was recovered which was subjected to silica gel column chromatography with solvent C. Previously described 11 and 12 were obtained, 66 mg (22%) and 105 mg (38%), respectively.

Base-Catalyzed Isomerization of α-(4',6'-Di-*O*-acetyl-2',3'-dideoxy-α-D-*erythro*-hex-2'-enopyranosyl)acetophenone (12). The α-*C*-glycoside 12 (78 mg, 0.23 mmol) was dissolved in dry benzene (10 mL), potassium *tert*-butoxide (ca. 5 mg, 0.04 mmol) was added, and the solution was stirred at 23 °C for 6 h. TLC of the reaction mixture showed no decomposition and little, if any, change after the initial 4-h period. The reaction mixture was poured into water, and the aqueous phase was extracted with methylene chloride. The methylene chloride extract was washed (water), dried (Na_2SO_4), and concentrated to an oil (60 mg), which was separated by column chromatography (solvent C) to yield two homogeneous (TLC) fractions. The less polar fraction (R_f 0.47 (C); 25.5 mg, 33%) was found to be identical with the β-*C*-glycopyranoside 11. The other fraction (R_f 0.04 (C); 25 mg, 32%) was shown by ^1H NMR to consist of approximately equal amounts of starting material 12 and an isomeric compound (or compounds). This mixture could not be resolved by TLC.

Acknowledgment. We are grateful to the National Sciences and Engineering Research Council of Canada for financial support.

Synthesis of 3-Glycofuranosyl-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thiones: Thioguanosine-Type *C*-Nucleosides

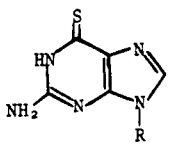
Edward M. Acton* and Kenneth J. Ryan

Bio-Organic Chemistry Laboratory, SRI International, Menlo Park, California 94025

Received July 25, 1983

The first *C*-nucleosides of the thioguanosine type are the 3-β-D-ribofuranosyl, 3-β-D-arabinofuranosyl, and 3-(2-deoxy-β-D-*erythro*-pentofuranosyl) derivatives of 5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione. Synthesis of these products employed $C_6H_5CH_2SC(Cl)=NCOC_6H_5$ as a new reagent for ring closure of the 3-glycofuranosyl-4-aminopyrazole-5-carbothioamide precursors. The new ring closure requires fewer steps and minimizes side reactions encountered in previous guanosine ring closures. The amino thioamide precursors are prepared from pyrazole *C*-nucleosides available as in previous formycin syntheses.

The furanosides of thioguanine (1) make up a series of synthetic nucleosides (2) that have consistently shown



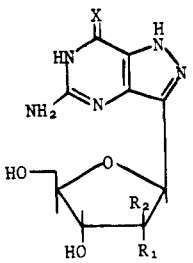
1, R = H

2, R = glycofuranosyl

2a, R = β-D-ribofuranosyl

2b, R = 2-deoxy-β-D-erythro-pentofuranosyl

2c, R = 2-deoxy-α-D-erythro-pentofuranosyl



3, X = O; R_1 = OH, R_2 = H (ribo)

4, X = S; R_1 = OH, R_2 = H (ribo)

5, X = S; R_1 = H, R_2 = OH (arabino)

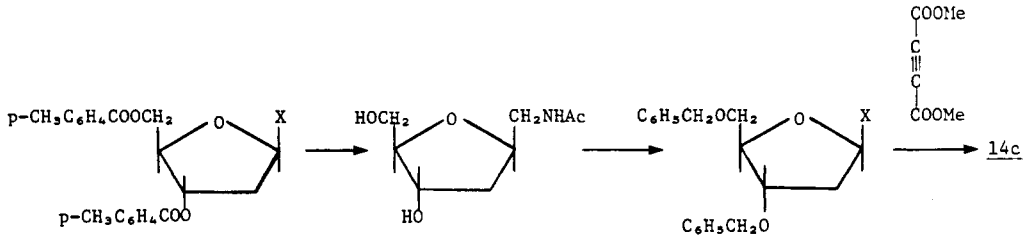
6, X = S; R_1 = R_2 = H (2-deoxy)

antitumor activity.[1-4] Almost invariably, however, 2 undergo biological cleavage at the nucleoside bond and are to some extent produgs of 1. This produces thioguanine toxicity and cross-resistance in addition to the antitumor effects and frustrates the potential advantage of the nucleoside over 1. These specifically were limitations encountered in the clinical trial[5] of thioguanosine[6] (2a) and more recently[7] of β-2'-deoxythioguanosine (2b)[8,9] which was designed[10] as a more proximate precursor of DNA incorporation in order to overcome these problems. The synthetic byproduct, α-2'-deoxythioguanosine (2c),[8] was an unusual nucleoside not only because it was an active α anomer but also because it was resistant to nucleoside cleavage, permitting high doses to be used in animals and in clinical trials.[11] Because it appears that absence of cleavage could provide distinct advantages, the inherently noncleavable *C*-nucleosides are analogues of interest. Despite this, no *C*-nucleoside related to thioguanine has previously been synthesized. There are only a handful of examples, recently reported,[12,13] that are related even to

(1) Goldin, A.; Wood, H. B., Jr.; Engle, R. R. *Cancer Chemother. Rep., Part 2, Suppl.* **1968**, *1*, 207.
(2) Kaneko, T.; LePage, G. A. *Cancer Res.* **1970**, *30*, 699.
(3) Acton, E. M.; Goerner, R. N.; Uh, H. S.; Ryan, K. J.; Henry, D. W.; Cass, C. E.; LePage, G. A. *J. Med. Chem.* **1979**, *22*, 518.
(4) Unpublished screening data from the National Cancer Institute on NSC 102635 (3'-deoxy-6-thioguanosine), NSC 106540 (3'-O-methyl-6-thioguanosine), NSC 113418 (β-D-arabinofuranosyl-6-thioguanine), and NSC 403581 (5'-deoxy-6-thioguanosine) are courtesy of Dr. H. B. Wood, Jr.
(5) Krakoff, I. H.; Ellison, R. R.; Tan, C. T. C. *Cancer Res.* **1961**, *21*, 1015.
(6) Fox, J. J.; Wempen, I.; Hampton, A.; Doerr, I. L. *J. Am. Chem. Soc.* **1958**, *80*, 1669.
(7) Loo, T. L.; Lu, K.; Benevento, J. A.; Rosenblum, M. G. *Cancer Chemother. Pharmacol.* **1981**, *6*, 131.
(8) Iwamoto, R. H.; Acton, E. M.; Goodman, L. *J. Med. Chem.* **1963**, *6*, 684.
(9) Omura, G. A.; Vogler, W. R.; Smalley, R. V.; Maldonado, N.; Brown, G. O.; Knospe, W. H.; Ahn, Y. S.; Faguet, G. B. *Cancer Treat. Rep.* **1977**, *61*, 1379.
(10) LePage, G. A.; Junga, I. G. *Cancer Res.* **1963**, *23*, 739.
(11) LePage, G. A.; Khaliq, A. *Cancer Treat. Rep.* **1979**, *63*, 53.

0022-3263/84/1949-0528$01.50/0

Scheme I



7, X = CN
8, X = CH_2NH_2
9, X = CH_2NHAc

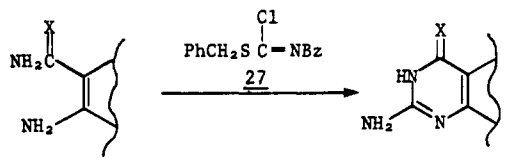
10

11, X = CH_2NHAc
12, X = CH_2NAc (NO)
13, X = CHN_2

the parent guanine. These include the guanosine analogue[13] (3) from the formycin series of 3-β-D-ribofuranosylpyrazolo[4,3-*d*]pyrimidines.

The formycin *C*-nucleosides are especially attractive as targets, because they appear to be excellent biochemical mimics of the purine counterparts, judging from comparisons between formycin and adenosine.[14,15] Hence, antitumor properties might be retained in thioguanosine analogues from the formycin series. This report describes synthesis of three such examples, the β-D-ribofuranosyl (4), β-D-arabinofuranosyl (5), and 2-deoxy-β-D-*erythro*-pentofuranosyl (6) derivatives of 5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione. For purposes of biological evaluation, it was important to prepare the 2-deoxy (6) and arabino (5) analogues for comparison with the riboside (4). In general, these compounds can be expected to show the various effects of agents that interfere with DNA or RNA biosynthesis or with the processing of DNA or RNA precursors. More specifically, initial activation to the nucleotide level may be required. In the case of 5 and 6, this can presumably be accomplished by the kinases known to exist for 2′-deoxyguanosine, for the α- and β-2′-deoxythioguanosines,[16] and for arabinosylguanine.[17] No kinase is known for guanosine, however. Consequently, the riboside 4 may require a novel mechanism of action, especially since (like all *C*-nucleosides) it is inherently excluded from the alternative phosphorylation via enzymatic exchange of an *N*-glycosyl moiety for an already phosphorylated sugar. Clearly, these new compounds are promising as biochemical probes as well as for possible therapeutic properties.

Several synthetic approaches to 4–6 were investigated. All involved use of pyrazole *C*-nucleoside intermediates bearing *o*-amino amide functions which undergo cyclization to form the pyrimidine ring (21 → 24). Such ring closures



21, X = S

24, X = S

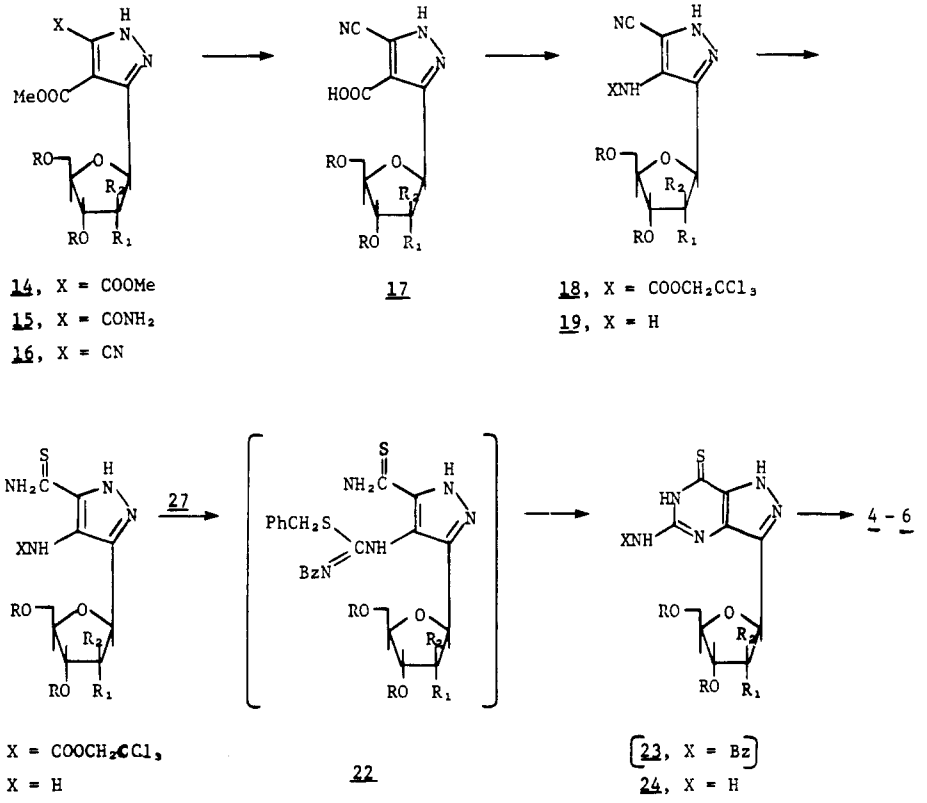
in guanosine syntheses generally involve several steps with various possibilities for side reactions.[18] Some of these difficulties were encountered[13] in the synthesis of the formycin-type guanosine analogue 3. In the successful approach to 4–6, we simplified this cyclization by introducing a new reagent, the imidoyl chloride 27. This may also have general applicability in the construction of fused pyrimidine rings.

Pyrazole *C*-nucleoside precursors were readily available from the previous total syntheses of formycin,[19] formycin B,[19,20] oxoformycin B,[21] and the arabino[22] forms of oxoformycin B. They were obtained from furanosyl 1-cyanides through the corresponding 1-acetamidomethyl[20,22,23] (rather than ureidomethyl[21]) analogue by nitrosation to form the 1-(diazomethyl)furanose derivatives. This sequence is illustrated in Scheme I for the now-added 2-deoxy analogues. Base-stable blocking groups on the hydroxyls (e.g., *O*-benzyl) must be in place during alkaline conversion of the nitroacetamide (e.g., 12) to the diazo function (13), so that the generated diazo sugar can be retained in the organic layer, washed free of the alkali, and used (without isolation) in a facile 1,3-dipolar addition with dimethyl acetylenedicarboxylate. Reduction of the nitrile 7 with sodium (trifluoroacetoxy)borohydride[24] occurred without loss of the aroyl esters (which did occur in reductions with lithium aluminum hydride[25] or with diborane) and permitted isolation of the amine 8 and its conversion to the acetamide 9 before the ester groups were cleaved and replaced with *O*-benzyls to give 11. The resultant pyrazole 4,5-diesters (Scheme II) with 3-β-D-ribofuranosyl[23] (14a) and 3-β-D-arabinofuranosyl[22] (14b) moieties have been described, but not the 2-deoxy analogue 14c.

Selective ammonolysis of these diesters to give the 5-carboxamides 15 is well established. The ester amides 15 were efficiently dehydrated with trifluoracetic anhydride in cold pyridine, the ester nitriles 16 were saponified, and the nitrile acids 17 were treated with diphenylphosphoryl azide in the presence of trichloroethanol, according to Kalvoda's use[19] of an elegant modification[26] of the Curtius reaction. The resulting urethanes 18 were obtained in

(12) (a) Tam, S. Y.; Klein, R. S.; Wempen, I.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4547. (b) Lim, M; Ren, W.; Otter, B. A.; Klein, R. S. *Ibid.* **1983**, *48*, 780.
(13) Lewis A. F.; Townsend, L. B. *J. Am. Chem. Soc.* **1982**, *104*, 1073.
(14) Suhadolnik, R. J. "Nucleoside Antibiotics"; Wiley-Interscience: New York, 1970; pp 357–389. Formycin, Formycin B, and oxoformycin B are naturally occurring C-nucleoside isomers of adenosine, inosine, and xanthosine.
(15) Suhadolnik, R. J. "Nucleosides as Biological Probes"; Wiley-Interscience: New York, 1979; pp 169–183.
(16) Nakai Y.; LePage, G. A. *Cancer Res.* **1972**, *32*, 2445.
(17) Müller, W. E. G.; Geurtsen, W.; Beyer, R.; Schuster, D. K.; Zahn, R. K.; Arendes, J. *Chem.-Biol. Interact.* **1981**, *34*, 301.
(18) Yamazaki, A.; Okutsu, M. *J. Heterocycl. Chem.* **1978**, *15*, 353.
(19) Kalvoda, L. *Collect. Czech. Chem. Commun.* **1978**, *43*, 1431.
(20) Acton, E. M.; Ryan, K. J.; Henry, D. W.; Goodman, L. *Chem. Commun.* **1971**, 986.
(21) Bobek, M.; Farkas, J.; Sorm, F. *Tetrahedron Lett.* **1970**, 4611. Farkas, J; Sorm, F. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2798.
(22) Acton, E. M.; Fujiwara, A. N.; Goodman, L.; Henry, D. W. *Carbohydr. Res.* **1974**, *33*, 135.
(23) Acton E. M.; Ryan, K. J. In "Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods, and Techniques"; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1978; Part 1, p 475.
(24) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* **1976**, 2875.
(25) Bobek, M.; Farkas, J. *Collect. Czech. Chem. Commun.* **1969**, *34*, 1684.
(26) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

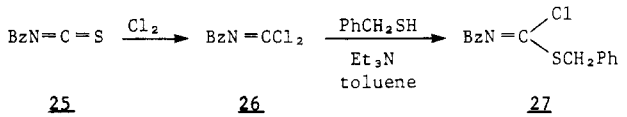
Scheme II[a]



[a] R = benzyl; series a, R_1 = OR, R_2 = H (ribo); series b, R_1 = H, R_2 = OR (arabino); series c, R_1 = R_2 = H (2-deoxy).

overall yields of up to 65% for the three steps. As the adjacent 5-substituent, CN is an excellent choice because it does not participate in or interfere with the Curtius rearrangement unlike adjacent $CONH_2$ or COOH which unavoidably gave spontaneous cyclization[9,11] with the intermediate N=C=O. Reductive cleavage of urethanes **18a** and **18c** with zinc–ammonium chloride, followed by treatment of the resulting amino nitriles **19a** and **19c** with H_2S in triethylamine–pyridine,[27-29] afforded the amino thioamides **21a** and **21c**. In the arabino series, these steps were reversed in order to take advantage of **20b** as a crystalline intermediate. Thus the thione function was always introduced simply, prior to ring closure.

The ring closure reagent **27** was synthesized from benzoylcarbonimidoyl dichloride (**26**)[30] by selective displace-



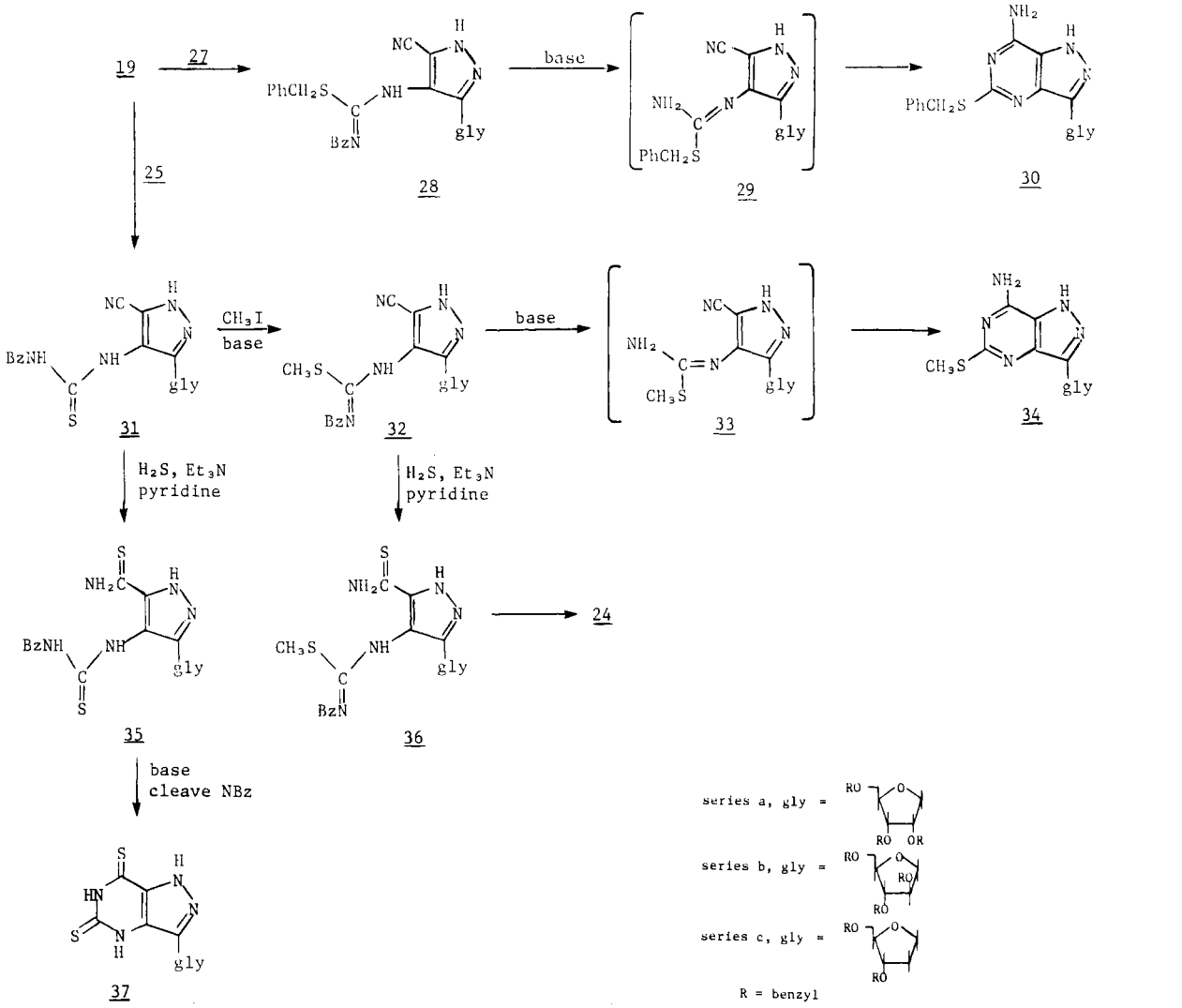
25 **26** **27**

ment of one Cl with 1 equiv of benzyl mercaptan and triethylamine in a nonpolar solvent. The resultant *S*-benzyl imidoyl chloride **27** was readily purified by chromatography without requiring extraordinary measures for protection from moisture. A few related compounds have been described[30-32] but apparently not used as reagents in cyclization reactions. The *S*-benzyl imidoyl chloride **27** reacted with the amino thioamides **21**, presumably in three stages, to form the 5-aminopyrazolo[4,3-*d*]pyrimidine-7-thiones **24**. Logically, the first step was displacement of the chloride at room temperature to form intermediate **22**. The advantage of **27** over other cyclization reagents (such as benzoylisothiocyanate[13,18]) is that it provides a preformed *S*-benzyl group to be ejected in the ring closure. Intermediate **22** would be cyclized immediately by treatment with ammonia and heating to form **23**. Removal of the *N*-benzoyl group was completed by further heating with alkali. The thioguanosine analogues **24** were obtained in 40–50% yields without isolation of the presumed intermediates. Removal of the *O*-benzyl blocking groups with BCl_3/CH_2Cl_2 completed the synthesis of **4–6**. Although we have encountered anomerization in other formycin *C*-nucleoside chemistry,[33] there appeared to be no anomerization whatever in any of the steps described. In each series, starting materials and intermediates are of known β configuration, and isomeric mixtures are not encountered in any step. The ^1H NMR data are consistent with assignment of the β configuration but do not offer conclusive proof without two isomers for comparison. Clearly, however, anomerization in any of the steps in this work would require the extremely unlikely complete inversion from β to α.

A minor byproduct (4%) was isolated from the ring closure to produce **24a**. By spectral analysis this appeared to be the 5-benzylthio 7-amine **30a** (Scheme III). Analogous minor byproducts of **24b** and **24c** were observed but not fully characterized. We speculate that **30** may have originated from a small amount of nitrile **19** that was present in **21**, either as an unreacted precursor to **21** or by

(27) Fairfull, A. E. S.; Lowe, J. L.; Peak, D. A. *J. Chem. Soc.* **1952**, 742.
(28) Yamazaki, A.; Kumashiro, I.; Takenishi, T.; Ikehara, M. *Chem. Pharm. Bull.* **1968**, *16*, 2172.
(29) Long, R. A.; Gerster, J. F.; Townsend, L. B. *J. Heterocycl. Chem.* **1970**, *7*, 863.
(30) Hegarty A. F.; Dignam, K. J. *J. Chem. Soc., Faraday Trans. 2* **1975**, 1046.
(31) Neidlein R.; Bottler, R. *Arch. Pharm. (Weinheim Ger.)* **1975**, 308, 379.
(32) Widdig, A.; Kuhle, E. German Patent 2332323, 1975; *Chem. Abstr.* **1975**, 83, 27965*u*. Kolling, H.; Thomas, H.; Widdig, A.; Wollweber, H. German Patent 2434183, 1976; *Chem. Abstr.* **1976**, *84*, 164503*b*.
(33) Acton, E. M.; Ryan, K. J.; Henry, D. W. "Abstracts, 7th International Symposium on Carbohydrate Chemistry"; Bratislava, Czechoslovakia, **1974**; p 70.

Scheme III



minor dehydrothiation of **21** with reagent **27**. Any **19** present would react with **27** to give the isothioureido nitrile **28**. Apparently **28** underwent cyclization to **30** after base cleavage of the *N*-benzoyl group, via intermediate **29**. Although a minor process, this was of interest because it illustrated the possibilities for mixtures of products in the more common guanosine-type ring closures[13,18] that we initially attempted using benzoyl isothiocyanate (**25**). For example, attempts to synthesize **24** in several steps by starting by treating **19** with benzoyl isothiocyanate led to **24** in only 15–25% yields. This approach required S-methylation of intermediate **31** and conversion of the nitrile **32** with H_2S to the thioamide **36** (*S*-methyl analogue of **22**). One byproduct appeared to be the 5-methylthio 7-amine **34**, through cleavage of the *N*-benzoyl group from **32**, as in the formation of **30**. Another byproduct appeared to be the 5,7-dithione **37**, by ring closure of the thioamide **35** formed after incomplete S-methylation of **31**. There were also various products of overmethylation with methyl iodide. Appreciable amounts of such byproducts of **24** by this approach were encountered in series **a**, **b**, or **c**. When isolated, yields of **34** or **37** ranged from 15% to 60%. Structural assignments for **30**, **34**, and **37** were largely based on mass spectral data which, in addition to the parent peaks, typically showed peaks for M – benzyl, M – PhCHO, and the B + 30 that is characteristic of *C*-nucleosides. In **34**, the ^1H NMR singlet at δ 2.52 was diagnostic for the SCH_3. Compounds **30** and **34** in methanol showed characteristic UV maxima at 312–314 nm, and **37** showed maxima at 267 and 319–322 nm.

Another obvious approach to **24** that was tried was the direct thiation of the guanosine analogues with phosphorus pentasulfide and related reagents under various conditions.[34] These attempts were abandoned because low yields were repeatedly encountered, especially on scale-up and even when the guanosine was protected by N-acetylation. Difficulties with a phosphorus pentasulfide thiation were also reported recently with a 9-deazainosine derivative, requiring alternative synthesis by ring closure of a thioamide.[12b] We tentatively attributed losses into the aqueous layer to N-phosphorylation.

Reagent **27** was used in a more direct approach (Scheme II) that did not require intermediate synthesis of the guanosines. However, reagent **27** should also find application in guanosine synthesis and other ring closures of *o*-amino functionalities.

Experimental Section

Solutions in organic solvents were dried over $MgSO_4$ and filtered. Evaporations were carried out in vacuo on a rotary evaporator. Melting points are uncorrected.

Spectra. UV–vis spectra were determined on a Perkin-Elmer Model 575 recording spectrometer, and mass spectra were determined on an LKB 9000 GC–MS at 12 eV interfaced with a PDP12 computer. IR spectra were determined with a Perkin-

(34) Acton, E. M.; Ryan, K. J. *Nucleic Acids Symp. Ser.* **1981**, *No. 9*, 243.

Elmer 735B spectrometer on liquid films, or, for solids, in Nujol mulls. Selected data are listed where diagnostic for individual compounds. Generally, bands at 3.0–3.1 μm were assigned to NH, those at 5.80–5.85 μm to ester C=O, those at 6.07–6.10 μm to amide C=O, and those at 5.75 μm to urethane C=O (in **18**). Bands at 4.45–4.48 μm in **16** and **17** (weak) or **18** or **19** (medium intensity) were assigned to CN. Strong bands at 6.28–6.30 μm in **21** were assigned to C=S. In **19**, **24**, and **4–6**, pairs of bands prominent near 6.2 and 6.3 μm were assigned to heterocyclic C=N. NMR spectra were determined by using a Varian EM390 spectrometer on solutions as noted with Me_4Si (δ 0.0) as an internal reference, except that **10** was run in D_2O with external Me_4Si. Signals were described as s (singlet), d (doublet, t (triplet), m (multiplet), and br (broad); integrated signal areas were as predicted from the structures. Coupling constants were sometimes determined by spectrum expansion.

Chromatography. The R_f values are for thin-layer analyses on silica gel plates (0.25 nm GF, Analtech). HPLC analyses were carried out on a Waters RCM100 radial compression separation system by using the 10-μm silica gel column for normal-phase separations and the 10-μm C-18 column for reverse-phase separations with HPLC-grade solvents. Preparative gravity column chromatography was done with Davisil 200–425-mesh silica gel (W. R. Grace, ca. 20 g/g of compound). Dry columns were run with silica gel 60 F254 (E. Merck, ca. 25 g/g of compound).

Preparative LC was performed on a Waters Associates Prep LC/System 500 instrument by using a Prep Pak-500/silica cartridge column and a refractive index detector. A C-18 cartridge column was used for the reverse-phase separations of **4–6**. A centrifugally accelerated radial preparative TLC system was used with **16c** and **18c**, as described.

1-Acetamido-2,5-anhydro-1,3-dideoxy-4,6-di-*O*-*p*-toluyl-D-*ribo*-hexitol (9). A solution of sodium (trifluoroacetoxy)borohydride in 120 mL of tetrahydrofuran (THF) was prepared[24] from 1.25 g (32.4 mmol) of sodium borohydride and 3.70 g (32.1 mmol) of 99% trifluoroacetic acid. It was treated with a solution of 11.1 g (29.3 mmol) of 2,5-anhydro-3-deoxy-4,6-di-*O*-*p*-toluyl-D-*ribo*-hexonitrile in 110 mL of THF. After 18 h of stirring at room temperature, the solution was cooled to 5 °C and treated dropwise with 5 mL of water to decompose the remaining hydride. The THF was evaporated, and the moist residue was partitioned between 200 mL of water and 200 mL of dichloromethane. The organic layer was washed with 100 mL of water, dried, and saturated with a stream of hydrogen chloride (g) for 10 min. The solution was evaporated, and the residue was stirred with 400 mL of ether–ethyl acetate (3:1) for 4 h. The supernatant was decanted from the semisolid residue. The hydrochloride (12.1 g; R_f 0.05 in hexane–ethyl acetate, 1:1) of **1-amino-2,5-anhydro-1,3-dideoxy-4,6-di-*O*-*p*-toluyl-D-*ribo*-hexitol (8)** was free of nitrile **7** (R_f 0.8).

A stirred solution of the hydrochloride in 75 mL of pyridine was treated with 2.60 g (31.7 mmol) of sodium acetate and 15 mL (155 mmol) of acetic anhydride. The mixture was stirred overnight at room temperature, cooled to 0 °C, treated with 30 mL of methanol to decompose the remaining anhydride, and evaporated. A solution of the residual syrup in 150 mL of dichloromethane was washed with 100-mL portions of 1 N hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The organic layer was dried and evaporated. The residual syrup (14 g) was crystallized from 75 mL of ether by adding 35 mL of cyclohexane and chilling for 3 days at −10 °C to produce the product: 6.71 g (54%); mp 137–138.5 °C. A second crop of 1.20 g (mp 137–138 °C) of product was recovered from the evaporated mother liquor by chromatography on silica gel developed with dichloromethane–ethyl acetate (2:1): total yield 7.91 g (63%); ^1H NMR ($CDCl_3$) δ 7.93 (d) and 7.89 (d) (H-2′ and H-6′ of *p*-toluyls), 7.22 (d, H-3′ and H-5′, J = 9 Hz), 6.19 (br t, NH), 5.45 (m, H-4), 4.6–4.2 (m, H-2, H-5, 2 H-6), 3.5 (m, 2 H-1), 2.40 (s, 2 CH_3), 2.5–1.8 (m, 2 H-3), 1.91 (s, NAc). Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.74; H, 6.40; N, 3.29. Found: C, 67.60; H, 6.25; N, 3.27.

1-Acetamido-2,5-anhydro-1,3-dideoxy-D-*ribo*-hexitol (10). A suspension of 11.1 g (26.1 mmol) of **9** in 180 mL of methanol was treated with 45.6 g (weighed solution) of 25% methanolic sodium methoxide (calcd 11.4 g, 52.8 mmol) and refluxed for 45 min. The clear solution was cooled and neutralized to pH 5–6 with concentrated hydrochloric acid. The mixture was evaporated, and the residue was partitioned between 100 mL of water and 100 mL of dichloromethane. The water layer was separated and evaporated to a semisolid residue, which was triturated with warm ethanol. The sodium chloride was collected on a filter, and the filtrate was evaporated. The residual product after drying in vacuo at 60 °C for 2 h weighed 5.32 g (108% of theory); TLC on silica gel in chloroform (R_f 0.05, detected by charring with sulfuric acid spray) showed that less polar impurities (e.g., **9**, R_f 0.9, UV detection) were absent: ^1H NMR (D_2O) δ 4.5–4.1 (m, H-2, H-4), 4.1–3.8 (m, H-5), 3.7 (m, 2 H-6), 3.4 (d, 2 H-1, $J_{1,2}$ = 6 Hz), 2.5–1.6 (m, 2 H-3), 2.01 (s, NAc).

1-Acetamido-2,5-anhydro-4,6-di-*O*-benzyl-1,3-dideoxy-D-*ribo*-hexitol (11). A solution of residual **10** (5.32 g, assumed 26.1 mmol) in 250 mL of anhydrous dimethyl sulfoxide was treated with 3.50 g (54.1 mmol) of powdered 86.8% potassium hydroxide and stirred for 30 min at 15 °C while being protected from moisture, and a solution of 6.85 g (54.1 mmol) of benzoyl chloride in 20 mL of dimethyl sulfoxide was added dropwise. After 2 h of stirring at 15–20 °C, the mixture was poured into 3 L of ice–water, and the solution was extracted with three portions of ether. The combined ether extracts were dried and evaporated to a solid, which was recrystallized from 25 mL of ether and 100 mL of cyclohexane with chilling at 10 °C: yield 3.0 g (31%); mp 90–92 °C. Chloroform extraction of the water layer recovered unreacted **10** and an intermediate monobenzyl derivative of **10**, which were then retreated. The purity of syrupy fractions could also be improved by chromatography on silica gel with chloroform–ethyl acetate (1:1): final yield 5.7 g (59%); mp 90–92 °C; R_f 0.45 (on silica gel in chloroform–ethyl acetate, 1:1); ^1H NMR δ 7.31 (s), 7.30 (s, 2 C_6H_5), 6.1 (br s, NH), 4.51 (s, $PhCH_2$), 4.46 (dd, $PhCH_2$), 4.55–3.95 (m, H-5, H-4, and H-2), 3.55 (m, 2 H-1), 3.40 (m, 2 H-6), 2.25–1.7 (2 H-3), 1.70 (s, NAc). The analytical sample had a melting point of 94–95 °C. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.35; N, 3.79. Found: C, 71.44; H, 7.35; N, 3.70.

2,5-Anhydro-4,6-di-*O*-benzyl-1,3-dideoxy-1-(nitrosoacetamido)-D-*ribo*-hexitol (12). To a solution of 6.60 g (17.9 mmol) of **11** in 75 mL of carbon tetrachloride and 75 mL of acetic acid was added 7.0 g (85 mmol) of sodium acetate as a buffer for the nitric acid to be liberated. The mixture was chilled in ice, treated with 15 mL of dinitrogen tetraoxide (causing a blue-green color), stirred for 2 h, and poured into 1 L of ice–water. The hydrolysate was stirred for 30 min, and the product was extracted with two 500-mL portions of dichloromethane. The combined extracts were washed with 500 mL of cold saturated aqueous sodium bicarbonate, dried, and evaporated (bath <40 °C) to a green oil: 7.7 g (108% of theory); IR showed complete absence of 3.0 (NH as in **11**) and 6.07 μm (NAc as in **11**) and appearance of 5.81 μm (AcN–NO); ^1H NMR ($CDCl_3$) δ 7.30 (s) and 7.25 (s) (2 C_6H_5), 4.51 (s) and 4.42 (s) (2 $PhCH_2$), 4.3–3.7 (m, H-2, H-4, H-5, and 2 H-1), 3.42 (m, 2 H-6), 2.69 (s, NAc), 2.22–1.83 (m) and 1.74–1.36 (m) (H-3A and H-3B).

2,5-Anhydro-4,6-di-*O*-benzyl-1,3-dideoxy-1-diazo-D-*ribo*-hexitol (13). A solution of **12** (7.7 g, assumed 17.9 mmol from **11**) in 150 mL of ether was added to a solution at 0 °C of 60 g (1.0 mol) of potassium hydroxide in 150 mL of water, and the mixture was stirred vigorously. The progress of the reaction was monitored by allowing a few drops of the ether layer to evaporate on a sodium chloride plate and following the appearance, in successive aliquots, of a strong IR band at 4.84 μm (CHN_2) along with the disappearance of the band at 5.81 μm (AcN–NO). After 5.5 h (a weak band near 5.8 μm remained), another 100 mL of ether was added, followed by 100 mL of water. The ether layer was separated, and the water layer was washed with 100 mL of ether. The combined ether layers were washed with water and dried with potassium hydroxide pellets and then by adding magnesium sulfate. The yellow ether solution was filtered and used immediately.

Dimethyl 3-(3,5-Di-*O*-benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazole-4,5-dicarboxylate (14c). The yellow solution of **13** (from 17.9 mmol of **11**) was added dropwise to a stirred, ice-chilled solution of 8.00 g (56.3 mmol) of dimethyl acetylenedicarboxylate in 350 mL of ether, with immediate discharge of the color. Stirring was continued for 15 min, and the solution was evaporated to a residual syrup (12.9 g, 150% of theory) containing unreacted acetylene diester as evidenced by

a ^{1}H NMR singlet near δ 3.6, which could be used in the next step; R_f 0.6 (in chloroform–ethyl acetate, 3:1) with minor impurities at R_f 0.2 and 0.9. A small sample was purified to homogeneity by preparative TLC: ^{1}H NMR ($CDCl_3$) δ 7.29 (s) and 7.26 (s) (2 C_6H_5), 5.59 (dd, H-1′, $J_{1',2'A}$ = 5.7 Hz, $J_{1',2'B}$ = 6.9), 4.55 (dd) and 4.42 (dd) (2 $PhCH_2$), 4.3–4.0 (m, H-3′, H-4′) 3.86–3.4 (m, 2 H-5′), 3.88 (s) and 3.76 (s) (2 COOMe), 2.75–2.4 (m) and 2.35–1.95 (m) (H-2′A and H-2′B).

Methyl 3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-carbamoylpyrazole-4-carboxylate (15a). A sample of diester **14a**[21,23] was 82% pure by analytical HPLC on silica gel in dichloromethane, which showed the presence of 10% unreacted acetylenic diester and five minor impurities. Purification was accomplished by silica gel column chromatography in dichloromethane or by preparative LC. The purified **14a** (99.1%) upon treatment[21] with cold anhydrous methanolic ammonia afforded **15a** that was 90% pure by HPLC analysis on silica gel in ethanol–chloroform (97:3), which showed the presence of 2% unreacted **14a** and 6% diamide [no OMe in the ^{1}H NMR; mass spectral peaks at *m/e* 556 (M), 465 (M − $C_6H_5CH_2$), 448 (M − $C_6H_5CH_2OH$), and 183 (base + 30)]. Preparative LC purification of **15a** on silica gel in dichloromethane and crystallization from ether–cyclohexane (2:1) gave purified product: yield 53%; mp 127–129 °C (a previous sample was described[21] as a syrup); IR m 2.92, 3.00, 3.11 (NH), 5.85 (ester C=O), 6.13 μm (amide C=O); ^{1}H NMR ($CDCl_3$) 7.29 (s) and 7.23 (s) (3 C_6H_5), 5.61 (s, H-1′), 4.73 (s), 4.62 (dd), 4.34 (dd) (3 $PhCH_2$), 4.55–4.0 (m, H-2′, H-3′, H-4′), 4.0–3.5 (m, 2 H-5′). Anal. Calcd for $C_{32}H_{33}N_3O_7$: C, 67.23; H, 5.82; N, 7.35. Found, C, 67.19; H, 5.98; N, 7.26.

Methyl 3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-carbamoylpyrazole-4-carboxylate (15b). A sample of chromatographically purified β anomer **15b**[22] began to crystallize after being stored for 1 week. Addition of seed crystals to a solution of 5.3 g of the syrup in 100 mL of ether gave 2.5 g of product, mp 85–90 °C. Recrystallization of 0.50 g from ether at −3 °C gave 0.39 g of an analytical sample: mp 93.0–94.5 °C; UV (MeOH, 0.1 N MeOH, pH 13) λ_{max} 257 nm (ε 10 600; lit.[22] 9650, on a syrup); IR 2.90, 3.00, 3.12 (NH), 5.85, 5.98, 6.22 μm (C=O); ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 2 C_6H_5), 7.25–7.15 (m) and 6.92–7.78 (m) (C_6H_5), 5.49 (d, H-1′, $J_{1',2'}$ = 4.3 Hz), 4.58 (s) and 4.50 (s) (2 $PhCH_2$), 4.45–3.95 (m, H-2′, H-3′, H-4′), 3.78–3.53 (m, 2 H-5′), 3.60 (s, COOMe). Anal. Calcd for $C_{32}H_{33}N_3O_7$: C, 67.23; H, 5.82; N, 7.35. Found C, 67.20; H, 5.69; N, 7.42.

Methyl 3-(3,5-Di-*O*-benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-5-carbamoylpyrazole-4-carboxylate (15c). The 12.9 g of impure diester **14c** (obtained from 17.9 mmol of **11**) was treated with 500 mL of saturated methanolic ammonia at 0 °C, and the solution was stored at 25 °C for 2 days. When the conversion to **15c** [R_f 0.15 (on silica gel in chloroform-ethyl acetate, 3:1)] was complete, the solution was evaporated, and the residual oil was purified by chromatography on silica gel eluted with chloroform–ethyl acetate (7:3); 4.0 g (60%) of **15c** was obtained and crystallized from 75 mL of carbon tetrachloride–cyclohexane (3:1) at 10 °C: yield 3.1 g (37%); mp 122–124 °C; ^{1}H NMR (acetone-d_6) δ 7.33 (s) and 7.31 (s) (2 C_6H_5), 5.56 dd (H-1′, $J_{1',2'A}$ = 6.6 Hz, $J_{1',2'B}$ = 8.5), 4.60 (s) and 4.52 (s) (2 $PhCH_2$), 4.22 (m, H-3′ and H-4′), 3.88 (s, COOMe), 3.60 (uneven d, 2 H-5′), 2.6–2.2 (m, 2 H-2′). Anal. Calcd for $C_{25}H_{27}N_3O_6 \cdot {}^2/_3H_2O$: C, 62.88; H, 5.98; N, 8.79. Found: C, 62.76; H, 5.76; N, 8.79. The mother liquor afforded 1.85 g of oil that was homogeneous to TLC and could be recombined (total yield 57%) with the crystals for the next step.

Methyl 3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-cyanopyrazole-4-carboxylate (16a). A solution of 28.0 g (49.0 mmol) of amide ester **15a** in 45 mL of dioxane and 25 mL of THF was treated with 9.1 mL (0.11 mol) of anhydrous pyridine (dried over 3-Å molecular sieves) and chilled to 0 °C. The temperature was kept below 5 °C while 16 mL (0.11 mol) of trifluoroacetic anhydride[35] was added in drops over 45 min. The mixture warmed to room temperature, was stirred for 18 h, was evaporated to half its volume, and was poured with stirring into 250 mL of ice–water. The solution was extracted with three 200-mL portions of chloroform, and the combined extracts were washed with two 500-mL portions of saturated aqueous sodium chloride. The chloroform solution was then dried and evaporated. The residual syrup (30 g, 110% of theory) was purified on silica gel in dichloromethane–ethyl acetate (95:5). The eluate was monitored by TLC in dichloromethane–ethyl acetate (90:10), with R_f 0.7 for **16a** compared to R_f 0.2 for **15a**. The resultant 18.5 g of syrup was crystallized from ether, first at 25 °C and then with chilling to −5 °C: yield 14.5 g (53%); mp 132.5–134 °C. An additional 2.5 g of product (mp 129–133 °C) was recovered by concentrating the filtrate and adding cyclohexane: total yield 63%; ^{1}H NMR ($CDCl_3$) δ 7.4–7.1 (m, 3 C_6H_5) 5.68 (s, H-1′), 4.88 (dd, $PhCH_2$, J_{gem} = 12 Hz), 4.60 (dd, $PhCH_2$, J_{gem} = 11 Hz), 4.21 (dd, $PhCH_2$, J_{gem} = 11 Hz), 4.35–3.95 (m, H-2′, H-3′, H-4′), 3.91 (s, COOMe), 3.8–3.3 (m, 2 H-5′). Anal. Calcd for $C_{32}H_{31}N_3O_6$: C, 69.43; H, 5.64; N, 7.59. Found: C, 69.32; H, 5.69; N, 7.58.

Methyl 3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-cyanopyrazole-4-carboxylate (16b). The syrupy product (110% of theory) was purified in two 20-g portions by preparative LC on silica gel in dichloromethane–ethyl acetate (98:2) and evaporated to a residual syrup: 54% yield; R_f 0.70 [in 9:1 dichloromethane–ethyl acetate (vs. R_f 0.05 for **15b**, with trace impurities at the solvent front)], 0.90 [in 1:1 hexane-ethyl acetate (vs. R_f 0.1 for **15b**)]; ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 2 C_6H_5), 7.3–7.1 (m) and 6.95–6.8 (m) (C_6H_5, presumably of 2′-*O*-benzyl, splitting due to steric or proximity effects with the pyrazole), 5.62 (d, H-1′, *J* = 4.5 Hz), 4.50 (s, 2 $PhCH_2$), 4.45–3.9 ($PhCH_2$, H-2′, H-3′, H-4′), 3.71 (s, COOMe), 3.62 (uneven d, H_2-5′).

Methyl 3-(3,5-Di-*O*-benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-5-cyanopyrazole-4-carboxylate (16c). The evaporated product [105% of theory; R_f 0.75 (in 9:1 dichloromethane–ethyl acetate) vs. R_f 0.05 for **15c**] was purified by radial preparative TLC centrifugally accelerated on a spinning disk (radius 10 cm) with 2 mm of silica gel (Chromatotron, Model 7924, Harrison Research, Palo Alto, CA), eluted with dichloromethane: 76% yield; ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 2 C_6H_5), 5.70 (dd, H-1′, $J_{1',2'A}$ = 8.2 Hz, $J_{1',2'B}$ = 4.8), 4.56 (dd, $PhCH_2$), 4.43 (dd, $PhCH_2$), 4.2 (m, H-3′, H-4′), 3.82 (s, COOMe), 4.0–3.4 (m, partly obscured, 2 H-5), 2.8–2.4 (m, H-2′A), 2.3–2.0 (m, H-2′B).

3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-cyanopyrazole-4-carboxylic Acid (17a). A mixture of 17.0 g (30.7 mmol) of **16a** in 150 mL of methanol and 150 mL of 1 N aqueous sodium hydroxide was boiled under reflux for 18 h, when the reaction was complete, according to TLC analysis (hexane–ethyl acetate, 1:1) for **17a** (R_f 0.3 streaked from origin) and for loss of **16a** (R_f 0.9). The methanol was removed by evaporation, the solution was poured into 1 L of ice–water containing 13.5 mL of concentrated hydrochloric acid (162 mmol), and the mixture was stirred for 45 min. The gummy solid was collected by filtration and dissolved in 400 mL of dichloromethane, and the solution was washed with 200 mL of saturated aqueous sodium chloride, dried, and evaporated. The residual yellow oil (17 g) crystallized from 100 mL of toluene and 20 mL of cyclohexane upon being chilled at 5 °C: yield 15.4 g (93%); mp 157–160 °C; IR 3.05 (NH), 3.8 (br, acid OH), 4.48 (weak, CN), 5.91 μm (acid C=O); ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 3 C_6H_5), 5.68 (s, H-1′), 4.82 (dd, $PhCH_2$, J_{gem} = 12 Hz), 4.59 (dd, $PhCH_2$), 4.30 (dd, $PhCH_2$), 5.0–3.6 (overlapping H-2′, H-3′, H-4′, and 2 H-5′). Anal. Calcd for $C_{31}H_{29}N_3O_6$: C, 69.00; H, 5.42; N, 7.79. Found: C, 68.96; H, 5.50; N, 7.67.

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-cyanopyrazole-4-carboxylic acid (17b) was crystallized from ether–cyclohexane in two crops: 71%; mp 152–154 °C; IR 3.15 (NH), 3.7, 3.8 (br, acid OH), 4.43 (weak, CN), 5.91 μm (acid C=O); ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 2 C_6H_5), 7.31–7.1 (m) and 6.95–6.8 (m) (C_6H_5), 5.69 (d, H-1′, $J_{1,2}$ = 4.8 Hz), 4.52 (s, $PhCH_2$), 4.51 (dd, $PhCH_2$), 4.28 (dd, $PhCH_2$), 4.4–3.9 (H-2′, H-3′, H-4′), 3.65 (uneven d, 2 H-5′, apparent $J_{4',5'}$ = 5.8 Hz). Anal. Calcd for $C_{31}H_{29}N_3O_6 \cdot 0.33H_2O$: C, 68.24; H, 5.62; N, 7.70. Found: C, 68.36; H, 5.45; N, 7.68.

3-(3,5-Di-*O*-benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-5-cyanopyrazole-4-carboxylic acid (17c) was crystallized from ether–carbon tetrachloride upon chilling to 10 °C: 81%; mp 161.5–164 °C; IR 3.20 (NH), 3.8 (br, acid OH), 4.50 (weak, CN), 5.96 μm (acid C=O); ^{1}H NMR (CD_3COCD_3) δ 7.33 (s) and 7.31 (s) (2 C_6H_5), 5.65 (dd, H-1′, $J_{1',2'A}$ = 6.2 Hz, $J_{1',2'B}$ = 9.0), 4.58 (s, 2 $PhCH_2$), 4.4–4.2 (m, H-3′, H-4′), 3.72 (uneven d, 2 H-5′), 2.9–2.55 (m, H-2′A), 2.3–1.9 (m, H-2′B). Anal. Calcd for

(35) Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813.

$C_{24}H_{23}N_3O_5 \cdot 0.5H_2O$: C, 65.14; H, 5.46; N, 9.50. Found: C, 65.42; H, 5.52; N, 9.51.

3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-[[(2,2,2-trichloroethoxy)carbonyl]amino]pyrazole-5-carbonitrile (18a). A solution of 14.5 g (26.9 mmol) of **17a** in 150 mL of toluene containing 3.2 g (32 mmol) of triethylamine was treated with 4.7 g (32 mmol) of 2,2,2-trichloroethanol and 8.7 g (32 mmol) of diphenyl phosphoryl azide. The solution was refluxed for 1.5 h when, as noted upon cooling below the boiling point, N_2 evolution had ceased. The cooled solution was washed with 250 mL of saturated aqueous sodium carbonate. The aqueous layer was washed with 75 mL of toluene, and the combined toluene solutions were dried and evaporated. The residual product (20 g, 108% of theory) was adsorbed onto 40 g of silica gel for dry-column chromatography by evaporation from a solution in 75 mL of dichloromethane, added to a dry column of 200 g of silica gel, and eluted with hexane–ethyl acetate (2:1) to afford 14.1 g (76%) of homogeneous light brown oil: R_f 0.45 (in hexane–ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$) δ 7.27 (s) and 7.26 (s) (C_6H_5), 5.60 (d, H-1′, $J_{1',2'}$ = 3.3 Hz), 4.61, 4.50, 4.37 (3 apparent dd, 3 $PhCH_2$), 4.7–4.1 (overlapping H-2′, H-3′, H-4′), 3.75 (qd, 2 H-5′, $J_{4',5'}$ = 3.3 Hz, J_{gem} = 10.5 Hz).

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-4-[[(2,2,2-trichloroethoxy)carbonyl]amino]pyrazole-5-carbonitrile (18b): 78% yield; R_f 0.5 (in hexane–ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$) δ 7.30 (s, 2 C_6H_5), 7.3–7.2 and 7.15–6.95 (C_6H_5), 5.12 (d, H-1′, $J_{1',2'}$ = 4.0 Hz), 4.70 (s), 4.55 (s), 4.45 (s, 3 $PhCH_2$), 4.3–4.0 (H-2′, H-3′, H-4′), 4.28 (q, OCH_2CCl_3), 3.65 (uneven d, 2 H-5′, apparent $J_{4',5'}$ = 8.1 Hz). A syrupy sample for analysis was obtained (189 mg from 300 mg) by preparative TLC on two 20 × 20 cm plates of 2-mm silica gel in chloroform–ethyl acetate (9:1). Anal. Calcd for $C_{33}H_{31}Cl_3N_4O_6 \cdot 0.5H_2O$: C, 57.03; H, 4.64; Cl, 15.30; N, 8.06. Found: C, 56.98; H, 4.85; Cl, 15.62; N, 7.80.

3-(3,5-Di-*O*-benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-4-[[(2,2,2-trichloroethoxy)carbonyl]amino]-pyrazole-5-carbonitrile (18c) was obtained in 81% yield after purification on a Chromatotron (cf. **16c**): R_f 0.8 (in 1:1 dichloromethane–ethyl acetate; R_f 0.1 for **17c**); ^{1}H NMR ($CDCl_3$) δ 7.33 (s) and 7.31 (s) (2 C_6H_5), 5.27 (t, H-1′, $J_{1',2'A}$ = 7.2 Hz, $J_{1',2'B}$ = 7.8), 4.80, 4.63, 4.49 (3 dd, 2 $PhCH_2$, OCH_2CCl_3), 4.3–4.1 (H-3′, H-4′), 3.95–3.4 (ddd, 2 H-5′), 3.1–2.0 (2 H-2′).

3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-aminopyrazole-5-carbonitrile (19a). A stirred solution of 14.1 g (20.5 mmol) of **18a** in 1 L of methanol was treated with 98 g (1.50 mol) of powdered zinc and 30 g (0.56 mol) of ammonium chloride. The mixture was heated under reflux for 1.5 h and filtered, and the filter cake was washed with 250 mL of hot methanol. The cloudy filtrate was evaporated, and the residue was partitioned between 450 mL of toluene and 600 mL of water containing 240 mL of concentrated ammonium hydroxide. The toluene layer was separated, the aqueous layer was washed with 100 mL of toluene, and the combined toluene solution was dried and evaporated to give 9.8 g (94%) of a residual syrup[19,36] that was carried on to the next step; R_f 0.5 (in 1:1 hexane–ethyl acetate), showing trace impurities.

4-Amino-3-(3,5-di-*O*-benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazole-5-carbonitrile (19c) was obtained as a residual oil: 96%; R_f 0.5 (in 1:1 hexane–ethyl acetate; R_f 0.9 for **18c**); ^{1}H NMR ($CDCl_3$) 7.30 (s, 2 C_6H_5), 5.13 (t, H-1′, $J_{1',2'A}$ = 7.2 Hz, $J_{1',2'B}$ = 8.4), 4.50 (s, 2 $PhCH_2$), 4.17 (br s, H-3′, H-4′), 3.60 (ddd, 2 H-5′), 2.38–2.08 (m, 2 H-2′).

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-4-[[(2,2,2-trichloroethoxy)carbonyl]amino]pyrazole-5-carbothioamide (20b). A solution of 8.7 g (12.7 mmol) of **18b** in 200 mL of pyridine was treated with 2.5 mL of triethylamine, and a stream of hydrogen sulfide (g) was introduced and maintained for 18 h. The mixture was evaporated, and the residual light yellow oil was partitioned between 200 mL of dichloromethane and 150 mL of cold 1.0 N hydrochloric acid. The organic layer was washed with 150 mL of saturated aqueous sodium bicarbonate and 150 mL of saturated aqueous sodium chloride, dried, and evaporated. The oil (9.4 g, 103% of theory) was crystallized from 100 mL of ether and 350 mL of cyclohexane with chilling: yield 7.2 g (78%); mp 134–137 °C; homogeneous in 3:1 hexane–ethyl acetate; R_f 0.4; IR 3.00 and 3.10 (NH), 5.70 (C=O), 6.11 (amide II), 6.42 μm (medium, C=S); ^{1}H NMR ($CDCl_3$) δ 7.23 (s), 7.20 (s), 7.08–6.93 (m, 3 C_6H_5), 5.50 (d, H-1′, $J_{1',2'}$ = 3.8 Hz), 4.74 (s), 4.52 (s), 4.44 (s) (3 $PhCH_2$), 4.29 (s, (OCH_2CCl_3), 4.35–3.9 (H-2′, H-3′, H-4′), 3.62 (uneven d, 2 H-5′, apparent $J_{4',5'}$ = 5.8 Hz). Anal. Calcd for $C_{33}H_{33}Cl_3N_4O_6S \cdot {}^1/_3H_2O$: C, 54.59; H, 4.77; Cl, 14.65; N, 7.72; S, 4.42. Found: C, 54.53; H, 4.65; Cl, 14.84; N, 7.57; S, 4.54.

3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-4-aminopyrazole-5-carbothioamide (21a). By the above procedure for **20b**, **19a** was converted to a homgeneous yellow oil: 94% yield; R_f 0.3 (in 1:1 hexane–ethyl acetate); IR 2.95, 3.08, 3.15 (NH), 6.30 (strong, C=S); ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 3 C_6H_5), 5.13 (d, H-1′, $J_{1',2'}$ = 3.8 Hz), 4.70–4.42 (sharp m, 3 $PhCH_2$), 4.4–4.0 (m, H-2′, H-3′, H-4′), 3.70 (ddd, 2 H-5′, $J_{4',5'A}$ = 1.9 Hz, $J_{4',5'B}$ = 2.7, J_{gem} = 10.5).

3-(3,5-Di-*O*-benzyl-β-D-*erythro*-pentofuranosyl)-4-aminopyrazole-5-carbothioamide (21c). Similarly, **19c** afforded a red foamed glass: 98% yield; R_f 0.4 (in 1:1 chloroform–ethyl acetate; R_f 0.7 for **19c**) with a trace contaminant at the origin; IR 2.95, 3.03, 3.13 (NH), 6.28 μm (strong, C=S); ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 2 C_6H_5), 5.20 (t, H-1′, $J_{1',2'A}$ = 7.5 Hz, $J_{1',2'B}$ = 7.9), 4.4 (m, 2 $PhCH_2$), 4.2 (br s, H-3′, H-4′), 3.85–3.40 (ddd, 2 H-5′), 2.35–2.15 (m, 2 H-2′).

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-4-aminopyrazole-5-carbothioamide (21b). By the procedure for **19a**, **18b** was converted to a red oil: 6.1 g (112% of theory); R_f 0.3 (in chloroform–acetone, 85:15), with both faster and slower contaminants. The product was purified on a gravity column of 220 g of silica gel in hexane–ethyl acetate (60:40): yield 4.4 g (81%) of syrup; R_f 0.3 (in 5.7:1 chloroform–acetone) with a trace contaminant at the origin; IR 2.95, 3.05, 3.15 (NH), 6.29 μm (strong, C=S); ^{1}H NMR ($CDCl_3$) δ 7.31 (s), 7.30–7.25 (m), 7.15–7.0 (m, 3 C_6H_5), 5.12 (d, H-1′, J = 3.6 Hz), 4.54 (s), 4.50 (s), 4.30 (s) (3 $PhCH_2$), 4.1 (rough d, H-2′, H-3′, H-4′), 3.62 (rough d, 2 H-5′, apparent J = 5.5 Hz). Anal. Calcd for $C_{30}H_{32}N_4O_4S \cdot 0.75H_2O$: C, 64.55; H, 6.05; N, 10.03; S, 5.74. Found: C, 64.73; H, 6.09; N, 9.79; S, 5.74.

***S*-Benzyl *N*-Benzoylcarbonochloridimidothioate (27).** A stirred solution of 6.00 g (29.7 mmol) of *N*-benzoylcarbonimidoyl dichloride[30] in 350 mL of dry toluene was chilled to 0 °C and treated with 3.70 g (29.7 mmol) of benzyl mercaptan, followed by a solution of 3.00 g (29.7 mmol) of triethylamine in 20 mL of toluene added in drops over 30 min. The solution warmed to room temperature, and analytical HPLC on silica gel in hexane–dichloromethane (1:1) showed the presence of 20% of dichloride starting material, 65% of **27**, and 8% of the bis(benzylthio) byproduct. An additional 0.78 g of triethylamine and 1.03 g of benzyl mercaptan in 20 mL of toluene solution was added dropwise at several intervals, and after about 2 h, the solution was evaporated to a residual oil (9.3 g, 108% of theory) containing 0.8% of the dichloride, 72% of **27**, and 27% of the bis(benzylthio) compound. Purification of **27** was accomplished by preparative LC on silica gel eluted with hexane–dichloromethane (2:1): yield 5.20 g (60%); 98.5% pure by analytical HPLC on silica gel (in dichloromethane–hexane, 55:45); IR 5.95 μm (C=O), with no bands in the OH region near 3.0; ^{1}H NMR ($CDCl_3$) δ 7.8–7.15 (m, C_6H_5C=O), 7.32 (s, $C_6H_5CH_2$), 4.27 (s, $PhCH_2$); contamination with C_6H_5CON=$C(SCH_2C_6H_5)_2$ was evidenced by δ 7.30 (s, $C_6H_5CH_2$) and 4.33 (s, $PhCH_2$).

3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione (24a). A stirred solution of 3.50 g (6.43 mmol) of **21a** in 40 mL of dry pyridine was protected from moisture, chilled in ice, and treated with 2.66 g of a sample of **27** (77% pure, 7.07 mmol) in 10 mL of toluene added in small portions. Stirring was continued for 1 h in ice and 1 h at room temperature, and the precipitated pyridine hydrochloride was collected on a filter and washed with 20 mL of dichloromethane. In subsequent runs, chloride **27** was dissolved in carbon tetrachloride (10 mL/g), and pyridine was removed upon evaporation of the mixture. The combined filtrate was evaporated (at 0.5 mm) to a residual oil, presumably mostly **22a**. A solution of this residue in 50 mL of methanol–concentrated ammonium hydroxide (1:1) was heated under reflux at 100 °C for 30 min and then for another 30 min while the methanol was allowed to distill away. The

(36) The tri-*O*-acetyl analogue of **19a** has been synthesized by an independent approach: Buchanan, J. G.; Edgar, A. P.; Hutchison, R. J.; Stobie, A.; Wightman, R. H. *J. Chem. Soc., Chem. Commun.* **1980**, 237.

aqueous mixture was diluted with 50 mL of ice–water and neutralized with 6 N hydrochloric acid to pH 3–4. The resultant gummy precipitate was collected on a filter, washed with 150 mL of water, and dissolved in 50 mL of dichloromethane. The solution was washed with 50 mL of saturated aqueous sodium chloride, dried, and evaporated to an oil (4.4 g), presumably mostly **23a**. A solution in 25 mL of methanol was diluted with 25 mL of 1 N aqueous sodium hydroxide and heated at 100 °C for 30 min and then for another 30 min with distillation of the methanol. The aqueous solution was diluted and neutralized as before, the gummy precipitate (crude **4**) was dissolved in dichloromethane, and the solution was washed, dried, and evaporated. The residual foamed glass (3.7 g, 100%) was purified by preparative LC with chloroform–acetone (85:15) as the eluent. The resultant 1.9 g of residue was crystallized from 15 mL of 2-propanol by adding 7 mL of water in several portions with heating and cooling near the cloud point: yield 1.52 g (41%); mp 94–98 °C; R_f 0.40 (in chloroform–ethyl acetate, 85:15); UV (MeOH) λ_{max} 233 nm (ϵ 14 000), 258 (6300), 292 (4300), 366 (14 000); ^{1}H NMR ($CDCl_3$) δ 7.25 (d, 3 C_6H_5), 5.58 (d, H-1′, $J_{1',2'}$ = 2.6 Hz), 5.2–4.0 (3 $PhCH_2$, H-1′, H-3′, H-4′), 3.50–4.02 (ddd, 2 H-5′). Anal. Calcd for $C_{31}H_{31}N_5O_4S\cdot O\cdot 4H_2O$: C, 64.54; H, 5.56; N, 12.14; S, 5.57. Found: C, 64.57; H, 5.52; N, 12.04; S, 5.77.

Further elution yielded 0.10 g of residual foamed glass that was a mixture (ca. 1:1) of **4** (R_f 0.4) and a byproduct (R_f 0.6, in chloroform–ethyl acetate, 85:15). Finally, 0.12 g of the byproduct was eluted as a residual oil that was nearly homogeneous (R_f 0.6). Purification by preparative TLC afforded 0.17 g (4%) of product identified as **3-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-5-(benzylthio)-7-aminopyrazolo[4,3-*d*]pyrimidine** by mass spectral analysis which showed diagnostic peaks for M (m/e 659), M – benzyl (m/e 568), and B + 30 (m/e 286) which is characteristic of *C*-nucleosides; ^{1}H NMR ($CDCl_3$) δ 7.27 (br s, C_6H_5), 5.58 (d, H-1′, J = 5.58 Hz); UV (MeOH) λ_{max} 244 nm (ϵ 16 600), 307–310 (4500).

3-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione (24b). The crude product was a residual gummy solid (3.7 g, 107% of theory). Preparative LC with chloroform–acetone (88:12) afforded 1.97 g of product which was crystallized from 30 mL of hot 2-propanol by adding nearly 30 mL of water and chilling to 0 °C: yield 1.67 g (48%); mp 184–185.5 °C. A second crop (0.85 g; mp 179–183 °C) was obtained from the filtrate by crystallization from carbon tetrachloride: total yield 51%; R_f 0.30 (in chloroform–acetone, 85:15); UV (MeOH) λ_{max} 235 (ϵ 13 900), 258 (6000), 304–306 (5000), 358–360 (12 800); ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 2 C_6H_5), 7.2–7.1 and 7.05–6.85 (C_6H_5), 5.40 (d, H-1′, $J_{1',2'}$ = 3.8 Hz), 4.56 (s) and 4.50 (s) (2 $PhCH_2$), 4.4–4.0 ($PhCH_2$, H-2′, H-3′, H-4′), 3.75 (uneven d, 2 H-5′, apparent $J \approx$ 5.4 Hz). Anal. Calcd for $C_{31}H_{31}N_5O_4S$: C, 65.36; H, 5.48; N, 12.29; S, 5.63. Found: C, 65.41; H, 5.59; N, 12.25; S, 5.98.

3-(3,5-Di-*O*-benzyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione (24c). Purification of the crude product (1.61 g, 116% of theory) by preparative LC with chloroform–acetone (88:12) afforded 0.61 g of purified product which was crystallized from 30 mL of chloroform–carbon tetrachloride (1:1): yield 0.56 g (41%); mp 240–255 °C. Residues from the mother liquor and from impure HPLC fractions were combined and chromatographed on 20 g of silica gel to yield additional product (0.078 g; mp 244–260 °C): total yield 46%; R_f 0.35 (in chloroform–acetone 85:15); UV (MeOH) λ_{max} 234–235 (ϵ 12 800), 291–296 (3500), 365–366 (13 700); ^{1}H NMR ($CDCl_3$–CD_3SOCD_3) δ 7.30 (s), 7.28 (s) (2 C_6H_5), 6.2 (br s, NH_2), 5.28 (dd, H-1′, $J_{1',2'A}$ = 5.8 Hz, $J_{1',2'B}$ = 10.2 Hz), 4.48 (s), 4.41 (s) (2 $PhCH_2$), 4.15 (rough t, H-3′, H-4′), 3.52 (uneven d, 2 H-5′), 2.9–2.45 (m) and 2.3–2.0 (m) (2 H-2′). Anal. Calcd for $C_{24}H_{25}N_5O_3S$: C, 62.19; H, 5.44; N, 15.11; S, 6.92. Found: C, 62.07; H, 5.34; N, 14.96; S, 6.92.

3-(β-D-Ribofuranosyl)-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione (4). A solution of 16 ± 0.5 mL of boron trichloride (from an inverted lecture bottle) in 300 mL of dichloromethane was stirred at –78 °C and treated with a solution of 1.45 g (2.55 mmol) of thione **24a** in 200 mL of dichloromethane added in drops. The cloudy solution clarified after 30 min, and stirring at –78 °C was continued for 3 h. Immediate separation of a precipitate when the solution was warmed to 0 °C presumably indicated incomplete reaction, and the mixture was chilled back to –78 °C and treated with 200 mL of dichloromethane and a stream of boron trichloride gas for 15 min. Stirring was continued without cooling for 1 h, allowing 30 min at room temperature, and then the mixture was cooled again to –70 °C and treated with 100 mL of dichloromethane–methanol (2:1) added dropwise to decompose excess boron trichloride, followed by 100 mL of dichloromethane–methanol (1:1) and 250 mL of methanol, which clarified the mixture. The solution was evaporated, and the residue was redissolved in 150 mL of methanol and reevaporated three times. Analysis of the product (1.0 g, 130% of theory) by reverse-phase HPLC on a C-18 RCM-100 column in methanol–0.004 M dihydrogen potassium phosphate at pH 4 (56:44) showed it was 86% pure (by UV absorbance). Purification by reverse-phase preparative LC on a Waters Prep 500 C-18 column with water–methanol (91:9) afforded 460 mg of product that was 98% pure by HPLC. Two recrystallizations from 15 mL of water and 8 mL of water yielded the product: 405 mg (51%); mp 168–174 °C; UV λ_{max} (MeOH) 239 μm (ϵ 12 800), 294 (4100), 362–363 (15 200), λ_{max} (0.1 N HCl) 240 (9600), 260 (5900), 339–340 (16 500), λ_{max} (pH 7) 229 (14 100), 292 (4900), 354–356 (12 700), λ_{max} (0.1 N NaOH) 231 (19 000), 279–281 (7700), 347.5 (12 000); IR 2.83, 2.93, 3.1 (OH and NH), 6.1, 6.2 μm (heterocyclic C=N); ^{1}H NMR (slurried in D_2O, evaporated, and redissolved in CD_3OD) δ 5.05 (d, H-1′), 4.50 (q, H-2′), 4.28 (q, H-3′), 4.15 (q, H-4′), 3.80 (dd, 2 H-5′), $J_{1',2'}$ = 7.3 Hz, $J_{2',3'}$ = 5.0 Hz, $J_{3',4'}$ = 2.7 Hz, $J_{4',5'A}$ = 2.3 Hz, $J_{4',5'B}$ = 2.8 Hz, $J_{5'A,5'B}$ = 12.2 Hz. Anal. Calcd for $C_{10}H_{13}N_5O_4S\cdot 0.75H_2O$: C, 38.40; H, 4.67; N, 22.39; S, 10.40. Found: C, 38.65; H, 4.83; N, 22.50; S, 10.18.

3-(β-D-Arabinofuranosyl)-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione (5). In the same way, a solution of 18 mL of boron trichloride in 400 mL of dichloromethane at –78 °C was treated with a suspension of 1.80 g (3.16 mmol) of **24b** in 300 mL of dichloromethane and washed in with another 200 mL of dichloromethane. The resultant orange solution was stirred for 1 h at –78 °C, warmed gradually to room temperature over 1.5 h, and stirred an additional 2 h. The separation of a precipitate after this time could not be explained. The mixture was cooled again, and the excess boron trichloride was decomposed, as for **4**. The evaporated crude product (1.0 g, 106% of theory) was 49% pure (based on UV absorbance) by reverse-phase HPLC analysis on a C-18 column in 0.04 M (pH 4) potassium dihydrogen phosphate–methanol (70:30). Partial purification was accomplished by reverse-phase preparative LC on a Prep 500 C-18 column with water–methanol (92:8), which eluted the product at the front; yield 0.6 g (60% pure by analytical HPLC). Purification was completed by rechromatography and elution with water–methanol (98:2); yield 125 mg (90% purity). A solution of the residual product in methanol was clarified by filtration and evaporated. The product (92 mg) was crystallized twice from 5 mL of water: yield 50 mg (5%); mp 224–225 °C dec; >99% purity by HPLC; UV λ_{max} (MeOH) 237 nm (ϵ 13 600), 295 (4700), 362 (14 400), λ_{max} (0.1 N HCl) 238 (10 700), 260 (6500), 339 (16 900), λ_{max} (pH7) 232 (14 600), 296 (5900), 354 (13 000), λ_{max} (0.1 N NaOH) 231 (14 300), 288 (6,200), 347 (14 300); ^{1}H NMR (CD_3OD) δ 5.25 (d, H-1′), 4.25 (dd, H-2′), 4.13 (dd, H-3′), 3.90 (m, H-4′, incompletely resolved), 3.75 (m, 2 H-5′), $J_{1',2'}$ = 4.1 Hz, $J_{2',3'}$ = 2.3 Hz, $J_{3',4'}$ = 3.6 Hz. Anal. Calcd for $C_{10}H_{13}N_5O_4S\cdot 1.5H_2O$: C, 36.81; H, 4.94; N, 21.46; S, 9.82. Found: C, 36.77; H, 4.80; N, 21.33; S, 10.15.

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-5-aminopyrazolo[4,3-*d*]pyrimidine-7-thione (6). The thione **24c** (474 mg, 1.02 mmol) only partially dissolved in 200 mL of dichloromethane. The suspension was slowly added to a stirred solution at –78 °C of 5 ± 0.2 mL of boron trichloride in 200 mL of dichloromethane and washed in with another 100 mL of dichloromethane. Although a small amount of solid still persisted after 8 h of stirring at –78 °C, the excess boron trichloride was then decomposed, as for **4**. The evaporated crude product (300 mg, 105% of theory) was 70–80% pure by reverse-phase HPLC analysis on a C-18 column in 0.04 M potassium dihydrogen phosphate. Purification was accomplished by reverse-phase preparative LC on a Waters Prep 500 C-18 column eluted (250 mL/min) with water–methanol (91:9), collecting 250-mL fractions combined as follows: 1 L, discarded; 500 mL, only 15 mg of impure **6**; 2 L, 120 mg of **6**; 1500 mL, 25 mg of impure **6**. A final methanol wash eluted some incompletely deblocked mono-*O*-benzyl de-

rivative of 6 and various impurities. The 120-mg fraction was crystallized from 5 mL of water chilled to 5 °C [yield 93 mg (32%); mp 235-250 °C] plus a second crop of 18 mg: total yield 37%; UV λ_{max} (MeOH) 238-239 nm (ϵ 13 800), 293-294 (4400), 363 (15 600), λ_{max} (0.1 N HCl) 239 (10 700), 259-261 (6100), 340 (16 400), λ_{max} (pH7) 232-233 (14 100), 293-294 (5400), 356-358 (12 800); λ_{max} (0.1 N NaOH) 231-232 (18 800), 280-281 (7300), 347-348 (12 000); IR 3.0-3.1 (NH, OH), 6.13 and 6.31 μm (heterocyclic C=N); ^{1}H NMR (slurried in D_2O, evaporated, and redissolved in CD_3OD) δ 5.43 (dd, H-1', $J_{1',2'A}$ = 6.0 Hz, $J_{1',2'B}$ = 10.5 Hz), 4.47 (rough dt, H-3', presumably ddd), 4.04 (m, H-4'), 3.85 (dd, H-5'A, $J_{4',5'A}$ = 3.6 Hz), 3.65 (dd, H-5'B, $J_{4',5'B}$ = 3.3 Hz, J_{gem} = 12 Hz), 2.5 (ddd, H-2'A, $J_{2'A,3'}$ = 6.0 Hz, $J_{1',2'A}$ = 1.05 Hz), 2.3 (ddd, H-2'B, $J_{2'B,3'}$ = 1.5 Hz, $J_{1',2'B}$ = 6.0 Hz, J_{gem} = 13.3 Hz). Anal. Calcd for $C_{10}H_{13}N_5O_3 \cdot {}^2/_3H_2O$: C, 40.67; H, 4.89; N, 23.71; S, 10.85. Found: C, 40.76; H, 5.02; N, 23.35; S, 10.63.

Acknowledgment. This investigation was supported by Grant CA 25948 awarded by the National Cancer Institute, DHHS. We thank Dennis Knowles and Lawrence Paddock for resynthesis of intermediates. We are indebted to Lawrence Paddock for the analytical samples of 9 and 11.

Registry No. 4, 88287-89-2; 5, 88287-90-5; 6, 88287-91-6; 7, 50908-41-3; 8·HCl, 88287-61-0; 9, 88287-60-9; 10, 88287-62-1; 11, 88287-63-2; 12, 88287-64-3; 13, 88287-65-4; 14a, 88287-67-6; 14c, 88287-66-5; 15a, 88335-33-5; 15b, 52646-33-0; 15c, 88287-68-7; 16a, 88287-69-8; 16b, 88287-70-1; 16c, 88287-71-2; 17a, 88287-72-3; 17b, 88287-73-4; 17c, 88287-74-5; 18a, 88295-39-0; 18b, 88287-75-6; 18c, 88287-76-7; 19a, 88287-77-8; 19c, 88287-78-9; 20b, 88287-79-0; 21a, 88287-80-3; 21b, 88287-82-5; 21c, 88287-81-4; 22a, 88287-84-7; 23a, 88287-85-8; 24a, 80523-94-0; 24b, 88287-87-0; 24c, 88287-88-1; 26, 3911-55-5; 27, 88287-83-6; 30a, 88287-86-9; dimethyl acetylenedicarboxylate, 762-42-5; benzyl mercaptan, 100-53-8.

Control of Regiochemistry in Photodimerization through Micellar Preorientational Effect: 2-Substituted Naphthalenes†

V. Ramesh and V. Ramamurthy*

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

Received June 20, 1983

Photodimerization of 2-substituted naphthalenes in organic solvents has been well explored. In contrast to their behavior in organic solvents, in anionic and cationic micellar media enhanced reactivity and pronounced regioselectivity are observed. Reactivity enhancement in micellar media is attributed to the local concentration effect. Enhanced reactivity in CTAC and DTAC compared to CTAB micelles is attributed to the counterion effect, and the regioselective photodimerization observed in anionic and cationic micelles leading exclusively to the cis dimer or the products derived therefrom is rationalized on the basis of the preorientational effect of micelles.

Control of stereo- and regiochemistry in photochemical reactions through the use of constrained systems such as molecular and liquid crystals, monolayers, and micellar assemblies has opened new vistas in photochemistry.[1] In particular the photocycloaddition reactions of cyclopentenones,[2] cyclohexenones,[3] pyridones,[4] and 9-(hydroxymethyl)anthracene[5] in micellar media have demonstrated the potential use of micellar effects in controlling the regiochemistry of photodimerization reactions. The ability of micelles to organize reactants in a specific geometry (preorientational effect) and the polar nature of the micellar interface are the two features that could affect the regiochemistry of photodimerization. Studies on photodimerization of coumarin[6] and 9-methylanthracene[7] in micellar media have revealed that in such systems the polarity effect is predominant in effecting a regioselective dimerization. During the photodimerization of 7-alkoxy- and 4-methyl-7-alkoxycoumarins[8] in micellar media, a failure to control the regiochemistry of the photodimerization was observed, thus suggesting limitations of micellar effects. A study of 2-substituted naphthalenes 1-6 (Scheme I) in micellar media was undertaken in order to understand the extent of micellar effects on regiochemical control of photodimerization reactions.

The photodimerization of 2-substituted naphthalenes in organic solvents has been well explored.[9-19] In organic solvents the trans dimer 7 is the major and the cis dimer 8 (or products derived therefrom) the minor product (Figure 1).[14] It has been established that the dimerization process is polarity independent,[9,12] hence the polarity effect of micelles can be excluded. Further, the 2-substituents—alkoxy, carbomethoxy, and nitrile—being hy-

† Respectfully dedicated to Prof. P. de Mayo on the occasion of his 60th birthday.

(1) Turro, N. J.; Gratzel, M.; Braun, A. N. *Angew. Chem., Intl. Ed. Engl.* **1980**, *19*, 675. Whitten, D. G.; Russell, R. C.; Schmehl, R. H. *Tetrahedron* **1982**, *38*, 2455. Thomas, J. M.; Morsi, S. E.; Desvergne, J. P. *Adv. Phy. Org. Chem.* **1977**, 63-151. Nerbonne, J. M.; Weiss, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 402.
(2) Lee, K. H.; de Mayo, P. *J. Chem. Soc., Chem. Commun.* **1979**, 493. Berenjian, N.; de Mayo, P.; Sturgeon, M.; Sydnes, L. K.; Weedon, A. C. *Can. J. Chem.* **1982**, *60*, 425.
(3) Furgues, R.; Maurette, M. T.; Oliveros, E.; Riviere, M.; Lattes, A. *Nouv. J. Chim.* **1979**, *3*, 487.
(4) Nakamura, Y.; Kato, T.; Morita, Y. *Tetrahedron Lett.* **1981**, *22*, 1205.
(5) Wolff, T. *J. Photochem.* **1981**, *16*, 343.
(6) Muthuramu, K.; Ramamurthy, V. *J. Org. Chem.* **1982**, *47*, 3976.
(7) Wolff, T.; Muller, N.; Von Bunau, G. *J. Photochem.* **1983**, *22*, 61.
(8) Muthuramu, K.; Ramnath, N.; Ramamurthy, V. *J. Org. Chem.* **1983**, *48*, 1872. Ramnath, N.; Ramamurthy, V. submitted for publication in *J. Org. Chem.*
(9) Bradshaw, J. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1963**, 85, 3953.
(10) Bradshaw, J. S.; Nielsen, N. B.; Rees, D. P. *J. Org. Chem.* **1968**, *33*, 259.
(11) Selinger, B. K. *Aust. J. Chem.* **1966**, *19*, 825.
(12) Wilairat, P.; Selinger, B. *Aust. J. Chem.* **1968**, *21*, 733.
(13) Collin, P. J.; Sugowdz, G.; Teitei, T.; Wells, D.; Sasse, W. H. F. *Aust. J. Chem.* **1974**, *27*, 227.
(14) Teitei, T.; Wells, D.; Spurling, T. H.; Sasse, W. H. F. *Aust. J. Chem.* **1978**, *31*, 85.
(15) Collin, P. J.; Roberts, D. B.; Sugowdz, G.; Wells, D.; Sasse, W. H. F. *Tetrahedron Lett.* **1972**, 321.
(16) Mattingly, T. W.; Lancaster, J. E.; Zweig, A. *J. Chem. Soc. D* **1971**, 595.

0022-3263/84/1949-0536$01.50/0