formyl derivative with ammonia).[6] Attempts to apply several of these approaches to **11** (α or β), however, met with little success.

An alternative approach to inosine analogue **13**β that would make use of the 3-amino-2-carboxamide derivative **14**β (Scheme II) by reaction with dielectrophiles[14] was next studied. Direct ammonolysis of ester **11**β under a variety of conditions (including saturated ammonia in methanol at 70 °C in a sealed vessel) was unsuccessful and led only to recovery of starting material. Analogous results were obtained with **2** (R′ = R″ = H; R‴ = Me), which was found to be inert to the action of sodamide in ammonia. The desired blocked carboxamide derivative **14**β (together with its α isomer) was finally obtained by primary synthesis from the treatment of mesylate **3** with freshly prepared 2-mercaptoacetamide in boiling ethanol and in the presence of sodium carbonate under nitrogen.[15] The isomeric pair **14**α, **14**β (~85% overall yield form **4**, $\beta/\alpha \sim 1$) was readily separable by silica gel column chromatography. Unblocking of **14**β with 6% methanolic hydrogen chloride afforded the AICA riboside[27] analogue **15**β as a crystalline hydrochloride salt in 95% yield. Facile ring closure of **14**β by treatment with hot (80 °C) triethyl orthoformate finally afforded the blocked inosine analogue **13**β in better yields (86%) than was obtained by ammonolysis of **12**β (Scheme II). Because of its convenience and efficiency, the synthetic route outlined in Scheme II has been adopted as our method of choice for the preparation of thieno[3,2-*d*]pyrimidin-4(3*H*)-one *C*-nucleosides. Unblocking of **13**β with methanolic hydrogen chloride finally led to the isolation of **1**β as its hydrochloride salt (88%).

An identical set of transformations was carried out starting from the corresponding α-isomer **14**α. Thus, methanolysis of **14**α afforded the unblocked C-4 α-ribo-

(10) Karl Thomae, G.m.b.H British Patent 1 057 612; *Chem. Abstr.* **1967**, *67*, P100149*g*. See also *Chem. Abstr.* **1971**, *74*, P125725*z*; *75*, P110329*v* and P110332*v*; **1972**, *76*, P99698*n* and P140866*f*; **1972**, *77*, P48495*g*, P34552*m*, P34553*n*, P88539*f*, and P88540*z*; **1973**, *78*, P72184*w* and P124620*g*; **1974**, *81*, P63656*m*. Zimmer, A.; Prox, A.; Pelzer, H.; Haukwitz, R. *Biochem. Pharmacol.* **1973**, *22*, 2213.

(11) De Bernardo, S.; Weigele, M. *J. Org. Chem.* **1977**, *42*, 109.

(12) Evidence for the formation of such diadducts was obtained from the similar ^{1}H NMR of two of the products. Only one of these could be purified further by crystallization. Its ^{1}H NMR exhibited the following: at δ 1.20–1.50, two methyl singlets (H_3C–C–CH_3) and two overlapping triplets (COO–CH_2–CH_3); at δ 3.46, two methylene singlets (S–CH_2–CO) and a quartet centered at δ 4.18, which integrated for *two* methylene ester groups (COO–CH_2–CH_3).

(13) Utilization of formamide acetals as formylating agents of carbon and nitrogen has been reviewed recently: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron.* **1979**, *35*, 1675.

(14) Lister, J. H. "Fused Pyrimidines, Part II, Purines"; Brown, D. J., Ed.; Wiley-Interscience: New York; 1971; Chapter III.

(15) Schneller, S. W.; Clough, F. W. *Heterocycles* **1975**, *3*, 135.

Table I. 100-MHz Proton Chemical Shifts (ppm)

compd	solvent[a]	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	H-2	H-6[b]	other
11α	A	5.18 (d)	4.96 (dd)	4.78 (d)	4.33 (dd)[c]	3.32 (m)				1.32 and 1.45 (2 s, isopropylidene), 3.73 (s, CH_3), 7.38 (m, trit and H-5), 5.91 (br s, NH_2)
11β	A		4.76 (m)		4.23 (m)	3.39 (m)				1.35 and 1.59 (2 s, isopropylidene), 3.81 (s, CH_3), 7.34 (m, trit and H-5), 5.92 (br s, NH_2)
13α	A	5.70 (d)	5.10 (dd)	4.78 (d)	4.40 (dd)[c]	3.31 (m)		8.16 (s)	7.97 (s)	1.27 and 1.39 (2 s, isopropylidene), 7.38 (m, trit), 11.8 (s, NH)
13β	A	5.49	4.95 (dd)	4.73 (dd)	4.39 (m)	3.31 (m)		8.15 (s)	7.81 (s)	1.37 and 1.63 (2 s, isopropylidene), 7.37 (m, trit), 11.9 (s, NH)
14α	A	5.19 (d)	4.96 (dd)	4.79 (d)	4.33 (dd)[c]	3.34 (m)				1.33 and 1.46 (2 s, isopropylidene), 5.19 and 6.03 (2 br s, NH_2's), 7.34 (m, trit and H-5)
14β	A		4.75 (m)		4.21 (m)	3.38 (m)				1.34 and 1.59 (2 s, isopropylidene), 5.25 and 6.11 (2 br s, NH_2's), 7.31 (m, trit)
15α	B	4.86 (d)		4.08 (m)	3.77 (m)	3.54 (m)				7.26 (s, H-5), 6.81 and 6.32 (2 br s, NH_2's), 4.67–4.8 (m, OH's exch with D_2O)
15β	B	4.58 (m)[d]	3.94 (m)		3.80 (m)	3.55 (m)				7.37 (s, H-5), 6.09 (m, OH's and NH_2's exch with D_2O)
1α	B	5.24 (d)	4.20 (m)		3.94 (m)	3.58 (m)		8.19 (s)	7.92 (s)	5.5–7.9 (m, OH's and NH, exch with D_2O)
1β	B	4.97	4.15 (dd)	3.92 (m)		3.57 (m)		8.25 (s)	8.17 (s)	5.5–7.5 (m, OH's and NH, exch with D_2O)

[a] A, $CDCl_3$; B, Me_2SO-d_6. [b] Allylic coupling (<1 Hz) with H-1′ is observable. [c] Apparent triplet.[26] [d] Virtual coupling between H-1′ and H-3′ is the cause of multiplicity.

Table II. First-Order Coupling Constants (Hz)

compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5',5'b}$
11α	3.7	5.8	<1	*a*	*a*	*a*
11β	*a*	*a*	*a*	3.3	3.7	−10.3
13α	4.3, *b*	6.1	<1	4.3	4.9	−10.0
13β	2.8, *b*	6.4	3.4	5.5	4.9	−11.0
14α	4.0	6.0	<1	3.7	4.1	−10.1
14β	*a*	*a*	*a*	3.2	4.0	−10.4
15α	2.0, *b*	*a*	*a*	*a*	4.7	−11.6
15β	*a*, *b*	*a*	*a*	*a*	*a*	*a*
1α	1.8, *b*	*a*	*a*	2.2	4.6	−12.0
1β	5.8, *b*	4.9	*a*	3.7	4.2	−10.5

[a] Unresolved. [b] Allylic coupling (<1 Hz) between aromatic thiophene proton and H-1′ was observed.

sylated 3-aminothiophene-2-carboxamide **15α**, while ring closure of **14α** in hot triethyl orthoformate, followed by deblocking with methanolic hydrogen chloride, gave the α-*C*-nucleoside **1α**. All yields were comparable to those obtained in the β series.

Structural assignments for the heterocyclic bases of *C*-nucleosides **1α**, **1β**, **15α**, and **15β** were confirmed by the close similarity of the ultraviolet spectra of **1α** and **1β** to that of thieno[3,2-*d*]pyrimidin-4(3*H*)-one[16] and of **15α** and **15β** to that of 3-amino-5-methylthiophene-2-carboxamide[17] (see Experimental Section).

Examination of the ^1H NMR spectra of **13α**, **13β**, **1α**, and **1β** (Table I) showed a small allylic coupling (<1 Hz) between the most shielded of the two aromatic protons and H-1′, consistent with their assignment as H-6. Additional confirmation was obtained in the case of inosine analogue **1β** from spin–lattice relaxation time (T_1) measurements. These showed that the proton giving rise to the signal at δ 8.17 (coupled with H-1′) has a smaller T_1 value than that at δ 8.25,[18] which is consistent with the closer proximity of H-6 to the protons of the ribosyl moiety.

Assignments of the epimeric configuration at C-1′ to all *C*-nucleosides are based on a comparison of the ^1H NMR of both epimers in the α,β epimeric pairs **1**, **11**, **13**, **14**, and **15** (see Table I). As has been observed with α- and β-*N*-nucleosides,[19] the chemical shifts of the H-1′ are consistently further downfield for the α anomers than for the corresponding β anomers. This relationship also holds true for all *C*-nucleosides, as has been found in the cases of the α,β epimers of ψ-uridine,[20] pyrazomycin,[21] and other purine-like *C*-nucleosides.[2,3,22] Furthermore, the β isomers in pairs **11**, **13**, and **14** exhibit larger Δδ numerical values for the difference in chemical shifts of their isopropylidene geminal dimethyl groups than do their corresponding α isomers.[23]

Inosine analogue **1β** was found to possess significant growth inhibitory activity against P-815 and L1210 leuk-

(16) Prepared from known **2** (R′ = R″ = H; R‴ = Me)[9] by treatment with DMF–dimethyl acetal and subsequent ring closure of the dimethylaminomethylenimine intermediate with methanolic ammonia. This product was found to be identical in all respects with that previously reported.[6]

(17) Obtained by reaction of 1-cyano-2-methylacetylene with the sodium salt of 2-mercaptoacetamide in THF at −75 °C. This novel general approach to functionalized thiophenes will be reported elsewhere.

(18) This technique has been useful in distinguishing between H-8 and H-2 resonances in adenosine nucleotides: Ts'o, P. O. P.; Barrett, J. C.; Kan, L. S.; Miller, P. S. *Ann. N.Y. Acad Sci.* **1973**, *222*, 290.

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(21) De Bernardo, S.; Weigele, M. *J. Org. Chem.* **1976**, *41*, 287.

(22) Tam, S. Y.-K.; Klein, R. S.; Wempen, I.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4547.

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

emic mouse cell lines (ID_{50} = 2.5 and 3.3 μg/mL, respectively). Unblocked intermediate **15β** was much less active in these same systems (ID_{50} = 56 and 9 μg/mL).[24]

The synthesis of several other members of this new class of purine-like *C*-nucleosides will be reported in the near future.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The ^1H 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 Model 15 and a Unicam Model SP-800A recording spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, and Galbraith Laboratories, Knoxville, TN. Flash column chromatography was performed on Merck silica gel (230–400 mesh ASTM). Thin-layer chromatography was performed on 250-μm silica gel plates (Analtech, Inc.), and substances were visualized by UV absorption and by spraying with 20% ethanolic sulfuric acid and charring.

3-(Methanesulfonyloxy)-2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-D-ribofuranosyl)acrylonitrile (3). To a solution of 24 g (46.6 mmol) of dimethylaminoacrylonitrile (**4**)[11] in chloroform (800 mL) was added a solution of trifluoroacetic acid (12 mL) in water (500 mL). The reaction mixture was stirred vigorously for 16 h at room temperature and washed thoroughly with water. The organic layer was then dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated to dryness in vacuo to afford 2-formylacetonitrile (**5**)[2,25] as a foam. Without further purification, **5** was dissolved in 160 mL of chloroform containing 8.30 mL of triethylamine and treated dropwise with a solution of 4.22 mL (54 mmol) of methanesulfonyl chloride in 160 mL of chloroform at 0 °C with efficient stirring. After 1 h at 0 °C, the reaction mixture was diluted to 500 mL with chloroform and washed well with brine. The organic layer was dried over sodium sulfate and evaporated to dryness to give a crude anomeric mixture of **3** obtained as a foam (22 gm). A small sample of the mixture was separated by preparative TLC (Analtech, 500 μm, benzene/ethyl acetate: 10:1), and each of the two bands (visible under UV light) was eluted with ethyl acetate. ^1H NMR of the slower-moving component exhibited a doublet for H-1′ at δ 5.45 ($J_{1',2'}$ = 4.3 Hz), a pseudotriplet for H-4′[26] at δ 4.35, and *one* sharp singlet for the mesyloxy group at δ 2.95. ^1H NMR of the faster band indicated the presence of two components (two mesyloxy signals at δ 3.20 and 3.14). No H-1′ resonance was observed between the trityl multiplet (δ 7.24–7.41) and δ 4.96. On the basis of the chemical shifts of the H-1′ and appearance of the H-4′ signal of the single component in the slow-moving band, the latter has been tentatively identified as an α epimer of **3**, while the faster-moving band is believed to contain both *E* and *Z* β epimers. (3β/3α ~10:1 by weight). Because of its relative instability, the crude material was utilized directly in the following step.

Methyl 3-Amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α- and -β-D-ribofuranosyl)thiophene-2-carboxylate (11α and 11β). To a cooled (0 °C) solution of **3** (22 g, 39 mmol) in 220 mL of chloroform was added DBN (22 mL, 177 mmol) and methyl 2-mercaptoacetate (22 mL, 179 mmol). The reaction mixture was stirred at 0 °C for 2 h and then washed with 0.1 N HCl (200 mL) and finally with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to give a mixture of **7** and **9**. The residue was dissolved in 220 mL of a 0.43 M solution of sodium methoxide in methanol, and the reaction mixture was allowed to stand at room temperature. After complete cyclization (1 h), the clear solution was evaporated in vacuo, and the residue was dissolved in chloroform. This was extracted wth brine, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo. The crude α,β anomeric mixture thus obtained was separated by column chromatography with toluene–ethyl acetate as eluent (10:1) to give first 3.4 g of **11β** as colorless crystals, mp 135–137 °C. One recrystallization from chloroform–petroleum ether gave an analytically pure sample.

Anal. Calcd for $C_{33}H_{33}NO_6S$: C, 69.34; H, 5.82; N, 2.45. Found: C, 69.37; H, 5.94; N, 2.53.

Later fractions afforded 5.2 g of **11α**, which was obtained as a syrup and identified by ^1H NMR and mass spectroscopy: ms, *m/e* 573 $(M + 1)^+$. The combined overall yield of **11** (α and β) from **4** (crystalline α isomer) was 33% (11α/11β ~3:2).

3-Amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α- and -β-D-ribofuranosyl)thiophene-2-carboxamide (14α and 14β). To a suspension of 3-(mesyloxy)acrylonitrile (**3**; 6.0 g, 10.7 mmol) in 180 mL of absolute ethanol was added 2-mercaptoacetamide (1.5 g, 16.4 mmol) and anhydrous sodium carbonate (1.7 g, 16.0 mmol). The reaction mixture was heated to reflux with stirring for 18 h under a nitrogen atmosphere, allowed to cool to room temperature, and filtered. The filtrate was evaporated to dryness in vacuo, and the residue containing the isomers 14α and 14β was chromatographed on a column of silica gel with toluene–ethyl acetate (20:1). This separation afforded pure 3-amino-2-carboxamido β-isomer **14β** as a foam (2.62 g) and the pure α-isomer **14α** also as a foam (2.94 g). The combined overall yield of **14** (α and β) was 85%.

Anal. Calcd for $C_{32}H_{32}N_2O_5S$ (**14α**): C, 69.04; H, 5.79; N, 5.03; S, 5.75. Found: C, 68.74; H, 5.73; N, 4.67; S, 5.47.

Anal. Calcd for $C_{32}H_{32}N_2O_5S$ (**14β**): C, 69.04; H, 5.79; N, 5.03; S, 5.75. Found: C, 68.72; H, 5.71; N, 4.92; S, 5.61.

3-Amino-4-β-D-ribofuranosylthiophene-2-carboxamide (15β). The blocked thiophene **14β** (180 mg, 0.32 mmol) was dissolved in 5 mL of the 6% methanolic solution of hydrogen chloride and allowed to react at room temperature for 2.5 h. The mixture was then evaporated to dryness in vacuo, and the residue was crystallized from a mixture of methanol and acetonitrile to give an analytically pure sample of **15β** as its hydrochloride salt (95 mg, 95%): mp 178 °C dec; UV λ_{max} (pH 7–10) 308 nm (ε 7900), 265 (6800); λ_{min} (pH 7–10) 282 nm (ε 4900); λ_{max} (pH 1) 305 nm (ε 3400), 242 (5900); λ_{min} (pH 1) 292 nm (ε 2900); inflection at 255 nm (ε 5700). This UV pattern bore close similarity to that of 3-amino-5-methylthiophene-2-carboxamide:[17] UV λ_{max} (pH 7–10) 305 nm (ε 4900), 267 (6100); λ_{min} (pH 7–10) 285 nm (ε 3900); λ_{max} (pH 1) 272 nm (ε 5900); inflections at 310 (ε 850) and 258 nm (ε 4700).

Anal. Calcd for $C_{10}H_{14}N_2O_5S$·HCl: C, 38.65; H, 4.86; N, 9.01; S, 10.31. Found: C, 38.48; H, 4.90; N, 8.88; S, 10.20.

3-Amino-4-α-D-ribofuranosylthiophene-2-carboxamide (15α). Unblocking of the α-isomer **14α** by an identical procedure afforded **15α** as a crystalline monohydrochloride: mp 110–112 °C with ultraviolet properties identical with those of **15β**.

Anal. Calcd for $C_{10}H_{14}N_2O_5S$·HCl: C, 38.65; H, 4.86; N, 9.01; S, 10.31; Cl, 11.40. Found: C, 38.61; H, 4.99; N, 9.13; S, 10.08; Cl, 11.48.

7-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (13β). (a) From 14β. To a suspension of the 3-aminothiophene-2-carboxamide **14β** (3.5 g, 6.29 mmol) in 20 mL of triethyl orthoformate was added 1 g of finely ground molecular sieve (4Å). The reaction mixture was heated at 95 °C and stirred for 24 h. After cooling to room temperature, it was filtered, and to the clear filtrate was added 10 mL of petroleum ether (40–60 °C) to precipitate the desired product as a white solid. This was collected by filtration, pressed into a cake, washed with petroleum ether, and dried in vacuo. This procedure afforded **13β** (2.0 g, 56%) as a white crystalline material, mp 128–130 °C.

Anal. Calcd for $C_{33}H_{30}N_2O_5S$: C, 69.94; H, 5.33; N, 4.94; S, 5.65. Found: C, 69.77; H, 5.42; N, 4.81; S, 5.61.

(b) From 11β. *o*-Amino ester **11β** (2.18 g, 3.8 mmol) was added to 4 mL (30 mmol) of *N,N*-dimethylformamide dimethyl acetal (DMF–DMA), and the mixture was heated at 90 °C with stirring for 20 h. The clear solution was evaporated to dryness under high vacuum to give dimethylaminomethylenimine intermediate **12β**

(24) The authors are indebted to Dr. Joseph H. Burchenal of this Institute for the communication of these results.

(25) Chu, C. K.; Watanabe, K. A.; Fox, J. J. *J. Heterocycl. Chem.* **1980**, *17*, 1435.

(26) Occurrence of the H-4′ signal as an apparent triplet in epimeric pairs of 2′,3′-*O*-isopropylidene ribonucleosides[26a] and *C*-ribonucleosides[26b,11] has been shown to belong to the α isomer: (a) MacCoss, M.; Robins, M. J.; Rayner, B.; Imbach, J. L. *Carbohydr. Res.* **1977**, *59*, 575. (b) Cousineau, T. J.; Secrist, III, J. A. *J. Org. Chem.* **1979**, *44*, 4351. Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.

(27) Abbreviated form of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide, which is a constituent of AICA ribotide, a biosynthetic precursor of purine nucleotides.

(2.2 g) as a clear syrupy material, which was homogeneous by TLC (toluene–ethyl acetate, 4:1, R_f 0.4). Further purification by chromatography was precluded by the relative instability of the methylenimine function to prolonged contact with silica gel. Intermediate 12β was therefore utilized immediately after evaporation of DMF–DMA and treated with 50 mL of methanolic ammonia (previously saturated at 0 °C) at 70 °C for 3 days in a sealed vessel. After evaporation of the final reaction mixture in vacuo, the residue containing 13β was separated by chromatography with toluene–ethyl acetate (4:1) as the eluent. Evaporation of several early fractions allowed recovery of 433 mg of *o*-amino ester precursor 11β. Further elution afforded 1.02 g of the desired 13β (47% yield from 11β) as a white crystalline product (mp 128–130 °C) identical in all respects with that obtained via 14β.

7-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-α-D-ribofuranosyl)-thieno[3,2-*d*]pyrimidin-4(3*H*)-one (13α). This compound was obtained by treatment of 14α with triethyl orthoformate under conditions identical with those utilized for the synthesis of 13β from 14β. This procedure afforded 13α in 37% yield as a white crystalline material, mp 207–210 °C.

Anal. Calcd for $C_{33}H_{30}N_2O_5S$: C, 69.94; H, 5.33; N, 4.94; S, 5.61. Found: C, 69.68; H, 5.54; N, 4.79; S, 5.50.

7-β-D-Ribofuranosylthieno[3,2-*d*]pyrimidin-4(3*H*)-one Hydrochloride (1β). A mixture of compound 13β (5.8 g, 10.2 mmol) in 50 mL of a 6% solution of hydrogen chloride in methanol was stirred at 20 °C for 20 min, and 120 mL of diethyl ether was then added to form a white precipitate. After 1 h, the crystalline product was filtered and washed with ether to give 2.56 g (88%) of the desired unblocked 1β as an analytically pure monohydrochloride salt: mp 211–214 °C; UV λ_{max} (pH 7) 288 nm (ε 7000), 238 (16 000); λ_{min} (pH 7) 258 nm (ε 5000); inflections at 300 nm (ε 5000) and 282 (6200); λ_{max} (pH 14) 293 nm (ε 7500), 238 (15 000); λ_{min} 270 nm (ε 4800); inflections at 303 nm (ε 5400), 285 (6900), and 255 (6400); λ_{max} (pH 0) 273 nm (ε 7500) and 248 (15 800); λ_{min} (pH O) 265 nm (ε 7400); inflection at 287 nm (ε 6000). These UV spectra bore a close similarity to those of 4-oxo-3*H*-thieno[3,2-*d*]pyrimidine:[16] λ_{max} (pH 7) 288 nm (ε 6200) and 236 (15 600); λ_{min} (pH 7) 253 nm (ε 4300); inflections at 300 nm (ε 3900) and 278 (5600); λ_{max} (pH 14) 293 nm (ε 7000) and 235 (16 700); λ_{min} (pH 14) 267 nm (ε 4300); inflections at 302 nm (ε 4800), 285 (6200), and 251 (6700); λ_{max} (pH 0) 270 nm (ε 9100) and 243 (20 500); λ_{min} (pH 0) 262 nm (ε 8900); inflection at 283 nm (ε 7000).

Anal. Calcd for $C_{11}H_{12}N_2O_5S$·HCl: C, 41.19; H, 4.08; N, 8.73; S, 9.99. Found: C, 41.59; H, 4.10; N, 8.65; S, 9.85.

7-α-D-Ribofuranosylthieno[3,2-*d*]pyrimidin-4(3*H*)-one (1α). This compound was obtained by deblocking of 13α in 6% methanolic HCl as above described for 1β. Crystallization of the product from a mixture of methanol/acetonitrile/ether afforded 1α (84% yield) as a colorless crystalline material (mp 182–183 °C), which analyzed correctly as a monohydrate.

Anal. Calcd for $C_{11}H_{12}N_2O_5S$·H_2O: C, 43.70; H, 4.66; N, 9.26; S, 10.60. Found: C, 43.77; H, 4.64; N, 9.26; S, 10.64.

Acknowledgment. We thank Marvin Olsen for recording the ^{1}H NMR spectra.

Registry No. 1β, 83232-27-3; 1α, 83248-17-3; α-**3**, 74458-03-0; (*E*)3β, 83289-75-2; (*Z*)-3β, 83289-76-3; **4**, 83289-74-1; **5**, 83348-75-8; **7**, 83232-17-1; **9**, 83248-80-0; 11β, 83232-18-2; 11-α, 83232-19-3; 12β, 83232-25-1; 13β, 83232-24-0; 13α, 83232-26-2; 14α, 83232-20-6; 14β, 83232-21-7; 15β·HCl, 83232-22-8; 15α·HCl, 83232-23-9; methyl 2-mercaptoacetate, 2365-48-2; 2-mercaptoacetamide, 758-08-7; triethyl orthoformate, 122-51-0; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5.

A Regiospecific Interaction of Meta-Substituted Diarylamines and Phosphorus Trichloride[1]

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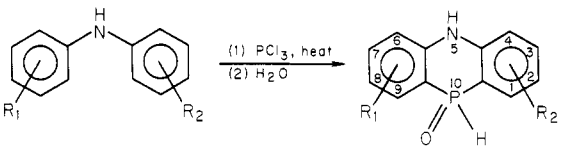
Received May 28, 1982

The effect of meta substituents and meta-directing groups on the uncatalyzed interaction of diarylamines and phosphorus trichloride at elevated temperatures has been investigated. The results show that the presence of *m*-trifluoromethyl groups on both aromatic rings prevents the formation of a dihydrophenophosphazine derivative. Each of the other diarylamines reacted in a regiospecific way to give a single derivative of this ring system. The structures of these compounds were unambiguously determined with the aid of ^{1}H NMR spectroscopy.

Previous papers[2] have described the synthesis of dihydrophenophosphazine oxides 1 via the interaction of diarylamines and phosphorus trichloride (cf. Scheme I). Although 11 amines were employed in these studies, none of the compounds contained a meta-directing group or a group meta to the nitrogen atom. The effect of such groups is of considerable interest, since a meta-directing group would be expected to inhibit (or even prevent) the required electrophilic attack on the aromatic rings, while the presence of a meta substituent introduces the possibility for the formation of isomeric products.

The interaction of meta-substituted diarylamines and arsenic trichloride has already been employed for the synthesis of dihydrophenarsazine derivatives.[3] In most cases the reaction product appeared to be homogeneous, but the orientation of the substituent with respect to the

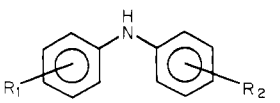
Scheme I[a]



1

[a] R_1,R_2 = H, Me, Cl, or benzo.

Chart I. Diarylamines Studied



2a, R_1 = 3-CF_3; R_2 = H
b, R_1 = 3-Me; R_2 = H
c, R_1 = 3-Me; R_2 = 3-CF_3
d, R_1 = 3-CF_3; R_2 = 3-CF_3
e, R_1 = 3,5-Me_2; R_2 = H

(1) Abstracted from the Ph.D. Thesis of H. S. Freeman and the M.S. Thesis of M. A. Muftah, North Carolina State University, 1981. Presented in part at the International Conference on Phosphorus Chemistry, Durham, NC, June 1–5, 1981; cf. Freeman, H. S.; Freedman, L. D. *ACS Symp. Ser.* **1981**, *no. 171*, 291.

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