Synthesis of "9-Deazaguanosine" and Other New Pyrrolo[3,2-*d*]pyrimidine *C*-Nucleosides[1]

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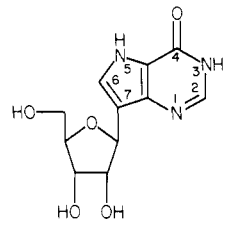
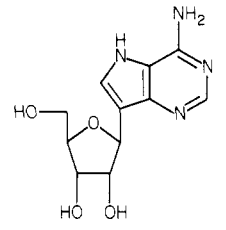
The syntheses of several new pyrrolo[3,2-*d*]pyrimidine (9-deazapurine) *C*-nucleosides (**3–5**) and an improved synthesis of 9-deazainosine (**1**) are described. 9-Deazaguanosine **5** was obtained from the blocked 4-ribosylated 3-amino-2-carbethoxypyrrole key intermediate **10β** by its initial conversion to thiourea derivative **23** followed by S-methylation, ring closure with ammonia, and deprotection in acid. 9-Deazainosine **1** was also obtained from intermediate **10β** by pyrimidine ring closure with formamidine acetate and final deprotection in acid. The 4-thiono and methylthio derivatives **3** and **4** were prepared via the corresponding 3-amino-2-cyanopyrrole **5** by its conversion to thioamide **16** and cyclization with triethyl orthoformate.

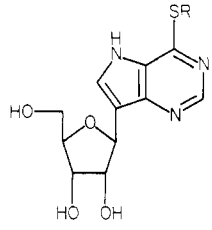
As part of our ongoing program directed toward the synthesis and biological evaluation of pyrrolo[3,2-*d*]pyrimidine *C*-nucleosides as potential anticancer agents, we have reported recently the synthesis of 9-deazainosine [**1**,



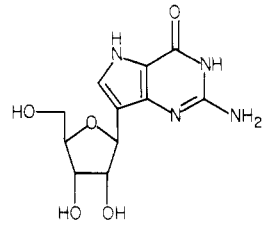
1



2



3, R = H
4, R = Me



5

7-(β-D-ribofuranosyl)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine][2a] and of 9-deazaadenosine [**2**, 4-amino-7-(β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine].[2b,3] Because of the pronounced growth inhibitory activity of the latter to several leukemic cell lines, the syntheses of 9-deaza-6-thioinosine (**3**), its SMe derivative **4**, and 9-deazaguanosine (**5**) as novel target analogues in this class of *C*-nucleosides were of particular interest. Of special relevance to the potential biological activity of compounds **3** and **5** was the possibility that these may behave as purine nucleoside phosphorylase (PNPase) inhibitors and may thus serve as useful probes for several important biological reactions.[4–6] We describe here the syntheses of **3–5**.[7]

A direct approach to the synthesis of 6-thioinosine analogue **3** was first envisaged by the thiation with P_2S_5[8–10] of a suitably protected derivative of 9-deazainosine (**1**). Our earlier synthesis of **1** depended on a two-step conversion of **11β** (Scheme I) into the fully blocked 5-benzyl-7-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**13**) followed by debenzylation and simultaneous detritylation with sodium naphthylide in THF. This procedure had readily afforded the isopropylidene derivative of **1** in 57% yield. The scale up of this synthesis, however, proved troublesome and afforded this product in reduced yield. An improved procedure was therefore developed that was based on our synthetic studies of 9-deazaadenosine (**2**). The synthetic precursor, the 2-formylacetonitrile **7**,[2a,11] readily accessible by the mild acid hydrolysis of the enamine **6**,[12] was thus condensed with glycine ethyl ester hydrochloride in aqueous methanol and in the presence of sodium acetate. As the reaction proceeded, the crystalline enamine **8** precipitated directly from the mixture. Recrystallization from methanol afforded a stereochemically pure product (60% from **6**). Its ^1H NMR spectrum was consistent with the enamine form (see Tables I and II) showing doublets at δ 3.97 (CH_2NH, J = 5.8 Hz) and at δ 6.75 (vinylic CHNH, J = 12.8 Hz), which collapsed into singlets upon D_2O exchange of the NH proton at δ 5.26. Furthermore, its infrared spectrum exhibited a single weak absorption band at 3430 cm^{-1}, consistent with the presence of a secondary amine. These results are also consistent with our earlier studies of a nonribosylated model compound similar to **8** which was also shown to exist exclusively in the enamine rather than the imine form.[13] Examination of the mother liquor from which product **8** was obtained indicated a complex mixture containing at least three other chromatographically similar components. While the difficulty in comparing crystalline product **8** with these other isomeric byproducts made its stereo-

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

(2) (a) Lim, M.-I.; Klein, R. S.; Fox, J. J *Tetrahedron Lett.* **1980**, *21*, 1013. (b) Lim, M.-I.; Klein, R. S. *Ibid.* **1981**, *22*, 25.

(3) The naming of all pyrrole and pyrrolo[3,2-*d*]pyrimidine intermediates utilizes the usual numbering system of these heterocycles (see illustration). The purine nucleoside analogues **1–5** and their blocked derivatives may be referred to as 9-deazapurine nucleosides and numbered after the parent purine system.

(4) Parks, R. E., Jr.; Stoeckler, J. D.; Cambor, C.; Savarese, T. M.; Crabtree, G. W.; Chu, S.-H. "Molecular Actions and Targets for Cancer Chemotherapeutic Agents"; Sartorelli, A. C., Lazo, J. S., Bertino, J. R., Eds; Academic Press: New York, 1981; p 229.

(5) Suhadolnik, R. J. "Nucleoside Antibiotics"; Wiley-Interscience: New York, 1970. Suhadolnik, R. J. "Nucleosides as Biological Probes"; Wiley-Interscience: New York, 1979.

(6) Lewis, A. F.; Townsend, L. B. *J. Am. Chem. Soc.* **1982**, *104*, 1073.

(7) Presented in part at the 182nd National Meeting of the American Chemical Society, New York, Aug 1981, CARB 48.

(8) Fox, J. J.; Wempen, I.; Hampton, A.; Doerr, I. L. *J. Am. Chem. Soc.* **1958**, *80*, 1669.

(9) Mizuno, Y.; Ikehara, M.; Watanabe, K. A.; Suzaki, S. *J. Org. Chem.* **1963**, *28*, 3331.

(10) Acton, E. M.; Ryan, K. J. *Nucleic Acids Res. Symp. Ser.* **1981**, *9*, 243.

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

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

(13) Lim, M.-I.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 3826 and references therein.

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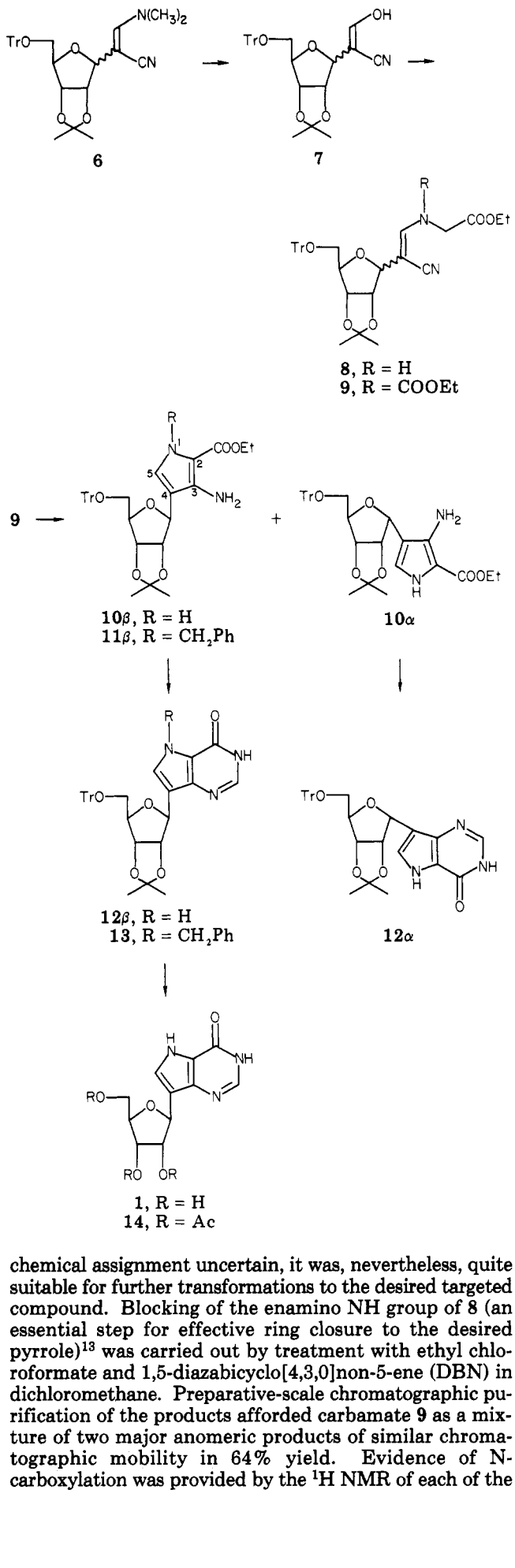
Scheme I



chemical assignment uncertain, it was, nevertheless, quite suitable for further transformations to the desired targeted compound. Blocking of the enamino NH group of 8 (an essential step for effective ring closure to the desired pyrrole)[13] was carried out by treatment with ethyl chloroformate and 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) in dichloromethane. Preparative-scale chromatographic purification of the products afforded carbamate 9 as a mixture of two major anomeric products of similar chromatographic mobility in 64% yield. Evidence of N-carboxylation was provided by the ^{1}H NMR of each of the components after more elaborate preparative TLC of a small sample of this mixture.

Without anomeric separations, 9 was utilized directly in the subsequent ring closure to 10. Initial attempts at carrying out such cyclization by direct treatment of 9 with DBN in dichloromethne (as had been successfully done for the ring closure of the corresponding (carbethoxyamino)acetonitrile derivative)[2b] were disappointing. In contrast to this precedent, cyclization of 9 under these same conditions was found to be much slower, requiring 2 or more days to reach completion. This was further complicated by partial N-deacylation of the initially produced pyrrole, thus affording a mixture of four products (10α and 10β where R = H and R = COOEt). These difficulties were circumvented by utilization of sodium ethoxide in ethanol (20 °C, 40 min), which afforded directly the unblocked anomers 10α and 10β only. These were readily separable by silica gel flash column chromatography, which afforded first 10β as a crystalline product (53% yield) followed by 10α (28% yield) obtained as an amorphous material. Assignment of the epimeric configuration at C-1′ to 10α and 10β was based on a comparison of their ^{1}H NMR spectra. Thus, the spectrum of 10α exhibited a signal for H-1′ appearing further downfield (δ 5.14) than that for 10β (δ 4.80)[14] as well as a consistently smaller $\Delta\delta$ value for the difference in the chemical shifts of its isopropylidene dimethyl group (20 vs. 23 Hz).[2a,15] It is noteworthy that, under these alkaline conditions, N-decarbethoxylation of uncyclized enamine 9 (and hence recovery of 8) was found to be negligible while N-decarbethoxylation of 10 (R = COOEt) obviously occurred much more rapidly.

While we have described here only the use of ethyl chloroformate for blocking of enamine 8, we have also found that other acylating agents (e.g., benzyl chloroformate) are as effective and lead to similar results.

Cyclization of 10β to give pyrrolo[3,2-d]pyrimidine 12β was accomplished by prolonged treatment (4 days) with an excess of formamidine acetate (5 equiv) in boiling ethanol. Purification by column chromatoography afforded 3*H*,5*H*–pyrrolo[3,2-*d*]pyrimidine *C*-nucleoside 12β in 77% yield. Although retention of the β configuration at C-1′ was anticipated on the basis of available precedents in a similar system,[2b] it was nevertheless deemed desirable to further confirm this assignment prior to deprotection of 12β to 1. The α-ribosylated 3-amino-2-carbethoxypyrrole 10α was therefore converted to the corresponding α-*C*-nucleoside 12α by an identical procedure. Again, comparison of the ^{1}H NMR of 12β and 12α confirmed the stereochemical assignments on the basis of the aforementioned criteria viz., the relative $\Delta\delta$ values of their isopropylidene groups and the relative H-1′ chemical shifts. Additional ^{1}H NMR spectral evidence was obtained by the observation that the H-4′ signal of 12α appears as a pseudotriplet ($J_{3',4'} \simeq 0$ Hz) while that of 12β is a multiplet ($J_{3',4'}$ = 3.8 Hz). These findings are consistent with similar

(14) This relationship between the chemical shifts of H-1′ for several α–β epimeric pairs of *N*-nucleosides[14a] and *C*-nucleosides[2,14b] has served as a reliable criterium for the epimeric assignment at C-1′: (a) Townsend, L. B. "Synthetic Procedures in Nucleic Acid Chemistry; Zorbach, W. W., Tipson, R. S., Eds.; Wiley-Interscience: New York, 1973; Vol. 2, p 330. (b) Tam, S. Y.-K.; Klein, R. S.; Wempen, I; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4547. Lerch, U.: Burdon, M. G.; Moffatt, J. G. *Ibid.* **1971**, *36*, 1507. De Bernardo, S.; Weigele, M. *Ibid.* **1976**, *41*, 287.

(15) (a) Imbach, J.-L.; Kam, B. L. *J. Carbohydr. Nucleosides, Nucleotides* **1974**, *1*, 271 and references therein. (b) The "relative" $\Delta\delta$ value of isopropylidene methyls has been found useful in the configurational assignment of several *C*-glycosides substituted at C-5′; see ref 17a. Sokolova, T. N.; Yartseva, I. V.; Preobrazhenskaya, M. N. *Carbohydr. Res.* **1981**, *93*, 19. Tam, S. K.-Y.; Klein, R. S.; de las Heras, F. G.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 4854.

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	$C(CH_3)_2$	other
8	A	4.61 (m)			4.24[c]	3.31 (dd)	3.14 (dd)	1.33 1.58	1.29 (t, CH_3), 3.97 (d, NH CH_2), 4.23 (q, CH_2CH_3), 5.26 (m, NH, D_2O exch), 6.75 (d, =CHNH), 7.24-7.41 (m, trityl)
10α	A	5.14 (d)	4.87 (m)		4.29[c]	3.28 (m)		1.34 1.54	1.32 (t, CH_3), 4.29 (m, CH_2CH_3), 4.56 (br s, NH_2, D_2O exch), 6.80 (d, H-5), 7.23-7.50 (m, trityl), 8.37 (br s, NH, D_2O exch)
10β	A	4.80 (s)			4.17[c]	3.31 (dd)	3.45 (dd)	1.35 1.58	1.31 (t, CH_3), 4.29 (m, CH_2CH_3), 4.61 (br s, NH_2, D_2O exch), 6.69 (d, H-5), 7.23-7.50 (m, trityl), 8.13 (br s, NH, D_2O exch)
12α	A	5.57 (d)	4.86 (m)		4.38 (t)[b]	3.28 (d)		1.30 1.52	7.22-7.53 (m, trityl and H-6), 7.98 (s, H-2), 11.01, 12.20 (2 br s, 2NH, D_2O exch)
12β	A	5.32 (d)	5.09 (dd)	4.77 (dd)	4.33 (m)	3.28 (d)		1.35 1.58	7.17-7.37 (m, trityl and H-6), 8.30 (br s, H-2), 11.00, 12.34 (2 br s, 2NH, D_2O exch)
1	C[e]	5.02 (m)[d]	4.25 (m)			3.87 (d)			7.70 (s, H-6), 8.74 (s, H-2)
14	B	5.09 (d)	5.67 (dd)	5.36 (dd)	4.08-4.40 (m)				2.00, 2.04, 2.07 (3 s, $3CH_3$), 7.49 (d, H-6), 7.83 (d, H-2), 11.95, 12.17 (2 br s, 2NH)
16	A	4.74 (m)			4.22 (m)	3.34 (m)		1.35 1.57	6.68 (d, H-5), 7.01 (br s, NH_2, D_2O exch), 7.22-7.47 trityl and NH_2), 9.04 (br s, NH, D_2O exch)
17	A	5.27 (d)	5.11 (dd)	4.76 (dd)	4.36 (m)	3.28 (m)		1.37 1.61	7.19-7.51 (m, trityl and H-6), 7.92 (s, H-2), 9.50, 11.33 (2 br s, 2NH, D_2O exch)
3	C[e]	5.06 (d)	4.32 (m)			3.87 (d)			7.89 (s, H-6), 8.59 (s, H-2)
18	A	5.33 (d)	5.20 (dd)	4.78 (dd)	4.34 (m)	3.29 (m)		1.36 1.60	2.73 (s, SCH_3), 7.16-7.47 (m, trityl and H-6), 8.74 (s, H-2), 9.01 (br s, NH, D_2O exch)
4	C[e]	5.12 (m)[d]	4.32 (m)			3.94 (d)			2.86 (s, SCH_3), 8.08 (s, H-6), 8.84 (s, H-2)
23	A	5.19 (d)	4.71 (dd)	4.57 (dd)	4.19[c]	3.25 (m)		1.26 1.51	1.28 (t, CH_3), 4.29 (m, CH_2CH_3), 6.94 (d, H-5), 7.20-7.85 (m, trityl and phenyl), 9.11, 9.18, 12.00 (3 br s, 3NH, D_2O exch)
24	A	4.93 (d)	4.62 (m)		4.16[c]	3.27 (m)		1.24 1.47	1.23 (t, CH_3), 2.53 (s, SCH_3), 4.26 (m, CH_2CH_3), 6.95 (d, H-5), 7.21-7.47 and 8.25-8.33 (m, trityl and phenyl), 9.18, 12.08 (2 br s, 2NH, D_2O exch)

Table I (*Continued*)

compd	solvent[a]	H-1′	H-2′	H-3′	H-4′	H-5′a	H-5′b	$C(CH_3)_2$	other
27	A	5.26 (m)		4.76 (dd)	4.34 (m)	3.30 (dd)	3.13 (dd)	1.36 1.62	2.36 (s, SCH_3), 7.14-7.46 (trityl and H-6), 10.81 (d, NH-5, D_2O exch), 11.57 (s, NH-3, D_2O exch)
28	B	4.99 (m)		4.66 (m)	4.04 (m)	3.10 (m)		1.27 1.47	5.86 (br s, NH_2, D_2O exch), 7.16-7.33 (m, trityl and H-6), 10.47, 11.50 (2 br s, 2NH, D_2O exch)
5	C[e]	4.90 (d)	4.21 (m)			3.86 (d)			7.47 (s, H-6)

[a] A, $CDCl_3$, B, Me_2SO-d_6; C, D_2O. [b] Apparent triplet.[16,17] [c] Partial overlap with the CH_2CH_3 signal obscuring its multiplicity. [d] Virtual coupling between H-1′ and H-3′ is the cause of its multiplicity. [e] 3-(Trimethylsilyl)-1-propanesulfonic acid sodium salt used as internal standard.

Table II. First-Order Coupling Constants (Hz)

compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	other
8	*a*	*a*	*a*	4.0	4.3	−10.1	J_{NH,CH_2} = 5.8, $J_{NH,CH}$ = 12.8
10β	*a*	*a*	*a*	3.6	3.9	−10.2	$J_{NH,H-5}$ = 3.4
10α	2.7	*a*	*a*	*a*	*a*	*a*	$J_{NH,H-5}$ = 3.4
12β	4.0	6.0	3.8	4.6	4.6	0	
12α	3.1	*a*	0	*a*	*a*	*a*	
1	*a*	*a*	*a*	3.1	3.1	0	
14	6.7	5.9	4.3	*a*	*a*	*a*	$J_{NH,H-6}$ = 2.7, $J_{NH,H-2}$ = 2.7
16	*a*	*a*	*a*	3.3	4.2	−10	$J_{NH,H-5}$ = 3.4
17	4.3	6.4	3.7	*a*	*a*	*a*	
3	7.0	*a*	*a*	3.0	3.0	0	
18	4.3	6.3	3.9	*a*	*a*	*a*	
4	*a*	*a*	*a*	3.8	3.8	0	
23	4.3	6.3	3.8	*a*	*a*	*a*	$J_{NH,H-5}$ = 3.1
24	3.4	*a*	*a*	*a*	*a*	*a*	$J_{NH,H-5}$ = 3.4
27	*a*	*a*	*a*	5.5	6.1	−9.5	$J_{NH,H-6}$ = 2.4
28	*a*	*a*	*a*	*a*	*a*	*a*	
5	7.3	*a*	*a*	3.1	3.1	0	

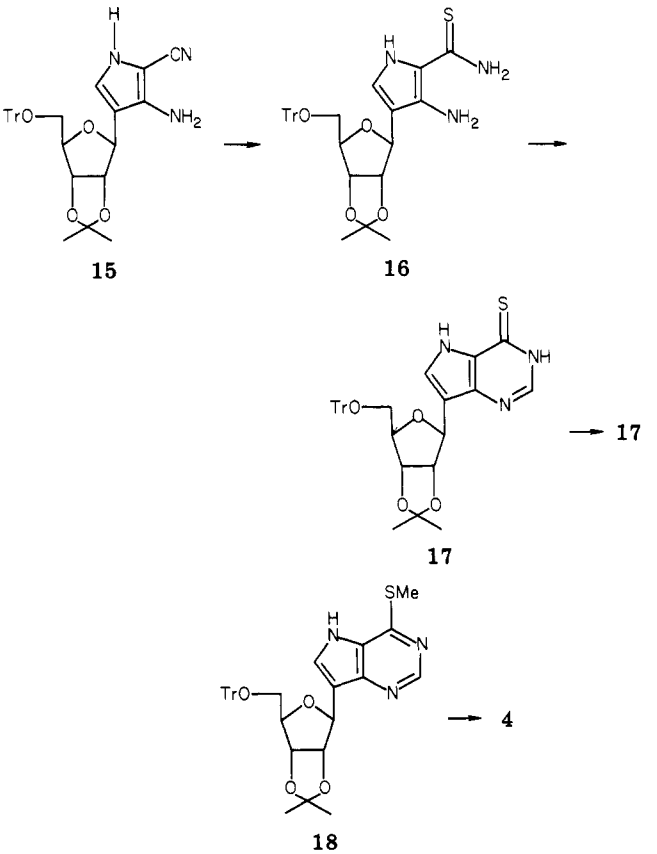
[a] Unresolved.

configurational relationships empirically derived from the study of several 2′,3′-O-isopropylidenated *N*-ribonucleosides[16] and *C*-ribonucleosides.[12,17] Further confirmation was obtained from the ^{13}C NMR spectra of the blocked anomers, which exhibited isopropylidene methyl signals at 25.4 and 27.3 ppm (for **12β**) and at 24.8 and 26.2 ppm (for **12α**). Such values are in excellent agreement with those originally established for *C*-glycosides derived from 2,3-*O*-isopropylidene-D-ribose,[17a,b,18] in which the methyl signals of the "β" series appear at 25.5 ± 0.2 and 27.5 ± 0.2 ppm while in the "α" series they appear at 24.9 ± 0.3 and 26.3 ± 0.2 ppm. These observations thus confirmed that no epimerization at C-1′ occurred in the conversions **10β** → **12β** or **10α** → **12α**. Since the anomers **12α** and **12β** possess very similar chromatographic migratory properties in several solvent systems, it has been found advantageous to perform the anomeric separation at the pyrrole *C*-nucleoside stage as we described above.

Final removal of the protecting groups of **12β** with 6% methanolic hydrogen chloride at 25 °C for 50 min readily afforded 9-deazainosine (**1**[2a]) as a unique anomeric product in 91% yield.

Several attempts to convert the tri-*O*-acetyl derivative **14** of 9-deazainosine (**1**) with phosphorus pentasulfide in

Scheme II



15 **16** **17** **18** → **17** → **4**

(16) McCoss, M.; Robins, M. J.; Rayner, B.; Imbach, J.-L. *Carbohydr. Res.* **1977**, *59*, 575.

(17) (a) Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Maddox, M. L.; Cristensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1973**, *97*, 4602. (b) Cousineau, T. J.; Secrist, J. A., III *J. Org. Chem.* **1979**, *44*, 4351. (c) Poonian, M. S.; Nawoswiat, E. F. *Ibid.* **1980**, *45*, 203. (d) Logue, M. S.; Sarangan, S. *Nucleosides Nucleotides* **1982**, *1*, 89.

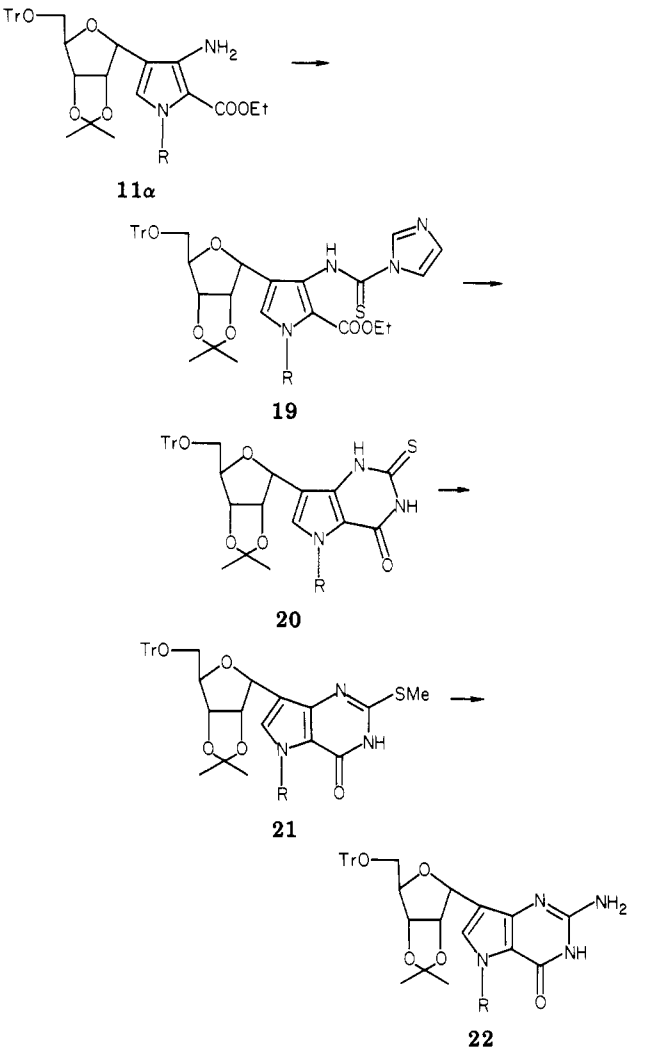
(18) Secrist, J. A., III *J. Org. Chem.* **1978**, *43*, 2925.

a variety of solvents were uniformly unsuccessful, leading to degradation of the starting material. Similar results were also obtained in the attempted thiation of the 2′,3′,5′-tri-*O*-benzoyl-5-*N*-benzyl derivative of **1**. The desired 4-thionopyrrolo[3,2-*d*]pyrimidine was finally obtained by an alternative method via 3-amino-2-cyanopyrrole **15**[2b] (Scheme II), which had previously served as our synthetic intermediate for the preparation of 9-deazaadenosine (**2**). Conversion of **15** into the 3-amino-2-thiocarboxamide **16** was achieved in 90% yield by treatment with hydrogen sulfide in pyridine and triethylamine[19] at 60 °C. Reaction of thioamide **16** with triethyl orthoformate at 90 °C[20] afforded, after chromatographic purfication on silica gel, the fully protected 9-deaza-6-thioinosine **17** in 82% yield. Deblocking with 12% methanolic hydrogen chloride finally gave the free *C*-nucleoside **3** (96% yield) as a light yellow, crystalline monohydrochloride without loss of configurational integrity. In addition to its ^{1}H NMR and elemental analyses, which are consistent with the assigned structure, **3** was further characterized by its ultraviolet spectrum. The latter exhibits a maximum at 336 nm (ϵ 17 900 in acid) that undergoes a hypsochromic and hypochromic shift in base to 313 nm (ϵ 12 300). These ultraviolet properties are very similar to those of thioinosine.[8,21]

Treatment of blocked intermediate **17** with methyl iodide in methanol in the presence of potassium carbonate folowed by chromatographic purification of the product gave the crystalline 4-methylthio derivative **18** isolated in 91% yield. Finally, unblocking of **18** with 12% HCl–MeOH afforded 9-deaza-6-(methylthio)inosine (**4**) as a unique anomeric product, isolated as a colorless hydrochloride salt in near quantitative yield.

Several possible synthetic approaches to 9-deazaguanosine (**5**) were investigated that were based on the ready availability of the 3-amino-2-carbethoxypyrroles **10** and **11**. In principle, the most direct route to guanosine analogue **5** would be by direct cyclization of **10** (or **11**) with guanidine by analogy to similar cyclization of a wide variety of cyclic enaminonitriles to the corresponding fused 2-aminopyrimidine system.[22] The attempted reaction of 3-aminopyrrole **10**β with guanidine carbonate in a high-boiling solvent such as 2-methoxyethanol resulted, however, in a partial rapid epimerization at C-1′ followed by a slower transesterification of the ester group by the solvent. No evidence of cyclization could be detected after 24 h. An alternative procedure was therefore investigated, based on the direct ammonolysis of a 2-methylthio derivative such as **21** (Scheme III) by analogy to the reported syntheses of several guanine derivatives,[23] of guanosine and of 8-azaguanosine,[24] by similar displacement of methylthio groups. For this study, pyrrole derivative **11**α, already in hand from a previous synthesis,[2a] was selected as a model precursor. Treatment of **11**α with *N*,*N*′-thiocarbonyldiimidazole in DMF at 90 °C for 5 h afforded imidazole thioamide **19**, which was readily cyclized to pyrrolo[3,2-*d*]pyrimidine **20** with methanolic ammonia in good overall

Scheme III[a]



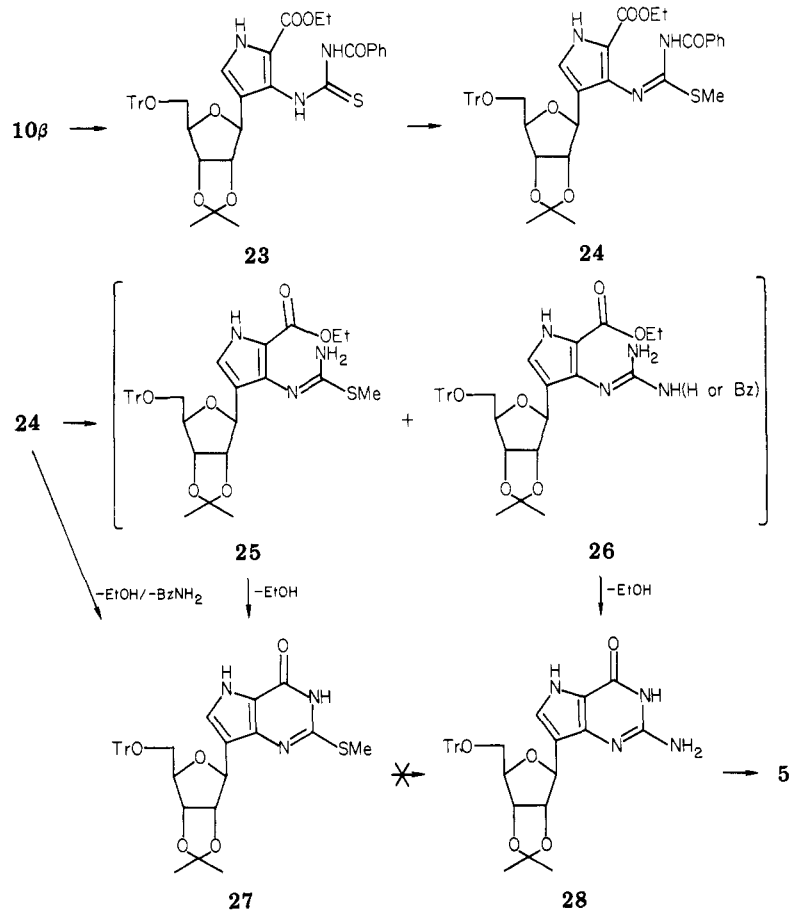
[a] R = CH_2Ph.

yields. Conversion to its *S*-methyl derivative **21** was carried out under standard methylating conditions with methyl iodide and sodium ethoxide in ethanol. Attempted ammonolysis of **21** into **22** under a variety of conditions, however, proved unsuccessful, resulting in complete recovery of the starting material in each instance. This lack of reactivity of the methylthio group probably reflects the π-excessive heteroaromatic character of the fused pyrrole ring and is consistent with the general observation that decreased reactivity toward nucleophilic displacement in several purine nucleoside analogues parallels a decrease in the number of endocyclic nitrogen atoms.[25]

The synthetic route finally adopted for the preparation of 9-deazaguanosine was based on the method reported by Yamazaki and co-workers[26] for the conversion of 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside) into guanosine by the utilization of benzoyl isothiocyanate under relatively mild conditions. In preliminary studies, we found that the carbalkoxy group of **10** was extremely resistant to ammonolysis, and ready access to the required amide was thus made difficult. A modification of the aforementioned procedure originally described with AICA riboside[26] was therefore employed

(19) Albert, A.; Lin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 210.
(20) Conversion of aromatic *o*-aminothioamides to the corresponding pyrimidinethione derivatives with triethyl orthoformate (either alone[20a] or in the presence of acetic anhydride[20b]) is well-known: (a) Taylor, E. C.; McKillop, A.; Vromen, S. *Tetrahedron* **1977**, *23*, 885. (b) Mautner, H. G. *J. Org. Chem.* **1958**, *23*, 1450 and references therein.
(21) A similar analogy to the UV spectrum of thioguanosine[8] has been used successfully for the structural assignment of its *C*-nucleoside analogue 5-amino-3-(β-D-ribofuranosyl)pyrazolo[4,3-*d*]pyrimidine-7-thione.[10]
(22) For a review, see Taylor, E. C.; McKillop, A. *Adv. Org. Chem.* **1970**, *7*, p 272.
(23) Elion, G. B.; Lange, W. H.; Hitchings, G. H. *J. Am. Chem. Soc.* **1956**, *78*, 217.
(24) Davoll, J. *J. Chem. Soc.* **1958**, 1593.
(25) Townsend, L. B. In "Nucleoside Analogues"; Walker, R. T., DeClercq, E., Eckstein, F., Eds.; Plenum Press: New York, 1979; p 193.
(26) Yamazaki, A.; Okutzu, M. *J. Heterocycl. Chem.* **1978**, *15*, 353 and references therein.

Scheme IV



that made use of ester 10β directly.

Treatment of 10β (Scheme IV) with benzoyl isothiocyanate in dichloromethane at 0 °C for 0.5 h afforded the desired 2-carbethoxy-3[(*N*-benzoylthiocarbamoyl)-amino]-1*H*-pyrrole **23** in 88% yield after purification by silica gel column chromatography. S-Methylation was carried out by treatment of **23** with methyl iodide in the presence of DBN in chloroform to give *S*-methylisothioureido derivative **24**, obtained in 98% yield after chromatographic purification. Both **23** and **24** could be obtained as crystalline materials of high purity readily identifiable by their ^{1}H NMR spectra and elemental analyses. Of particular significance in the spectrum of **24** was the presence of a methyl singlet signal appearing at δ 2.53, which afforded conclusive evidence for the S-methylation of **23**. Treatment of **24** with saturated methanolic ammonia at 100 °C overnight in a sealed vessel gave a mixture containing two major products. Separation by column chromatography on silica gel gave first the least polar of these, which was identified as 7-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-2-(methylthio)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**27**, 21% yield) followed by the desired blocked 9-deazaguanosine **28** (45% yield). For preparative purposes, it was found advantageous to extract the considerably more soluble *S*-methylthio derivative **27** (together with other minor byproducts) from the evaporated reaction mixture by trituration with diethyl ether prior to chromatographic purification of **28**. The identity of **28** was ascertained conclusively from its ^{1}H NMR spectrum, which exhibited two broad NH signals at δ 10.47 and 11.50 and one NH_2 signal at δ 5.86 (all exchangeable with D_2O), as well as an H-4′ signal appearing as a multiplet characteristic of the β configuration at C-1′.[12,16,17]

Structural assignment to **27** was similarly based on its ^{1}H NMR spectrum, which exhibited two NH signals at δ 11.57 (a singlet) and 10.81 (a doublet, indicating a coupling between NH-5 and CH-6 of 2.4 Hz) and an SMe signal at δ 2.36. It is noteworthy that application of a similar synthetic procedure to the conversion of 4-amino-3-(β-D-ribofuranosyl)pyrazole-5-carboxamide into 5-aminoformycin B (a guanosine *C*-nucleoside congener) reportedly[6] has also afforded the corresponding 5-(methylthio)formycin B analogous to **27**. Attempts to convert **27** into **28** under ammonolytic conditions identical with those leading to **28** were unsuccessful. This anticipated finding is consistent with the previously observed unreactivity of **21** toward ammonia (Scheme III) and precludes the possible role of **27** as an intermediate for the formation of **28**. Also, since 10β was found to be resistant to conversion to the corresponding amide, it is also unlikely that conversion of **24** into **27** or **28** would have involved formation of the amide of **24** as its first step. On the basis of these observations, a plausible mechanism for this conversion is shown in Scheme IV. Compound **27** might arise directly from the cyclization of **24** or, alternatively, via the debenzoylated (methylthio)pseudoureido intermediate **25**. Blocked 9-deazaguanosine **28** on the other hand must necessarily have formed via either of the guanidine intermediates **26** and subsequent ring-closure. The sequence for the debenzoylation in this latter case is uncertain.

Deprotection of compound **28** by treatment with 12% methanolic hydrogen chloride at ambient temperature for 1 h afforded 9-deazaguanosine **5** as a unique chromatographically homogeneous product, which was isolated as its crystalline monohydrochloride salt (84% yield). Structural assignment to **5** was made principally on the basis of its ^{1}H NMR, UV, and analytical data.

Convincing confirmatory evidence that deblocking of **17**, **18**, and **28** had occurred without concurrent epimerization at C-1′ and that the unblocked nucleosides obtained (**3–5**) had the expected β configuration was derived from the following observations. Each of **3**, **4**, and **5** was converted into its corresponding 2′,3′-*O*-isopropylidene derivative by conventional methods (acetone and 2,2-dimethoxypropane). As was the case for synthetic precursors **17**, **18**, and **28** (see Table I), the ^{1}H NMR spectrum of each isopropylidene derivative displayed the occurrence of the H-4′ signal as a complex multiplet characteristic of the β configuration.[12,17] Furthermore, the ^{13}C NMR spectra of these same derivatives exhibited methyl signals with chemical shifts in perfect agreement with those established for similar β-*C*-glycosides (25.5 ± 0.2 and 27.5 ± 0.2 ppm).[17a,b,18] Thus, the values obtained for the derivative of **3** were 25.4 and 27.4 ppm, for that of **4**, 25.4 and 27.3 ppm, and for **5**, 25.5 and 27.5 ppm.

Studies designed to evaluate the biological activity of some of the 9-deazapurine *C*-nucleosides described above will be reported elsewhere.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were obtained with a JEOL PFT-100 spectrometer, and chemical shifts are reported as δ values with Me_4Si as the internal standard. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI, Galbraith Laboratories, Knoxville, TN, and M.H.W. Laboratories, Phoenix, AZ. Thin-layer chromatography was performed on 250-μm silica gel GF plates (Analtech, Inc.), and the substances were visualized with a short-wave (254 nm) UV mineral light and/or by spraying with 10% ethanolic sulfuric acid and charring. Preparative column chromatography was performed by standard techniques on Merck silica gel 60 (70–230 mesh ASTM) or by flash chromatographic techniques[27] on Merck silica gel 60 (230–400 mesh ASTM). Purification by HPLC was performed on a 3.9 mm × 30 cm μBondapack C-18 column (Waters Assoc.) using methanol–water (1/1) as the mobile phase. Light petroleum ether (bp 30–60 °C) was used whenever this solvent was required.

***N*-[2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-2-cyanovinyl]glycine Ethyl Ester (8).** To a solution of (dimethylamino)acrylonitrile **6**[12] (18 g, 35 mmol) in chloroform (360 mL) was added a solution of trifluoroacetic acid (9 mL) in water (600 mL). The two-phase reaction mixture was stirred vigorously at ambient temperature for 16 h, and the organic layer was washed thoroughly with water. It was then dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo to afford 2-formylacetonitrile **7**, obtained as a white foam. Without further purification, **7** was dissolved in a mixture of methanol (150 mL) and water (9 mL), and to this solution were added glycine ethyl ester hydrochloride (6.0 g, 43 mmol) and sodium acetate trihydrate (6.0 g, 44 mmol). The reaction mixture was then stirred overnight at ambient temperature. The desired enamine **8**, which had precipitated as a white solid (12.0 g) was collected by filtration. After evaporation of the filtrate to dryness, the residue was extracted with chloroform and washed with water and then brine, and the organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. A concentrated solution of the residue in methanol deposited another 2 g of the product. Recrystallization of the combined crops from MeOH afforded 12 g of enamine **8** (60% yield from **6**) as an analytically pure, white crystalline, chromatographically homogeneous material: mp 116–118 °C; IR ($CHCl_3$) 3430 (NH), 2200 (C≡N), 1740 (C=O), 1630 cm^{-1} (C=C).

Anal. Calcd for $C_{34}H_{36}N_2O_6$: C, 71.81; H, 6.38; N, 4.93. Found: C, 71.78; H, 6.54; N, 4.75.

***N*-Carbethoxy-*N*-[2-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-2-cyanovinyl]glycine Ethyl Ester (9).** To a magnetically stirred solution of enamine **8** (25 g, 44 mmol) and DBN (7.1 g, 57 mmol) in dichloromethane (200 mL) was added at 0 °C ethyl chloroformate (5.7 g, 53 mmol). The reaction mixture was stored at ambient temperature for 16 h, then diluted with dichloromethane (300 mL), washed several times with water, and dried over anhydrous sodium sulfate. After evaporation to dryness, the residue was chromatographed on silica gel (petroleum ether–ethyl acetate, 5/1) by flash chromatographic techniques to give anomeric mixture **9** (18 g, 64%) obtained as a white foam. An analytically pure sample was obtained by preparative TLC; IR ($CHCl_3$) 2200 (C≡N), 1730 (C=O), 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{37}H_{40}N_2O_8$: C, 69.36; H, 6.29; N, 4.37. Found: C, 69.30; H, 6.41; N, 4.31.

Preparative TLC of a small sample and collection of the uppermost and lowermost portions of the partially resolved bands afforded a pure sample of each isomer. The ^{1}H NMR spectrum of the faster component exhibited two sets of triplets ($2CH_2CH_3$) centered at δ 1.31 and two corresponding overlapping quartets ($2CH_2CH_3$) centered at δ 4.25. Also evident were a singlet (vinylic proton) at δ 7.74 and an H-1′ signal at δ 4.74. The ^{1}H NMR of the slower components, although of poorer resolution, exhibited nevertheless two overlapping quartets (δ 4.30, $2CH_2$-CH_3), a signal for H-1′ at δ 4.78 and a vinylic signal at δ 7.66. The absence of an NH signal which was a characteristic of the spectrum of **8** (δ 5.26) and the apparent downfield shift of the vinylic protons at δ 7.74 and 7.66 (from δ 6.75 in **8**) all support the structural assigment to **9**.

Ethyl 3-Amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-α-(and β-)D-ribofuranosyl)-1*H*-pyrrole-2-carboxylate (10α and 10β). Enamine **9** (18 g, 28 mmol) was dissolved in 71 mL of ethanolic sodium ethoxide (0.43 N), and the reaction mixture was stored at ambient temperature for 40 min. After evaporation of ethanol, the residue was partitioned between water and chloroform. The organic layer was washed three times with water, once with brine, then dried over anhydrous sodium sulfate, and evaporated to dryness. Flash chromatography of the residue (petroleum ether–ethyl acetate, 3/1) and elution of the fast-moving component afforded the β-anomer 10β (8.5 g, 53%) as a foam. Crystallization from petroleum ether–ethyl acetate gave the analytical sample: mp 183–184 °C; R_f by TLC (petroleum ether–ethyl acetate, 3/1) 0.63.

Anal. Calcd for $C_{34}H_{36}N_2O_6$: C, 71.81; H, 6.38; N, 4.93. Found: C, 71.75; H, 6.37; N, 4.97.

Elution of the slower moving α-anomer afforded 4.5 g (28% yield) of material as a white foam (R_f by TLC 0.51) identified by its ^{1}H NMR and its further conversion to 12α.

7-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (12β). A mixture of 10β (2.84 g, 5.0 mmol) and formamidine acetate (2.08 g, 20.0 mmol) in ethanol (80 mL) was heated at reflux for 4 days. The mixture was then cooled, diluted with chloroform (500 mL), washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. Flash chromatography of the residue (dichloromethane–methanol, 20/1) afforded 2.10 g (76.5%) of 12β obtained as a white solid, mp 246–249 °C.

Anal. Calcd for $C_{33}H_{31}N_3O_5$: C, 72.11; H, 5.69; N, 7.65. Found: C, 71.97; H, 5.74; N, 7.51.

7-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-α-D-ribofuranosyl)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (12α). By a procedure identical with that described above for the synthesis of 12β, the anomer 12α was obtained from the reaction of 10α (2.0 g, 3.5 mmol) with formamidine acetate (1.46 g, 14 mmol) as a colorless foam (1.68 g, 87%).

Anal. Calcd for $C_{33}H_{31}N_3O_5 \cdot 1/4CH_3OH$: C, 71.61; H, 5.78; N, 7.53. Found: C, 71.63; H, 5.93; N, 7.37.

7-β-D-Ribofuranosyl-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (1, "9-Deazainosine"). A suspension of intermediate 12β (550 mg, 1 mmol) in 6% methanolic hydrogen chloride (12 mL) was stirred at ambient temperature, and the course of the deblocking reaction was followed by TLC (methanol–chloroform 4/1). After completion (~50 min) the mixture was evaporated to dryness. The residue was then triturated with diethyl ether and decanted three times. Resuspension in ether, filtration, and a final washing with ether afforded 9-deazainosine (1) as a white crystalline hydrochloride salt (277 mg, 91%). Recrystallization from methanol afforded an analytically pure sample which started

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

to decompose (darkening) at 220 °C with no visible melting up to 270 °C. UV λ_{max} (pH 1) 238 nm (ε 27 090); inflexion at 262 nm (ε 9560); λ_{max} (pH 7) 261 (ε 9540), 231 (ε 28 480); λ_{min} (pH 7) 245 (ε 6980); λ_{max} (pH 13) 267 (ε 9060), 228 (ε 26 830); λ_{min} (pH 13) 245 (ε 5480). The UV spectra were characteristically similar to those reported for the aglycon.[28]

Anal. Calcd for $C_{11}H_{13}N_3O_5$·HCl: C, 43.50; H, 4.65; N, 13.84. Found: C, 43.07; H, 4.62; N, 13.83.

7-(2′,3′,5′-Tri-*O*-acetyl-β-D-ribofuranosyl)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (14). To a solution of 9-deazainosine hydrochloride (1, 180 mg, 0.60 mmol) in 5 mL of anhydrous pyridine was added 0.5 mL of acetic anhydride, and the reaction mixture was stirred overnight at ambient temperature for 16 h. After evaporation to dryness, the residue was directly applied to two preparative TLC plates (Analab 500-μm precoated silica gel GF plates), which were developed with dichloromethane–methanol (10/1) to give 190 mg of tri-*O*-acetate **14** (81%). Recrystallization from methanol afforded the analytical sample, mp 240–241 °C.

Anal. Calcd for $C_{17}H_{19}N_3O_8$: C, 51.91; H, 4.87; N, 10.68. Found: C, 51.66; H, 5.00; N, 10.63.

3-Amino-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-1*H*-pyrrole-2-thiocarboxamide (16). A solution of **15**[2b] (15 g, 28.8 mmol) in a mixture of pyridine (80 mL) and triethylamine (10 mL) was saturated at 23 °C with hydrogen sulfide. The mixture was stored at 60 °C in a sealed vessel for 24 h, then cooled to ambient temperature, and evaporated to dryness in vacuo. The dark brown residue containing **16** was purified on a silica gel column by flash chromatography (ethyl acetate–petroleum ether, 2/1) to give the desired thioamide **16** as a yellow foam (15.6 g, 98%). Attempts to obtain an analytically pure sample by repeated chromatographies were unsuccessful. It was readily identified and characterized by its ^1H NMR spectrum and its subsequent conversion to **17**.

7-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-4-thioxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (17). A magnetically stirred solution of thioamide **16** (16 g, 28.8 mmol) in triethyl orthoformate (50 mL) was heated at 90 °C for 5 h. After completion of the reaction, the mixture was cooled to ambient temperature and evaporated to dryness under high vacuum. Purification of the residue by flash chromatography on silica gel (dichloromethane–methanol, 30/1) gave the fully protected 9-deazathioinosine **17** as a foam (13.4 g, 82%) which crystallized as fine yellow needles from methanol, mp 211 °C dec.

Anal. Calcd for $C_{33}H_{31}N_3O_4S$: C, 70.06; H, 5.52; N, 7.43; S, 5.67. Found: C, 70.14; H, 5.51; N, 7.42; S, 5.65.

7-(β-D-Ribofuranosyl)-4-thioxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (3). *C*-Nucleoside **17** (1.0 g, 1.8 mmol) was deblocked by dissolving in a 12% solution of methanolic hydrogen chloride (25 mL) and stirring at room temperature for 2 h. Evaporation to dryness afforded a yellow residue whcih was extracted repeatedly with diethyl ether by trituration and decantation. The final solid was collected by filtration and washed with diethyl ether to give 540 mg (95%) of desired product **3** obtained as its hydrochloride salt. An analytically pure sample was obtained by recrystallization from methanol. Upon heating, the sample started darkening at 200 °C but did not melt up to 260 °C. UV λ_{max} (pH 1) 336 nm (ε 17 940), 263 (ε 4920); λ_{min} (pH 1) 282 nm (ε 3580), 248 (ε 4250); λ_{max} (pH 7) 328 (ε 23 030), 263 (ε 6290); λ_{min} (pH 7) 281 (ε 3520), 247 (ε 4860); λ_{max} (pH 13) 313 (ε 12340); λ_{min} (pH 13) 268 (ε 4610); inflexion at 250 (ε 6880).

Anal. Calcd for $C_{11}H_{13}N_3O_4S$·HCl: C, 41.31; H, 4.41; N, 13.14; S, 10.03; Cl, 11.09. Found: C, 41.42; H, 4.44; N, 13.00; S, 10.03; Cl, 10.92.

7-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-4-(methylthio)-5*H*-pyrrolo[3,2-*d*]pyrimidine (18). A mixture of 4-thioxo derivative **17** (8 g, 14.1 mmol), methyl iodide (1.50 mL, 24 mmol), and K_2CO_3·1/2H_2O (2.57 g, 17.5 mmol) in methanol was stirred at room temperature for 4 h and then filtered. To the solid thus collected was then added chloroform (250 mL), and the organic layer was washed with water and then brine, dried (anhydrous sodium sulfate), and evaporated. The residue containing **18** was chromatographed by standard techniques using dichloromethane–methanol (100/1) as eluent to afford 7.5 g (91%) of the blocked methylthio derivative **18**. Recrystallizations from methanol afforded the analytical sample, mp 122–123 °C.

Anal. Calcd for $C_{34}H_{33}N_3O_4S$·CH_3OH: C, 68.71; H, 6.10; N, 6.87; S, 5.24. Found: C, 69.01; H, 6.08; N, 6.96; S, 5.37.

4-(Methylthio)-7-(β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidine (4). Blocked methylthio derivative **18** (100 mg, 0.172 mmol) was added to 1.5 mL of a 12% solution of hydrogen chloride in methanol, and the reacton mixture was stirred until the compound dissolved (~10 min). Ether (15 mL) was then gradually added, and the suspension was stirred for 1 h. Filtration of the solid and washing with ether afforded 55 mg (97%) of **4** as its analytically pure crystalline monohydrochloride salt, mp 195–197 °C. UV λ_{max} (pH 1) 312 nm (ε 23 260); λ_{min} (pH 1) 270 (ε 1810); inflexion at 245 (ε 6160); λ_{max} (pH 7) 294 (ε 15 470), 247 (ε 10 000); λ_{min} (pH 7) 262 (ε 4170), 236 (ε 7170); λ_{max} (pH 13) 296 (ε 14 310), 252 (17 030); λ_{min} (pH 13) 270 (ε 4930), 240 (ε 12 140).

Anal. Calcd for $C_{12}H_{15}N_3O_4S$·HCl: C, 43.17; H, 4.84; N, 12.59; S, 9.60; Cl, 10.62. Found: C, 42.93; H, 4.85; N, 12.49; S, 9.46; Cl, 10.51.

Ethyl 3-[(*N*-Benzoylthiocarbamoyl)amino]-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-1*H*-pyrrole-2-carboxylate (23). To a solution of **10β** (6.0 g, 10.6 mmol) in dichloromethane (20 mL) was added a solution of benzoylisothiocyanate (1.9 g, 12 mmol) in dichloromethane (2 mL) at 0 °C. After completion (30 min), the reaction mixture was evaporated to dryness, and the residue was flash chromatographed on silica gel (petroleum ether–ethyl acetate, 3/1) to afford **23** as a white foam (6.8 g, 88%). Crystallization from ethanol afforded the analytical sample, mp 154–157 °C.

Anal. Calcd for $C_{42}H_{41}N_3O_7S$: C, 68.93; H, 5.65; N, 5.74; S, 4.38. Found: C, 68.72; H, 5.53; N, 5.62; S, 4.28.

Ethyl 3-[(*N*-Benzoyl-*S*-methylisothiocarbamoyl)-amino]-4-(2′,3′-*O*-isopropylidene-5′-*O*-trityl)-1*H*-pyrrole-2-carboxylate (24). To a solution of thioureido derivative **23** (3.73 g, 5.1 mmol) and DBN (744 mg, 6 mmol) in chloroform (50 mL) was added methyl iodide (1 mL, 16 mmol). The reaction mixture was stirred at ambient temperature for 1 h and then extracted three times with water. The organic layer was then dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was chromatographed on a silica gel column by standard techniques using dichloromethane–methanol (30/1) to afford **24** (3.72 g, 98%) as an amorphous foam which was crystallized from ethyl acetate–petroleum ether, mp 197–199 °C.

Anal. Calcd for $C_{43}H_{43}N_3O_7S$: C, 69.24; H, 5.81; N, 5.63. Found: C, 69.40; H, 5.79; N, 5.64.

2-Amino-7-(2′,3′-*O*-isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (28) and 7-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-β-D-ribofuranosyl)-2-(methylthio)-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (27). A suspension of **24** (1.10 g, 1.47 mmol) in methanol (50 mL) was saturated with ammonia at room temperature and stored in a sealed steel vessel at 90 °C for 16 h. The mixture was then slowly cooled to room temperature and evaporated to dryness. The residue was chromatographed by standard techniques on a silica gel column with chloroform to give methylthio derivative **27** (188 mg, 21%), obtained as a white solid and identified by its ^1H NMR. Further elution with chloroform–methanol (20/1) afforded the desired fully blocked 9-deazaguanosine **28**, (374 mg, 45%) obtained as an amorphous solid that could not be crystallized.

Anal. Calcd for $C_{33}H_{32}N_4O_5$: C, 70.20; H, 5.71; N, 9.92. Found: C, 69.97; H, 5.94; N, 9.75.

Larger scale preparations of **28** were carried out more advantageously by a time-saving modification. Thus, after ammonolysis of 3.30 g (4.4 mmol) of **24** and evaporation of the reaction mixture to dryness, the residue was repeatedly extracted by trituration with ether to remove **27** and other undesired minor byproducts. The remaining solid residue was purified by chromatography using chloroform–methanol (50/1 followed by 20/1) to give the blocked 9-deazaguanosine **28** (1.18 g, 47%).

2-Amino-7-β-D-ribofuranosyl-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (5, "9-Deazaguanosine"). Blocked intermediate **28** (600 mg, 1.06 mmol) was dissolved in 12% methanolic hydrogen chloride (12 mL) and the mixture stirred at ambient temperature. As the reaction proceeded, some product **5** crystallized out. After 1 h, a small amount (~2 mL) of diethyl ether was added, and

(28) Imai, K. *Chem. Pharm. Bull. Jpn.* **1964**, *12*, 1030.

the mixture was cooled at 0 °C. Filtration of the precipitated product followed by washing with ether afforded **5** (285 mg, 84%) as a crystalline monohydrochloride salt. Recrystallizaton from methanol gave the analytical sample, mp >280 °C. UV λ_{max} (pH 1) 271 nm (ϵ 14620), 234 (ϵ 17850); λ_{min} (pH 1) 250 (ϵ 8000); λ_{max} (pH 7) 269 (ϵ 8920), 230 (ϵ 22460); λ_{min} (pH 7) 249 (ϵ 6000); λ_{max} (pH 13) 285 (ϵ 6920), 257 (ϵ 6620), 223 (ϵ 23540); λ_{min} (pH 13) 271 (ϵ 6120), 249 (ϵ 6450).

Anal. Calcd for $C_{11}H_{14}N_4O_5$·HCl: C, 41.45; H, 4.74; N, 17.58. Found: C, 41.45; H, 4.85; N, 17.50.

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Registry No. 1·HCl, 74458-08-5; 3·HCl, 84649-09-2; 4·HCl, 84649-10-5; 5·HCl, 84649-11-6; 6α, 84710-19-0; 6β, 84710-20-3; 7α, 84710-21-4; 7β, 84710-22-5; 8α, 84649-12-7; 8β, 84710-23-6; 9α, 84649-13-8; 9β, 84710-24-7; 10α, 84649-14-9; 10β, 84649-15-0; 11α, 74458-06-3; 12α, 84649-16-1; 12β, 84649-17-2; 14, 84649-18-3; 15, 77691-00-0; 16, 83060-69-9; 17, 84649-19-4; 18, 84649-20-7; 19, 84649-21-8; 20, 84649-22-9; 21, 84649-23-0; 22, 84649-24-1; 23, 84649-25-2; 24, 84649-26-3; 27, 84680-83-1; 28, 84649-27-4; benzoyl isothiocyanate, 532-55-8; triethyl orthoformate, 122-51-0; *N,N'*-thiocarbonyldiimidazole, 6160-65-2; glycine ethyl ester hydrochloride, 623-33-6; formamidine acetate, 3473-63-0.

(3-Carbethoxy-2-oxopropylidene)triphenylphosphorane. A Reagent for "3 + 3" Cyclohexenone Annulation[1]

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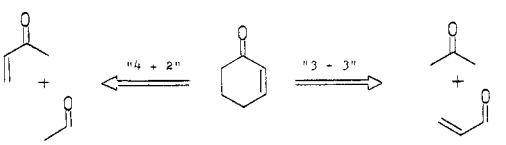
The development of a new cyclohexenone annulation reaction of general scope which utilizes α,β-unsaturated aldehydes and (3-carbethoxy-2-oxopropylidene)triphenylphosphorane is reported.

The cyclohexenone system has been a target of innumerable synthetic endeavors for years.[2] In a retrosynthetic analysis of cyclohexenones,[3] "4 + 2" and "3 + 3" disconnections are ultimately designated as the two principal approaches to these compounds (Scheme I). In sharp contrast to the "4 + 2" annulation reaction which is commonly known as the Robinson annulation[4] and which has proven extraordinarily useful in synthetic practice,[2,5] the "3 + 3" annulation of cyclohexenones has rarely been addressed as an alternative.[6] From the many compounds which are likely to compose a pair of reactants suitable for a "3 + 3" annulation reaction, esters of acetoacetic acid and α,β-unsaturated aldehydes stand out for their simplicity and ready accessibility. However, only a few individual examples of the synthesis of cyclohexenones directly from these substrates could be found in the literature.[7] We reasoned, therefore, that rendering such a route to cyclohexenones general would possess considerable synthetic utility.

Scheme I



It has recently been shown[8,9] that the introduction of a terminal phosphorus substituent into the ethyl acetoacetate molecule produced a synthetically attractive equivalent of this simple unit. Such a γ-phosphorylated ethyl acetoacetate, e.g., **1**, was found to form a dianion under relatively mild conditions and then to react with aldehydes and ketones exclusively at its phosphorylated terminus to give δ,γ-unsaturated β-keto esters with a simultaneous removal of the auxiliary phosphorus grouping.[8,9] The reaction of **1** with conjugated aldehydes[8] followed exactly the same pattern (eq 1). Apparently the reaction between the two harder centers of these ambident reactants competed favorably with other possible reaction paths. It was therefore logical to expect that a replacement of the highly nucleophilic phosphonate carbanion of **1** with the more delocalized ylide group[10] (such as in **2**) would

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(2) For an excellent review of annulation, see: Jung, M. E. *Tetrahedron* **1976**, *32*, 3.
(3) Corey, E. J.; Johnson, A. P.; Long, K. *J. Org. Chem.* **1980**, *45*, 2051.
(4) Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285.
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(6) For a recent example, see: Martin, S. F.; Desai, S. *J. Org. Chem.* **1977**, *42*, 1664.
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(9) van der Goorbergh, J. A. M.; van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 3621.

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