Synthesis and Chemistry of Some Pyridazine Nucleosides Related to Certain 5-Substituted Pyrimidine Nucleosides

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Condensation of 3,4-dichloro-6-[(trimethylsilyl)oxy]pyridazine (**3**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4**), by the stannic chloride catalyzed procedure, has furnished 3,4-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**5**). Nucleophilic displacement of the chloro groups and removal of the benzoyl blocking groups from **5** has furnished 3-chloro-4-methoxy-, 3,4-dimethoxy-, 4-amino-3-chloro-, 3-chloro-4-methylamino-, 3-chloro-4-hydroxy-, and 4-hydroxy-3-methoxy-1-β-D-ribofuranosylpyridazin-6-one. An unusual reaction of **5** with dimethylamine is reported. Condensation of 4,5-dichloro-3-nitro-6-[(trimethylsilyl)oxy]pyridazine with **4** yielded 4,5-dichloro-3-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**24**). Nucleophilic displacement of the aromatic nitro group from **24** is discussed. Condensation of **3** with 3,5-di-*O*-*p*-toluoyl 2-deoxy-D-*erythro*-pentofuranosyl chloride (**28**) afforded an α,β mixture of 2-deoxy nucleosides. The synthesis of certain 3-substituted pyridazine 2'-deoxy nucleosides are reported.

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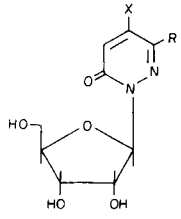
Several 5-substituted derivatives of naturally occurring pyrimidines and pyrimidine nucleosides have demonstrated (1) substantial *in vitro* and/or *in vivo* antitumor and antiviral activity. In connection with our studies on the synthesis of pyridazine nucleosides (2,3), we would now like to report our investigations on the synthesis of pyridazine nucleosides related to some therapeutically useful 5-substituted pyrimidine nucleosides.

Our approach to the synthesis of compounds of type **1** involved the use of a suitably substituted pyridazine that



1, X = OH, NH_2
R = Cl, OMe, etc

would contain a substituent in the 4-position which was highly susceptible to nucleophilic displacement. In addition, we needed a pyridazine compound with another substituent in the 3-position which could under more forcing conditions be nucleophilically displaced. This would allow us to exploit the difference in the reactivity of these two leaving groups. A perusal of the literature revealed that 3,6-dichloropyridazin-4-one had been used previously in the synthesis of some pyridazine nucleosides (4). Although this synthetic methodology could provide 5-substituted uridine analogs, the synthesis of cytidine analogs by this route would be somewhat indirect and tedious. Therefore, we chose to use 3,4-dichloropyridazin-6-one (**4**) as our starting base since a variance in reactivity of the two halogen substituents toward nucleophilic displacement is well documented (5) and should allow the facile synthesis of both uridine and cytidine derivatives.

Scheme I

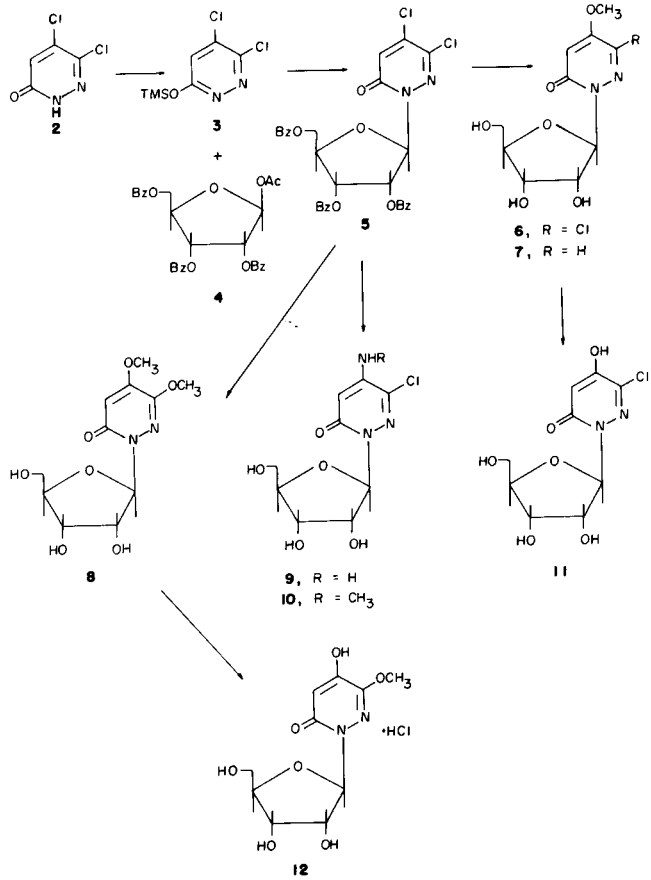


Table II

Ultraviolet Spectral Data for Some Pyridazine Nucleosides
λ max nm (ε × 10^{-3})

Compound No.	Methanol	*p*H 1	*p*H 11
5	274 (4.99)	—	—
	282 (4.81)	—	—
	305 (4.02)	—	—
6	251 (3.87)	250 (4.92)	250 (5.30)
	287 (2.58)	280 sh (2.78)	277 sh (3.78)
7	247 (4.63)	247 (5.66)	247 (5.12)
	278 (3.20)	270 sh (3.70)	270 (3.37)
8	240 (5.53)	239 (6.62)	240 (7.60)
	285 (2.85)	280 (2.97)	280 (3.97)
9	292 sh (11.4)	292 sh (11.9)	291 sh (12.4)
	301 (12.3)	300 (12.5)	300 (13.2)
	315 sh (7.55)	312 sh (8.00)	312 sh (8.72)
10	232 (4.90)	232 (4.70)	232 (5.22)
	239 sh (3.79)	239 sh (3.76)	239 sh (4.43)
	290 sh (6.15)	301 (7.20)	290 sh (6.50)
	301 (7.06)	314 sh (5.05)	301 (7.50)
	314 sh (4.67)		314 sh (5.25)
11	274 (5.01)	254 (4.72)	274 (6.39)
	303 sh (2.94)	283.5 sh (2.91)	302 sh (2.82)
12	247 (6.77)	243 (7.66)	266 (14.8)
	272 sh (4.50)	280 (3.35)	
13	239 (14.2)	242 (14.5)	242 (13.2)
	301 (5.78)	301 (5.32)	303 (4.80)
14	242 (4.68)	241 (5.59)	242 (3.94)
	250 sh (3.36)	250 sh (3.91)	320 (10.5)
	208 sh (9.72)	320 (10.8)	—
	319 (11.9)	—	—
	334 sh (7.98)	—	—
16	317 (11.1)	317 (9.74)	317 (10.2)
10a	245 (25.7)	245 (27.0)	245 (25.2)
	353 (3.12)	353 (2.93)	353 (2.58)
20b	234 (32.4)	232 (31.4)	232 (31.4)
	347 (3.50)	340 (3.34)	340 (3.22)
20c	246 (25.3)	247 (25.1)	247 (24.8)
	329 (2.42)	329 (2.35)	326 (2.28)
21	274 (5.51)	—	—
	282 (5.34)	—	—
	300 sh (3.08)	—	—
24	275 (5.82)	—	—
	281 (5.82)	—	—
	302 (4.45)	—	—
25	250 (3.88)	248 (4.49)	248 (4.49)
	300 (3.91)	296 (4.26)	296 (4.07)
26	245 (4.81)	245 (5.52)	245 (6.43)
	300 (3.33)	294 (3.71)	292 (4.49)
27	286 (5.22)	282 (5.33)	283 (5.19)
29	281 (3.21)	—	—
	306 (3.26)	—	—
30	281 (6.36)	—	—
	306 (6.52)	—	—
31	292 sh (13.6)	291 sh (13.8)	291 sh (13.7)
	301 (14.4)	299 (14.6)	299 (14.6)
	315 sh (8.63)	313 sh (8.95)	313 sh (8.95)
32	250 (6.92)	250 (7.69)	250 (7.75)
	286 (4.76)	280 (4.48)	280 (4.56)
33	240 sh (9.69)	239 (10.5)	239 (10.4)
	285 (3.40)	279 (4.82)	280 (4.98)

Silylation of 3,4-dichloropyridazin-6-one (**2**) (6,7) was accomplished using hexamethyldisilazane with a catalytic amount of ammonium sulfate to provide a quantitative yield of 3,4-dichloro-6-[(trimethylsilyl)oxy]pyridazine (**3**). The crude silyl derivative **3**, without further purification, was condensed with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4**) using the stannic chloride catalyzed procedure (8). The condensation furnished a single nucleoside in 92% yield which was assigned the structure 3,4-dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**5**). As expected from our previous studies (3), debenzoylation of **5** under a variety of conditions did not afford the desired dichloro nucleoside. For example, treatment of **5** with sodium methoxide in a mixture of methanol and tetrahydrofuran at 5-10° effected a removal of the benzoyl blocking groups, but was also accompanied by a simultaneous displacement of the 4-chloro substituent to yield 3-chloro-4-methoxy-1-β-D-ribofuranosylpyridazin-6-one (**6**) in greater than 90% yield. Treatment of **5** with sodium methoxide under more forcing conditions, tenfold excess of sodium methoxide in methanol/tetrahydrofuran at reflux temperature for 72 hours, effected a displacement of both chloro substituents to furnish 3,4-dimethoxy-1-β-D-ribofuranosylpyridazin-6-one (**8**) in 85% yield. To determine the actual site of ribosylation, dehalogenation of **6** furnished 4-methoxy-1-β-D-ribofuranosylpyridazin-6-one (**7**). Nucleoside **7** was identical in all respects to this same nucleoside previously synthesized (3) from an alternative procedure. In the previous investigation we established unambiguously the site of ribosylation for **7** as N-1 by ultraviolet comparison, and the anomeric configuration as β by ^{1}H nmr, and, therefore, the same assignments may

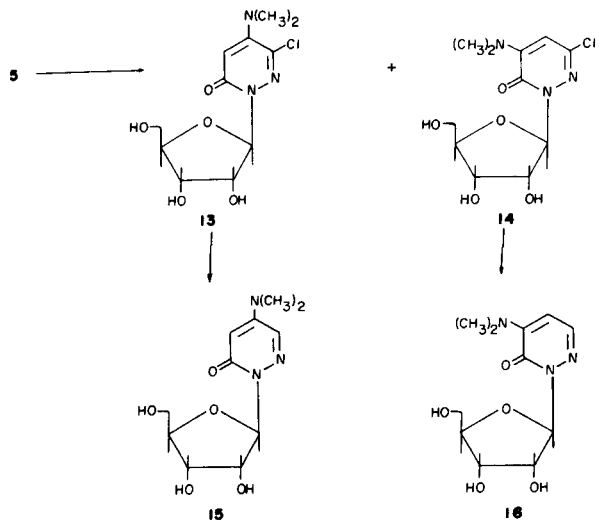
be made for compound **5** and all the compounds derived from **5**.

We found that the 4-methoxyl group in both **6** and **8** could be selectively hydrolyzed with aqueous alkali to yield the desired analogs of 5-substituted uridine nucleosides. Thus, treatment of **6** with aqueous potassium hydroxide at reflux gave 3-chloro-4-hydroxy-1-β-D-ribofuranosylpyridazin-6-one (**11**). Similar treatment of **8** yielded 4-hydroxy-3-methoxy-1-β-D-ribofuranosylpyridazin-6-one (**12**) which was isolated as the hydrochloride salt. The nucleoside **12** is of particular interest in view of the recent isolation of 5-methoxyuridine as a minor constituent of tRNA from *Bacillus subtilis* (9). To the best of our knowledge, compound **12** is the first analog of 5-methoxyuridine to be synthesized containing a modified nitrogen heterocycle.

Compound **5** served as a useful starting material for the synthesis of several additional pyridazin-6-one nucleosides substituted in the 3 and 4 positions. Treatment of **5** with liquid ammonia at 110° for 17 hours effected a removal of the blocking groups with a concomitant displacement of the 4-chloro moiety to give 4-amino-3-chloro-1-β-D-ribofuranosylpyridazin-6-one (**9**) in 77% yield. Similar treatment of **4** with monomethylamine yielded 3-chloro-4-methylamino-1-β-D-ribofuranosylpyridazin-6-one (**10**) in 67% yield.

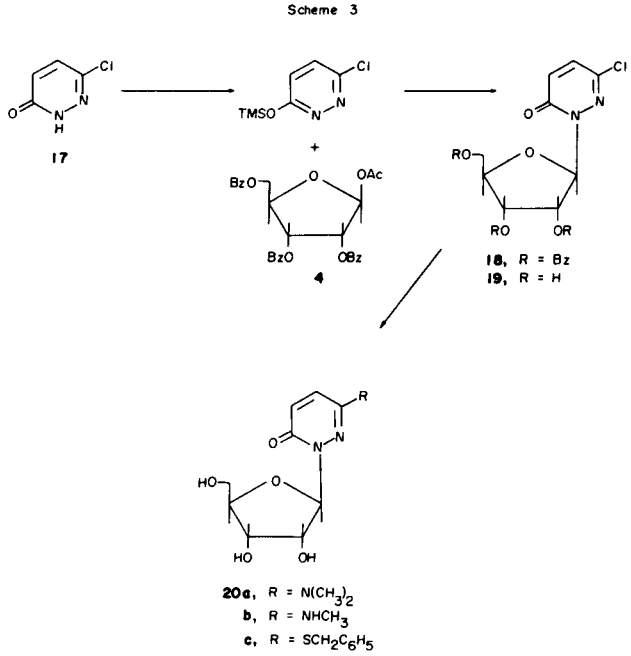
The reaction of nucleoside **5** with dimethylamine was carried out at 125° for 45 hours and led to the isolation of two distinct nucleoside products in approximately equal amounts. The elemental analyses and ^{1}H nmr spectral data indicated that these two products were isomeric monochloro, mono-dimethylamino pyridazine nucleosides. This was an unexpected result since in all previous reactions in this series, either a simple nucleophilic displacement of the more reactive 4-chloro group had occurred or both the 3- and 4-chloro substituents were displaced to furnish

Scheme 2



3,4-disubstituted derivatives. To ascertain the identity of the products, both of these nucleosides (**13** and **14**) were dehalogenated since the resulting dimethylamino-1-β-D-ribofuranosylpyridazin-6-ones would allow us to directly compare the ^{1}H nmr spectra of these compounds with the ^{1}H nmr spectra of known compounds. Dehalogenation of **13** gave a 95% yield of 4-dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**15**) identical in all respects to **15** synthesized from 4,5-dichloro-1-(β-D-ribofuranosyl)pyridazin-6-one (3). Thus, **13** could be assigned the structure 3-chloro-4-dimethylamino-1-β-D-ribofuranosylpyridazin-6-one. Dehalogenation of the second mono-chloro, monodimethylamino nucleoside (**14**) afforded a different monodimethylamino-1-β-D-ribofuranosylpyridazin-6-one isolated in 90% yield. However, this nucleoside did not possess the expected structure. We had anticipated that this nucleoside would be 3-dimethylamino-1-β-D-ribofuranosylpyridazin-6-one which we had synthesized through the following series of reactions. The trimethylsilyl derivative of 3-chloropyridazin-6-one (**17**) was condensed with the halogenose **4** in the presence of stannic chloride to yield a single nucleoside product in 98% yield. The product was assigned the structure 3-chloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**18**) on the basis of subsequent transformations. In this case, a removal of the benzoyl blocking groups of **18** without a concomitant nucleophilic reaction at the 3-position of the heterocycle

Scheme 3



was possible using methanolic sodium methoxide at low temperature. The resulting deblocked nucleoside, 3-chloro-1-β-D-ribofuranosylpyridazin-6-one (**19**), possessed physical properties identical to literature values (10). Since **19** had been previously converted (10) to 1-β-ribofuranos-

ylpyridazin-6-one, for which an unequivocal structure proof exists (3), the anomeric configuration and site of ribosylation for **19** was firmly established. The 3-chloro substituent in nucleoside **19** was easily displaced by nucleophiles to yield 3-substituted pyridazin-6-one nucleosides. Thus, treatment of **19** with dimethylamine gave the desired 3-dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**20a**) in 85% yield. In addition, treatment of **19** with methylamine or sodium benzylmercaptide gave 3-methylamino-1-β-D-ribofuranosylpyridazin-6-one (**20b**), and 3-benzylthio-1-β-D-ribofuranosylpyridazin-6-one (**20c**) in 95% and 66% yields, respectively. Compounds **1** and **20a-c** all exhibited ^{1}H-nmr spectra consistent with substitution at the 3-position (11) ($J_{4,5}$ = 9-10 Hz). However, the 3-dimethylamino derivative (**19**) was not identical to the nucleoside **16** which had been prepared by dehalogenation of **14**.

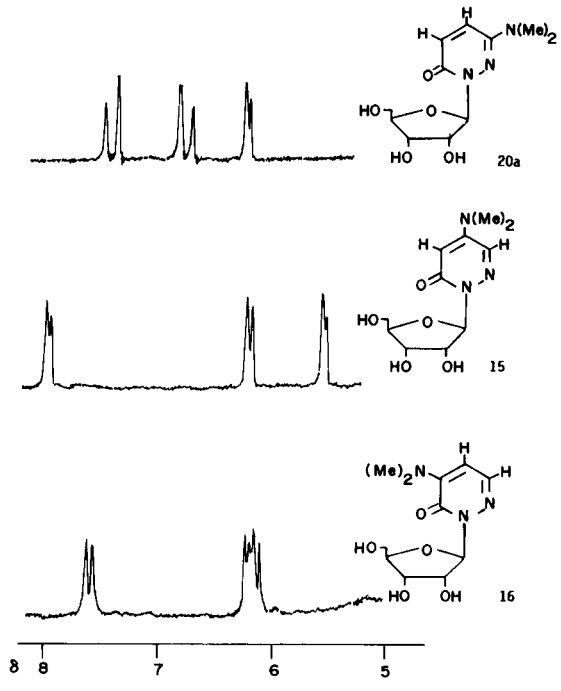
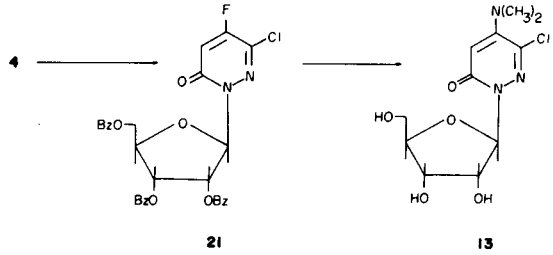


FIGURE 1

Partial Proton Nuclear Magnetic Resonance Spectra of Dimethylaminopyridazin-6-one Nucleosides

Since we now had the three possible isomers in hand, a distinction could easily be made between the three isomers on the basis of the position of the resonance signals in the ^{1}H nmr of the aromatic protons and the coupling constants between the protons (see Figure 1). Each compound exhibited three sets of signals in the δ 5.0-8.0 region, one of which could be assigned to the resonance of the anomeric proton of the ribosyl moiety while the remaining two sets of signals in this region of the spectra derive from the two aromatic protons of the pyridazin-6-one ring system. The aromatic protons in nucleoside **15**, the 4-substituted derivative, exhibited a small through bond coupling constant ($J_{3,5}$ = 2 Hz) which has been shown to be characteristic of 4-substituted pyridazin-6-ones (3,12). The coupling constant of the aromatic protons in compound **20a** ($J_{4,5}$ = 10 Hz) also compared well to those reported (11) for other 3-substituted pyridazin-6-ones, but were indeed different from those observed for the nucleoside **16**. The ^{1}H nmr spectrum of **16** revealed the presence of two aromatic protons in the molecule with a coupling constant ($J_{3,4}$ = 5 Hz) which is characteristic of a 1-alkyl-pyridazin-6-one monosubstituted in the 5-position. Although the coupling constants were similar to those observed for **15**, the chemical shifts demonstrated that **15** and **16** were clearly different compounds.

Scheme 4



To avoid formation of **14**, we introduced a more reactive leaving group in the 4-position of the heterocycle. When **5** was allowed to react with the crown ether complex of potassium fluoride (13) in acetonitrile at reflux, 3-chloro-4-fluoro-1-(2,3,5-tri-*O*-benzoy-β-D-ribofuranosyl)pyridazin-6-one (**21**) was isolated. The presence of one fluorine atom in the molecule was confirmed by elemental analysis and the appearance of the resonance signal for H_5 was a distinct doublet ($H_{H,F}$ = 9 Hz) in the ^{1}H nmr spectrum. When **21** was allowed to react with dimethylamine under the identical conditions used for the reaction with compound **5**, a single nucleoside product was isolated which was identical in all respects to nucleoside **13**.

The reported bacteriocidal and antiviral activities of 5-nitrouracil (14,15) and 5-nitro-2′-deoxyuridine (16) prompted us to investigate the synthesis of similar compounds in the pyridazine nucleoside series. 4,5-Dichloro-3-nitropyridazin-6-one (**22**) (17) was silylated with hexamethyldisilazane, and the silyl derivative (**23**) was condensed with the halogenose **4** by the stannic chloride catalyzed procedure to yield a single nucleoside product in 62% yield. This product was assigned the structure 4,5-dichloro-3-nitro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-pyridazin-6-one (**24**) on the basis of subsequent transformations. When nucleoside **24** was treated with methanolic sodium methoxide, two isomeric products (**25** and **26**) were isolated in 18% and 29% yields, respectively. Analytical data for the two products indicated that in addition to a

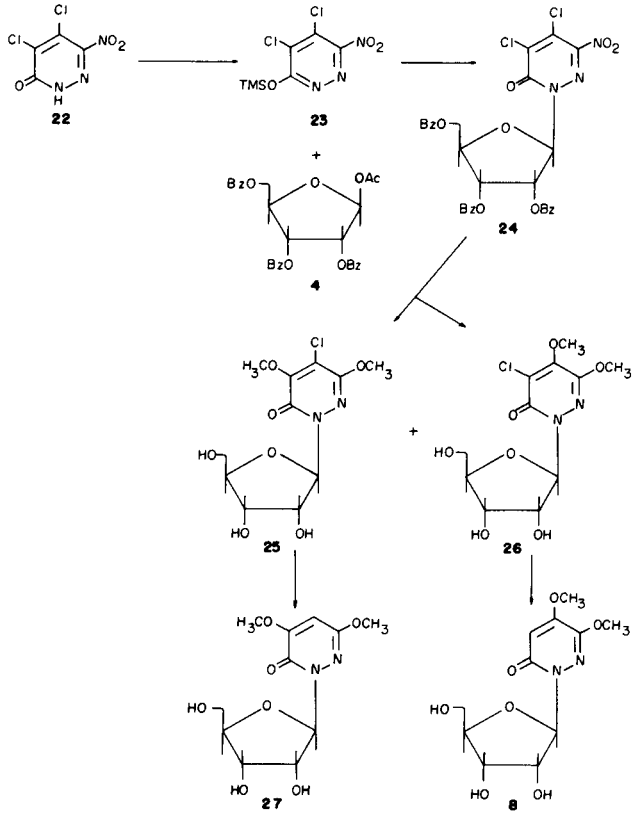
Table III

^{1}H NMR Spectral Data for Certain Pyridazine Nucleosides

Compound No.	Solvent (a)	$H_{1'}$	$J_{1',2'}$ Hz	Others (b)
5	D	6.71 (d)	2	7.3-8.2 (m, b) 6.06 (m, $H_{2'}$ + $H_{3'}$) 4.91 (m, $H_{4'}$) 4.73 (m, $H_{5'}$)
6	D	6.17 (d)	4	6.50 (s, H_5) 3.96 (s, OCH_3)
7	D	6.18 (d)	4	7.81 (d, H_3, $J_{3,5}$ = 3) 6.26 (d, H_5) 3.84 (s, OCH_3)
8	D	6.20 (d)	3	6.30 (s, H_5) 3.87 (s, OCH_3) 3.96 (s, OCH_3)
9	D	6.22 (d)	4	7.03 (bs, NH_2) 6.31 (s, H_5)
10	D	6.22 (d)	3	7.37 (bq, N-H) 6.06 (s, H_5) 2.78 (d, NCH_3, J = 5)
11	D			6.20 (bs, $H_{1'}$ + H_5)
12	D	6.20 (d)	2	6.09 (s, H_5) 3.87 (s, OCH_3)
13	D	6.10 (d)	4	6.03 (s, H_5) 2.92 (s, NMe_2)
14	D			6.20 (m, H_4 + $H_{1'}$) 3.14 (s, NMe_2)
15	D	6.12 (d)	4	7.88 (d, H_3, $J_{3,5}$ = 3) 5.46 (d, H_5) 2.98 (s, NMe_2)
16	D	6.22 (d)	3	7.61 (d, H_3, $J_{3,4}$ = 5) 6.14 (d, H_4) 3.03 (s, NMe_2)
18	D	6.70 (d)	2	7.3-8.1 (m, bz H's) 7.17 (d, H_5, $J_{4,5}$ = 10) 5.9-6.1 (m, $H_{2'}$ + $H_{3'}$) 4.5-4.9 (m, $H_{4'}$ + $H_{5'}$)
19	D	6.22 (d)	3	7.59 (d, H_4, $J_{4,5}$ = 10) 7.09 (d, H_5)
20a	D	6.27 (d)	4	7.47 (d, H_4, $J_{4,5}$ = 10) 6.81 (d, H_5) 2.93 (s, NMe_2)
20b	D	6.22 (d)	2	6.98 (d, H_4, $J_{4,5}$ = 9) 6.72 (d, H_5) 6.49 (bq, NH) 2.71 (d, NCH_3)
20c	D	6.25 (d)	3	7.3-7.5 (m, bzl H's) 6.87 (d, H_5, $J_{4,5}$ = 10) 4.37 (s, bzl CH_2)
21	D	6.61 (d)	2	7.3-8.1 (m, bz H's) 7.13 (d, H_5, $J_{H,F}$ = 9) 5.96 (m, $H_{2'}$ + $H_{3'}$) 4.81 (m, $H_{4'}$) 4.60 (m, $H_{5'}$)
24	D	6.77 (d)	4	7.2-8.1 (m, bz H's)
25	D	6.19 (d)	3	4.13 (s, OCH_3) 3.87 (s, OCH_3)
26	D	6.20 (d)	3	4.06 (s, OCH_3) 3.89 (s, OCH_3)
27	D	6.21 (d)	3	6.49 (s, H_4) 3.87 (s, OCH_3) 3.81 (s, OCH_3)
29	C	6.83 (t)	6	7.8-8.0 (m, *ortho* H's toluoyl), 7.1-7.3 (m, *meta* H's toluoyl) 7.02 (s, H_5) 5.69 (m, $H_{3'}$) 4.57 (s, $H_{4'}$ + $H_{5'}$) 2.8-3.1 (m, $H_{2'}$) 2.4-2.6 (m, $H_{2'}$) 2.39 (s, CH_3) 2.37 (s, CH_3)
30	C	6.67 (dd)	3 7	7.8-8.0 (m, *ortho* H's toluoyl), 7.1-7.3 (m, *meta* H's toluoyl) 6.99 (s, H_5) 5.52 (m, $H_{3'}$) 4.91 (m, $H_{4'}$) 4.57 (d, $H_{5'}$, $J_{4',5'}$ = 4 Hz) 2.8-3.1 (m, $H_{2'}$) 2.5-2.7 (m, $H_{2'}$) 2.38 (s, CH_3, CH_3)
31	D	6.66 (t)	6	6.96 (bs, NH_2) 6.22 (s, H_5)
32	D	6.53 (t)	6	6.43 (s, H_5) 5.19 (d, $C_{3'}OH$, $J_{3',3'OH}$ = 5), 4.63 (t, $C_{5'}OH$, $J_{5',5'OH}$ = 5.5) 4.21 (m, $H_{3'}$) 3.96 (s, OCH_3) 2.1-2.5 (m, $H_{2'}$)
33	D	6.57 (t)	6	6.21 (s, H_5) 3.81 (s, OCH_3)

(a) D = DMSO-d_6; C = deuteriochloroform. (b) Coupling constant (J) in hertz. Abbreviations used: Bz = benzoyl, Bzl = benzyl, d = doublet, dd = doublet of doublets, s = singlet, t = triplet, m = multiplet, bs = broad singlet, bq = broad quartet.

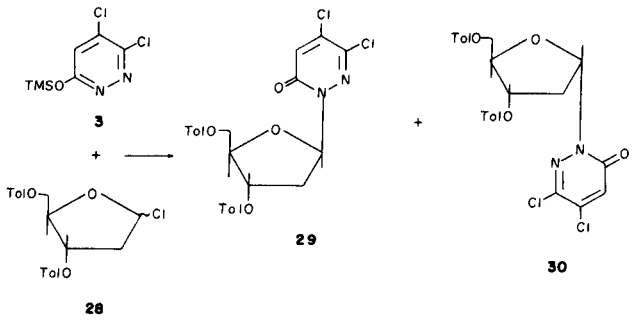
Scheme 5



removal of the benzoyl blocking groups and the displacement of a chloro group, nucleophilic displacement of the nitro group at position 3 had also occurred. Since both products resulted from a nucleophilic displacement of the 3-nitro group, the products were easily identified by a catalytic removal of the remaining chlorine atom. When nucleoside **26** was treated with hydrogen (40 psi), in the presence of a 10% palladium on carbon catalyst, the nucleoside **8** was obtained by a removal of a chlorine atom from the 5-position. Nucleoside **26** was therefore assigned the structure 5-chloro-3,4-dimethoxy-1-β-D-ribofuranosylpyridazin-6-one (**27**), with spectral properties clearly different from those of nucleoside **8**. Nucleoside **25** was thus assigned the structure 4-chloro-3,5-dimethoxy-1-β-D-ribofuranosylpyridazin-6-one.

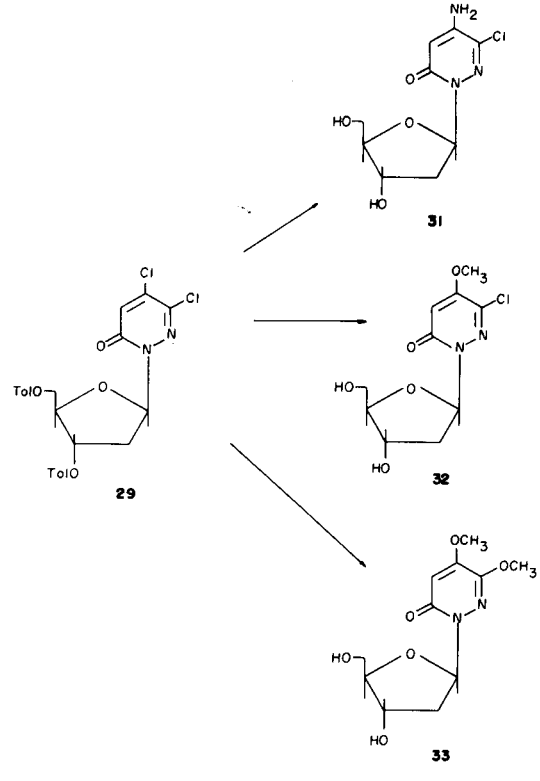
To investigate the synthesis of 2-deoxy pyridazine ribonucleosides the silyl derivative **3** was condensed with 3,5-di-*O*-*p*-toluoyl-2-deoxy-D-*erythro*-pentofuranosyl chloride (**28**) (18) in dichloroethane at 5° in the presence of stannic chloride. From the reaction mixture, two nucleoside products (**29** and **30**) were isolated in 57% and 20% yields, respectively. Elemental analyses and ultraviolet spectral data indicated that the compounds were an anomeric pair of N-1 glycosides. The assignment of anomeric configuration for **29** and **30** could be made by a comparison of their proton magnetic resonance spectra. For the major product (**29**) the signal for the anomeric proton appeared as a pseudotriplet centered at δ 6.83 and having a $J_{1',2'} = 6$ Hz which is indicative of a 2'-deoxy nucleoside having a β

Scheme 6



configuration. The analogous signal for compound **30** appeared as a doublet of doublets (δ 6.67, $J_{1',2'} = 3$ Hz, $J_{1',2'} = 7$ Hz) which supported the assumption that **30** possessed the α anomeric configuration. Furthermore, the signal for the $H_{4'}$ proton of the sugar moiety in compound **30** showed a 0.5 ppm downfield chemical shift relative to the same proton in the β anomer **28**. Previous studies (19) have shown that such a chemical shift is characteristic of α anomers of pyridazine deoxyribosides. Therefore, compounds **29** and **30** were assigned the structures 3,4-dichloro-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one and 3,4-dichloro-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-α-D-*erythro*-pentofuranosyl)pyridazin-6-

Scheme 7



one, respectively. Chemical transformations of nucleoside **29** were accomplished in a manner similar to those described for nucleoside **4**, however, extreme care was necessary when using a strongly acidic ion exchange resin, since exposure of these deoxy nucleosides to protic conditions at room temperature for even a short period of time caused a cleavage of the glycosidic linkage. Thus, treatment of **29** with liquid ammonia at 115° for 31 hours gave a 74% yield of 4-amino-3-chloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one (**31**). Treatment of **29** with methanolic sodium methoxide at low temperature yielded 3-chloro-4-methoxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrid-azin-6-one (**32**) in 84% yield, whereas treatment of **29** with the same reagent at reflux gave 3,4-dimethoxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one (**33**) in 88% yield. Compounds **31**, **32** and **33** all exhibited a distinct triplet ($J_{1',2'}$ = 6 Hz) in the ^{1}H nmr as the pattern of peaks for the anomeric proton.

This investigation has provided several pyridazine nucleosides substituted in a manner analogous to the substitution pattern present in the important class of antimetabolites, the 5-substituted pyrimidines. All new compounds failed to inhibit *in vitro* cell growth of L1210 mouse leukemic cell growth at 10^{-4} *M* concentrations or exhibit an ILS of greater than 25% at 400 mg/kg and were considered inactive. The unusual substitution reaction of nucleosides **5** and **24** may suggest useful synthetic routes which could be applied to the synthesis of novel pyridazine derivatives.

EXPERIMENTAL

Proton nuclear magnetic resonance (^{1}H nmr) spectra were obtained on JEOL C60H, Varian A56/60 and Varian EM-390 spectrometers (solution in DMSO-d_6 or deuteriochloroform) with chemical shift values reported in δ units (parts per million) relative to an internal standard (sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane). Ultraviolet absorption spectra (uv) were recorded on a Beckman Acta CIII spectrophotometer. Mass spectra were recorded on an LKB 9000S spectrometer; electron impact, ionizing voltage 70 eV, filament current 60 μa; direct insertion. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The optical rotations were measured with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Preparative thin layer chromatography was performed on glass plates coated with silica gel (1.5 mm, SilicAR 7GF, Mallinckrodt). Analytical thin layer chromatography was performed on glass plates coated with silica gel (0.25 mm, SilicAR 7GF, Mallinckrodt). Compounds of interest were detected either by an ultraviolet lamp (254 nm) or treatment with sulfuric acid followed by charring. Open-bed column chromatography was carried out on SilicAR CC7 (Mallinckrodt) using gravity flow. The columns were packed as slurries with the elution solvent. All solvent proportions are given by volume. Evaporations were performed under reduced pressure (provided by a water aspirator) or *in vacuo* at 40° with a rotary evaporator unless otherwise stated. All compounds were dried *in vacuo* at 80° for 10 to 15 hours before submission for elemental analysis. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. The presence of water of crystallization in the elemental analyses was verified by ^{1}H nmr spectroscopy.

3,4-Dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**5**).

3,4-Dichloropyridazin-6-one (6,7) (**2**, 3.6 g, 22 mmoles) was silylated by heating in 70 ml of hexamethyldisilazane at reflux for 2 hours in the presence of a catalytic amount of ammonium sulfate. The excess hexamethyldisilazane was removed by distillation (35-40° aspirator pressure) and the remaining syrup was used without further purification. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (10 g, 20 mmoles), dissolved in dry 1,2-dichloroethane (100 ml), was added to the above silyl derivative. The reaction was cooled in an ice bath for 10 minutes, and then stannic chloride (6 ml, 50 mmoles) was added, and the reaction mixture was brought to immediate reflux. After 45 minutes, heating was discontinued, and the reaction mixture was cooled to 10° with an icewater bath. Ethanol (50 ml) and sodium bicarbonate (14 g, 259 mmoles) were added and the mixture became semisolid after stirring for 4 hours. The solvent was then removed under reduced pressure, the remaining residue was ground to a powder and extracted in a Soxhlet extractor for 15 hours using boiling chloroform (300 ml) as the extracting solvent. The chloroform extract was concentrated under reduced pressure to yield a foam. The foam was dissolved in a mixture of boiling ethanol (100 ml) and ethyl acetate (10 ml) and on cooling to room temperature, **5** deposited as white needles: yield 11.2 g (18 mmoles, 92%), mp 113-114°; optical rotation $[\alpha]_D^{25}$ -80.2° (c 1, chloroform).

Anal. Calcd. for $C_{30}H_{22}Cl_2N_2O_8$: C, 59.12; H, 3.64; N, 4.60. Found: C, 59.29; H, 3.74; N, 4.60.

3-Chloro-4-methoxy-1-β-D-ribofuranosylpyridazin-6-one (**6**).

Nucleoside **5** (5 g, 8.21 mmoles) was dissolved in a mixture of tetrahydrofuran (50 ml) and methanol (100 ml). The solution was cooled to 10°, sodium methoxide (2.5 g) was added and the reaction mixture then stirred for 48 hours at 10°. Amberlite IR-120 resin (H^+ form, 10g) was added and the mixture was stirred for 3 hours, filtered and the residue washed with boiling methanol (100 ml). The combined filtrates were coevaporated with silica gel (7 g) and the silica gel then applied to the top of an open bed silica gel column (4.5 × 20 cm). The column was washed with a methanol/chloroform (1:9) mixture (500 ml) to remove methyl benzoate. The major product was then eluted with methanol/chloroform (3:17, 500 ml). The eluant containing product evaporated to a foam which was crystallized from ethyl acetate (50 ml) to give **6** as white needles, yield 2.2 g (7.51 mmoles, 91%), mp 116-118°; optical rotation: $[\alpha]_D^{25}$ -107° (c 1, methanol).

Anal. Calcd. for $C_{10}H_{13}ClN_2O_6$: C, 41.04; H, 4.48; N, 9.57. Found: C, 41.31; H, 4.69; N, 9.47.

4-Methoxy-1-β-D-ribofuranosylpyridazin-6-one (**7**).

Nucleoside **6** (500 mg, 1.71 mmoles) was dissolved in methanol (75 ml). The solution was cooled to 5° and thoroughly purged with nitrogen. Palladium on carbon catalyst (10%, 100 mg) was added and the mixture was treated with hydrogen gas at one atmosphere pressure for 30 minutes. The mixture was filtered through a Celite pad, and the pad was washed with boiling methanol (100 ml). The combined filtrates were coevaporated with 1 g of silica gel and applied to a short open-bed silica gel column (4.5 × 7 cm). The product was then eluted with a methanol/chloroform (1:4) mixture. The eluant fractions containing the product were combined and evaporated under reduced pressure to furnish an oil which was crystallized from ethyl acetate to give a white powder, yield 250 mg (0.97 mmole, 57%), mp 137-140°. Recrystallization of a small sample from ethyl acetate/methanol yielded a powder, mp 142-143° (lit (3) 143-144°).

3,4-Dimethoxy-1-β-D-ribofuranosylpyridazin-6-one (**8**).

Nucleoside **5** (5 g, 8.21 mmoles) was dissolved in a mixture of tetrahydrofuran (50 ml) and methanol (100 ml). Sodium methoxide (2.5 g) was added, and the reaction mixture was heated at reflux for 72 hours. After cooling to room temperature, Amberlite IR-120 resin (H+ form, 10 g) was added and the mixture stirred at room temperature for 48 hours. The mixture was filtered, and the resin washed (200 ml). The combined filtrates were evaporated under reduced pressure and the residue crystallized from ethyl acetate to furnish a white powder, yield 2 g (6.94 mmoles, 85%), mp 157-159°.

Anal. Calcd. for $C_{11}H_{16}N_2O_7$: C, 45.83; H, 5.59; N, 9.72. Found: C,

45.61; H, 5.38; N, 10.00.

3,4-Dimethoxy-1-β-D-ribofuranosylpyridazin-6-one (**8**) from **32**.

Nucleoside **32** (100 mg, 0.31 mmole) was dissolved in 50 ml of methanol and 0.3 ml of 0.1 *N* aqueous sodium hydroxide was added. The solution was cooled to 5° and purged with nitrogen. Palladium on carbon catalyst (10%, 100 mg) was added and the reaction mixture was treated with hydrogen gas at 40 psi in a Parr hydrogenation apparatus for 6 hours. The mixture was filtered through a Celite pad and the pad was washed with boiling methanol (50 ml). The filtrates were combined with 20 ml of ethanol. The ethanol was decanted and concentrated *in vacuo* to an oil which crystallized on standing to give a light yellow solid, yield 72 mg (0.25 mmole, 81%), mp 158-160°.

4-Amino-3-chloro-1-β-D-ribofuranosylpyridazin-6-one (**9**).

Nucleoside **5** (3.7 g, 6.08 mmoles) was suspended in liquid ammonia (20 ml). The mixture was sealed in a stainless steel reaction vessel, and was heated for 17 hours at 110°. The reaction vessel was cooled to room temperature and the excess ammonia was allowed to evaporate. The resulting residue was triturated with ethanol (150 ml) at room temperature. The ethanol was decanted and the solution evaporated under reduced pressure to an oil. Crystallization of the oil from chloroform gave a beige powder, yield 1.3 g (4.67 mmoles, 77%), mp 193-196°. Recrystallization of a small sample from water furnished an analytical sample, mp 195-196°.

Anal. Calcd. for $C_9H_{12}ClN_3O_5$: C, 38.93; H, 4.36; N, 15.13. Found: C, 38.79; H, 4.29; N, 15.21.

3-Chloro-4-methylamino-1-β-D-ribofuranosylpyridazin-6-one (**10**).

Nucleoside **5** (1 g, 1.64 mmoles) was suspended in liquid monomethylamine (20 ml). The mixture was sealed in a stainless steel reaction vessel and was heated for 16.5 hours at 115°. The reaction was cooled to room temperature and the excess monomethylamine was allowed to evaporate. The remaining residue was dissolved in methanol (10 ml) and coevaporated with 1.5 g of silica gel. The silica gel was then applied to an open bed silica gel column (4.5 × 10 cm). The column was eluted with methanol/chloroform (1:19, 160 ml) and methanol/chloroform (1:9, 90 ml) to remove partially blocked nucleosides and *N*-methylbenzamide. The product was then eluted from the column with an additional 110 ml of the solvent mixture. The fractions containing product were combined and concentrated under reduced pressure to yield an oil. The oil was crystallized from ethyl acetate with the addition of a small amount of methanol to give white needles, yield 320 mg (1.10 mmoles, 67%), mp 151-152°.

Anal. Calcd. for $C_{10}H_{14}ClN_3O_5$: C, 41.18; H, 4.84; N, 14.41. Found: C, 40.92; H, 4.62; N, 14.24.

3-Chloro-4-hydroxy-1-β-D-ribofuranosylpyridazin-6-one (**11**).

Potassium hydroxide (5 g) was dissolved in distilled water (25 ml).To this solution, nucleoside **6** (450 mg, 1.54 mmoles) was added and the mixture heated at reflux for 1 hour. After cooling to 0°, the solution was carefully acidified to *p*H 5 and concentrated hydrochloric acid (7 ml). The mixture was concentrated *in vacuo* and the resulting residue was then triturated with ethanol (50 ml) for 3 hours at room temperature. The mixture was filtered, and the precipitated salt was washed with an additional amount of ethanol (50 ml). The combined ethanol filtrates were coevaporated with 2 g of silica gel, and the silica gel applied to the top of an open-bed silica gel column (4.5 × 7 cm). The product was eluted with methanol/chloroform (1:4). The fractions containing product were then combined and evaporated under reduced pressure. The resulting residue was crystallized from methanol to give a white powder, yield 290 mg (1.01 mmoles, 65%), mp 182-183°.

Anal. Calcd. for $C_9H_{11}ClN_2O_6 \cdot \frac{1}{2}H_2O$: C, 37.59; H, 4.21; N, 9.74. Found: C, 37.35; H, 4.23; N, 9.62.

4-Hydroxy-3-methoxy-1-β-D-ribofuranosylpyridazin-6-one Hydrochloride (**12**).

Potassium hydroxide (5 g) was dissolved in distilled water (25 ml). The nucleoside **8** (500 mg, 1.73 mmoles) was added and the mixture heated at reflux for 1 hour. After cooling to 0°, the solution was carefully acidified with concentrated hydrochloric acid (7 ml). The mixture was concentrated *in vacuo* and the resulting residue was then triturated with ethanol (40 ml) for 3 hours at room temperature. The mixture was filtered and the precipitated salt washed with ethanol (50 ml). The combined ethanol filtrates were coevaporated with 2 g of silica gel, and the silica gel was applied to an open-bed silica gel column (4.5 × 9 cm). The column was eluted with methanol/chloroform (1:4). The fractions containing the product were combined and evaporated under reduced pressure. The residue was crystallized from methanol to give a light yellow powder: yield 341 mg (1.04 mmoles, 60%); mp 162-165°.

Anal. Calcd. for $C_{10}H_{14}N_2O_7 \cdot HCl \cdot H_2O$: C, 36.54; H, 5.21; N, 8.52. Found: C, 36.17; H, 5.17; N, 8.36.

3-Chloro-4-dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**13**) and 3-Chloro-5-dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**14**).

Nucleoside **5** (2 g, 3.28 mmoles) was suspended in liquid dimethylamine (20 ml). This mixture was then sealed in a stainless steel reaction vessel and heated at 125° for 45.5 hours. After cooling, the excess dimethylamine was allowed to evaporate at room temperature. The remaining residue was dissolved in methanol (40 ml) and coevaporated with 5 g of silica gel. The silica gel was applied to an open-bed silica gel column (4.5 × 24 cm), and the products were eluted from the column with methanol/chloroform (1:19). The eluant was collected in 20 ml fractions. Fractions 14-23 contained *N,N*-dimethylbenzamide, fractions 43-62 the nucleoside **14** and the fractions 78-100 the second nucleoside **13**. Fractions 43-62 were evaporated to dryness and crystallized from cyclohexane to give **14**, yield 190 mg (0.62 mmole, 19%), mp 147-148°.

Anal. Calcd. for $C_{11}H_{16}ClN_3O_5$: C, 43.22; H, 5.28; N, 13.74. Found: C, 43.08; H, 5.34; N, 13.65.

Fractions 78-100 were evaporated to dryness under reduced pressure and crystallized from cyclohexane to give **13** 190 mg (0.62 mmole, 19%), mp 178-188°.

Anal. Calcd. for $C_{11}H_{16}ClN_3O_5$: C, 43.22; H, 5.28; N, 13.74. Found: C, 43.03; H, 5.18; N, 13.58.

3-Chloro-4-dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**13**) from **21**.

Nucleoside **21** (500 mg, 0.84 mmole) was suspended in liquid dimethylamine (20 ml). The mixture was sealed in a stainless steel reaction vessel and heated at 125° for 48 hours. After cooling to room temperature, the excess dimethylamine was allowed to evaporate. Only one nucleoside product was detectable by thin layer chromatography. The remaining residue was triturated with chloroform (20 ml) to remove *N,N*-dimethylbenzamide. The remaining solid was triturated with ethanol (100 ml) to remove the product. The ethanol solution was filtered and the filtrate evaporated to give a light yellow solid, yield 120 mg (0.39 mmole, 47%), mp 174-176°. The spectral properties of **13** synthesized by this method were identical to those of **13** synthesized from **5**.

4-Dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**15**).

Nucleoside **13** (10 mg, 0.33 mmole) was dissolved in methanol (50 ml) and 1 *N* aqueous sodium hydroxide (0.3 ml) was then added. The reaction mixture was cooled to 5° and purged with nitrogen. Palladium on carbon catalyst (10%, 100 mg) was added and the reaction mixture was treated with hydrogen gas (40 psi) in a Parr hydrogenation apparatus for 10 hours. The mixture was boiled, filtered through a Celite pad, and the pad was washed with boiling methanol (50 ml). The combined methanol filtrates were concentrated under reduced pressure, and the resulting residue was triturated with ethanol (50 ml) at room temperature. After filtration, the ethanol was evaporated to dryness *in vacuo* to give a white solid, yield 85 mg (0.31 mmole, 95%), mp 168-170° (lit (3) mp 168-170°).

5-Dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**16**).

Nucleoside **14** (100 mg, 0.33 mmole) was dissolved in methanol (50 ml). The solution was then cooled to 5° and purged with nitrogen. Palladium on carbon catalyst (10%, 50 mg) was added and the mixture was then treated wtih hydrogen gas, under atmospheric pressure at room tempera-

ture for 0.5 hour. The mixture was then boiled and filtered through a Celite pad and the pad was washed with boiling methanol (50 ml). The combined methanol filtrates were concentrated *in vacuo* to furnish a homogenous oil which could not be brought to analytical purity, yield 80 mg (30 mmoles, 90%); ms: 273 (M^+ + H), 272 (M^+, $C_{11}H_{17}N_3O_5$), 140 (B + H), 139 (B).

3-Chloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**18**).

3-Chloropyridazin-6-one (20) (**17**, 10 g, 77 mmoles) was heated at reflux for 2 hours in hexamethyldisilazane (100 ml) and then allowed to cool to room temperature. The excess hexamethyldisilazane was removed by distillation (aspirator pressure, 35-40°) and the remaining oil was used without further purification. A solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**4**, 35 g, 69 mmoles) in dry dichloroethane (200 ml) was added and the mixture cooled to 5°. Stannic chloride (18 ml, 154 mmoles) was added with stirring. The initial exothermic reaction brought the reaction temperature to ≅45°. The mixture was then allowed to cool to room temperature and stirred an additional 1.5 hours. The reaction mixture was then cooled to 5° and diluted with ethanol (25 ml) and dichloroethane (50 ml). Sodium bicarbonate (35 g, 648 mmoles) was added over a 1 hour period and the resulting gelatinous mass was evaporated to dryness under reduced pressure. The powdery residue was pulverized and the product extracted from the salts with boiling chloroform (700 ml) in a Soxhlet extractor for 15 hours. The chloroform extract was evaporated to an oil which was crystallized from ethanol (100 ml) to give **18** as white needles, yield 39 g (68 mmoles, 98%), mp 113-114°.The compound has been previously reported as an oil (10).

3-Chloro-1-β-D-ribofuranosylpyridazin-6-one (**19**).

Nucleoside **18** (12 g, 21 mmoles) was dissolved in a mixture of tetrahydrofuran (150 ml) and methanol (300 ml) and the mixture was cooled to 5°. Sodium methoxide (7.5 g) was then added and the reaction mixture stirred at 5-10° for 12 hours. Amberlite IR-120 resin (H^+ form, 30 g) was added and the mixture stirred for an additional 12 hours. The mixture was filtered and the resin was washed with boiling methanol (200 ml). The combined filtrates were evaporated under reduced pressure to afford a syrup. Boiling ethyl acetate (100 ml) was added and the resulting solution allowed to cool to room temperature. The product which deposited a white powder was collected by filtration, yield 4.6 g (17 mmoles, 84%), mp 151-152° (lit (10) mp 152-153°).

3-Dimethylamino-1-β-D-ribofuranosylpyridazin-6-one (**20a**).

Nucleoside **19** (500 mg, 1.91 mmoles) was dissolved in liquid dimethylamine (20 ml) and heated in a sealed stainless steel reaction vessel at 115° for 8 hours. After cooling, the excess dimethylamine was allowed to evaporate at room temperature. The residue was dissolved in methanol/chloroform (3:17, 7.5 ml) and applied to an open-bed silica gel column (3 × 15 cm). The product was eluted from the column using the above solvent system, collecting 20 ml fractions. The product eluted in fractions 10-25 which were combined and evaporated under reduced pressure to afford a yellow solid which was crystallized from a mixture of ethyl acetate and methanol to furnish yellow needles, yield 440 mg (1.62 mmoles, 85%), mp 168-169°.

Anal. Calcd. for $C_{11}H_{17}N_3O_5$: C, 48.70; H, 6.32; N, 15.49. Found: C, 48.70; H, 6.59; N, 15.36.

3-Methylamino-1-β-D-ribofuranosylpyridazin-6-one (**20b**).

Nucleoside **19** (500 mg, 1.91 mmoles) was dissolved in liquid methylamine (20 ml) and heated in a sealed stainless steel reaction vessel at 115° for 18 hours. After cooling, the excess methylamine was allowed to evaporate at room temperature. The reaction mixture was dissolved in methanol (50 ml) and the solution coevaporated with 2 g of silica gel. The silica gel was applied to an open-bed silica gel column (3 × 14 cm). The product was eluted from the column with methanol/chloroform (1:4), collecting 20 ml fractions. The product was eluted in fractions 3-16. These fractions were evaporated to dryness and the remaining solid was crystallized from a minimum amount of methanol to give beige crystals, yield 470 mg (1.83 mmoles, 95%) mp 210-211°.

Anal. Calcd. for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88; N, 16.33. Found: C, 46.78; H, 5.80; N, 16.43.

3-Benzylthio-1-β-D-ribofuranosylpyridazin-6-one (**20c**).

Sodium metal (150 mg, 6.52 mmoles) was dissolved in methanol (50 ml). Benzylmercaptan (1 ml, 8.54 mmoles) was added and the mixture stirred at room temperature for 5 minutes. Nucleoside **19** (500 mg, 1.91 mmoles) was added and the reaction mixture was then stirred for 2 hours at 50°. Amberlite IR-120 resin (H^+ form, 1 g) was added and the mixture stirred an additional 12 hours. The mixture was filtered and the resin washed with methanol (50 ml). The combined filtrates were concentrated *in vacuo*, and the oily residue was dissolved in methanol/chloroform (1:9, 15 ml). The solution was applied to an open-bed silica gel column (4 × 16 cm) and the product was eluted with the above solvent mixture, collecting 20 ml fractions. The product appeared in fractions 7-10 which were combined and evaporated *in vacuo* to furnish an oil which was crystallized from ethyl acetate to give white needles, yield 440 mg (1.26 mmoles, 66%), mp 159-160°.

Anal. Calcd. for $C_{16}H_{16}N_2O_5S$: C, 54.85; H, 5.18; N, 7.99. Found: C, 55.07; H, 5.14; N, 8.03.

3-Chloro-4-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyridazin-6-one (**21**).

Potassium fluoride (20 g) and dicyclohexyl-18-crown-6 (1 g) were suspended in dry acetonitrile (200 ml) and the mixture stirred vigorously for 1 hour. The nucleoside **5** (5 g, 8.21 mmoles) was added and the mixture heated at reflux for 43 hours. The mixture was filtered and the remaining salt was washed with chloroform (100 ml). The combined filtrates were coevaporated with 10 g of silica gel and applied to an open-bed column (3 × 80 cm). The column was eluted with a hexane/acetone/chloroform (25:5:3) solution. The eluant containing the product was concentrated and crystallized from cyclohexane to give **21** as white needles, yield (1.3 g, 2.19 mmoles, 27%), mp 124-125°.

Anal. Calcd. for $C_{30}H_{22}ClFN_2O_8$: C, 60.77; H, 3.74; N, 4.72. Found: C, 60.82; H, 3.56; N, 4.55.

4,5-Dichloro-3-nitro-1-(2,3,5-tri-*O*-benzoyl-1-β-D-ribofuranosyl)pyridazin-6-one (**24**).

4,5-Dichloro-3-nitropyridazin-6-one (7) (**22**, 2.3 g, 11 mmoles) was silylated by heating at reflux for 2 hours in hexamethyldisilazane (50 ml) in the presence of a catalytic amount of ammonium sulfate. The excess hexamethyldisilazane was removed by distillation under reduced pressure, and the remaining solid was used without further purification. The silylated heterocycle and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (, 5.04 g, 10 mmoles) were dissolved in dry dichloroethane (50 ml) and the solution was cooled to 0°. Stannic chloride (2.5 ml, 9 mmoles) was added and the solution heated at reflux temperature for 0.5 hour. The reaction mixture was cooled to 0° and ethanol (50 ml) and sodium bicarbonate (7 g) were added, and the mixture was stirred for 3 hours. The resulting gelatinous mass was evaporated to dryness under reduced pressure. The remaining solid mass was triturated with boiling chloroform (3 × 500 ml). The chloroform extracts were combined and passed through a short (4 × 10 cm) silica gel column. The eluant was evaporated under reduced pressure to give a homogeneous light yellow powder: yield 4.5 g (6.9 mmoles, 62%) mp 101-102°. Recrystallization of a small sample from ethanol yielded an analytical sample, mp 116-118°.

Anal. Calcd. for $C_{30}H_{21}Cl_2N_3O_{10}$: C, 55.06; H, 3.23; N, 6.42. Found: C, 55.11; H, 3.55; N, 6.45.

4-Chloro-3,5-dimethoxy-1-β-D-ribofuranosylpyridazin-6-one (**25**) and 5-Chloro-3,4-dimethoxy-1-β-D-ribofuranosylpyridazin-6-one (**26**).

Nucleoside **24** (2 g, 3.06 mmoles) was dissolved in a mixture of methanol (80 ml) and tetrahydrofuran (80 ml). Sodium methoxide (700 mg) was added and the mixture was stirred for 22 hours at room temperature. Amberlite IR-120 resin (H^+ form, 4 g) was added and the mixture stirred for an additional 24 hours. The mixture was filtered and the resin was washed with boiling methanol (100 ml). The combined filtrates were coevaporated with 5 g of silica gel, and the silica gel was applied to the

top of an open-bed column (4.5 × 23 cm). The column was eluted with 400 ml of methanol/chloroform (1:19). After the first 400 ml of solvent, 20 ml fractions were then collected. Nucleoside products were detected in fractions 43-54 and fractions 61-75. Fractions 43-54 were combined and evaporated under reduced pressure and crystallized from ethyl acetate to give **25** as a white powder, yield 180 mg (0.56 mmole, 18%) mp 110-111°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_7$: C, 40.94; H, 4.69; N, 8.68. Found: C, 40.56; H, 4.84; N, 8.41.

Fractions 61-75 were combined and evaporated to dryness and the residue was crystallized from ethyl acetate to give **26** as a white powder, yield 290 mg (0.90 mmole, 29%), mp 169-173°.

Anal. Calcd. for $C_{11}H_{15}ClN_2O_7$: C, 40.94; H, 4.69; N, 8.68. Found: C, 40.53; H, 4.83; N, 8.63.

3,5-Dimethoxy-1-β-D-ribofuranosylpyridazin-6-one (**27**).

Nucleoside **25** (140 mg, 0.43 mmole) was dissolved in methanol (50 ml) and 0.4 ml of 0.1 *N* sodium hydroxide was added. The solution was cooled and purged with nitrogen. Palladium on carbon catalyst (10%, 100 mg) was added and the reaction mixture was treated with hydrogen gas, at 50 psi, in a Parr hydrogenation apparatus for 3 hours. The mixture was filtered through a Celite pad and the pad was washed with 50 ml of boiling methanol. The filtrates were evaporated to dryness and the residue was then triturated wtih 20 ml of ethanol. The ethanol was concentrated *in vacuo* to a homogeneous oil which could not be brought to analytical purity: yield 105 mg (0.36 mmole, 85%); ms: 288 (M^+, $C_{11}H_{16}N_2O_7$).

3,4-Dichloro-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one (**29**) and 3,4-Dichloro-1-(3,5-di-*O*-*p*-toluoyl-2-deoxy-α-D-*erythro*-pentofuranosyl)pyridazin-6-one (**30**).

3,4-Dichloropyridazin-6-one (6,7) (4 g, 24.2 mmoles) was added to hexamethyldisilazane (50 ml) to which a catalytic amount of ammonium sulfate had been added and the reaction mixture was heated at reflux for 3 hours. The excess hexamethyldisilazane was removed by distillation under reduced pressure and the crude silyl derivative was used without further purification. The silyl derivative was dissolved in dry dichloroethane (50 ml) and the solution was cooled to 5°. To this solution was added 3,5-di-*O*-*p*-toluoyl-2-deoxy-*erythro*-pentofuranosyl chloride (18) (**28**, 10 g, 25.7 mmoles) in dichloroethane (75 ml), and the mixture was stirred for 10 minutes at 5°. Stannic chloride (6 ml, 19.6 mmoles) was added and the mixture was stirred for 2 hours, maintaining the temperature at 0-5°. Ethanol (25 ml) and sodium bicarbonate (7 g, 130 mmoles) was then added to the reaction mixture, with stirring. The mixture was allowed to warm up and evaporate to dryness (72 hours) at room temperature. The solid residue was pulverized and extracted in a Soxhlet extractor with chloroform (300 ml). The chloroform extract was concentrated under reduced pressure to afford an oil. Boiling ethanol (200 ml) was added to the oil and the solution then allowed to stand for 5 hours at room temperature during which time crystals formed. The crystals of **29** were collected by filtration: yield 7.1 g (13.7 mmoles, 57%) mp 143-145°; optical rotation: $[\alpha]_D^{25}$ −100 (c 1, chloroform).

Anal. Calcd. for $C_{25}H_{22}Cl_2N_2O_6$: C, 58.04; H, 4.29; N, 5.42. Found: C, 58.02; H, 4.56; N, 5.32.

The mother liquor was concentrated to a volume of 150 ml and on standing for 4 hours at room temperature, this solution deposited **30** as beige needles which were collected by filtration, yield 2.5 g (4.84 mmoles, 20%), mp 105-106°; optical rotation: $[\alpha]_D^{25}$ +62° (c 1, chloroform).

Anal. Calcd. for $C_{25}H_{22}Cl_2N_2O_6$: C, 58.04; H, 4.29; N, 5.42. Found: C, 58.19; H, 4.18; N, 5.18.

4-Amino-3-chloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one (**31**).

Nucleoside **29** (500 mg, 0.97 mmole) was suspended in liquid ammonia (20 ml). The mixture was sealed in a stainless steel reaction vessel and heated at 115° for 31 hours. Excess ammonia was allowed to evaporate at room temperature and the remaining residue was triturated with ethanol (20 ml). The ethanol was decanted, concentrated to a volume of 6 ml and applied to a preparative thick layer chromatographic plate (20 × 40 cm). The plate was developed with methanol/chloroform (1:9) and the main band (R_f = 0.4) collected. The silica gel was extracted with boiling methanol (200 ml). The methanol extract was concentrated under reduced pressure to yield an oil. This oil was crystallized from ethyl acetate to give **31**, yield 193 mg (0.72 mmole, 74%), mp 155-156°.

Anal. Calcd. for $C_9H_{12}ClN_3O_4$: C, 41.32; H, 4.62; N, 16.06. Found: C, 41.07; H, 4.45; N, 16.05.

3-Chloro-4-methoxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one (**32**).

Nucleoside **29** (1 g, 1.93 mmoles) was dissolved in a mixture of methanol (30 ml) and tetrahydrofuran (30 ml) and the solution was cooled to 5°. Sodium methoxide (450 mg) was added and the reaction mixture was stirred at 5-10° for 48 hours. The mixture was cooled to 0° and Amberlite IR-120 resin (H^+ form, 2 g) was added. The mixture was then stirred for 15 minutes at 0° and immediately filtered. The filtrate was coevaporated with 2 g of silica gel and applied to the top of an open-bed silica gel column (4.5 × 20 cm). The column was eluted with methanol/chloroform (1:19). Concentration of the fractions containing the product gave **32** as a homogeneous foam, yield 450 mg (1.62 mmoles, 84%); ms: m/z (relative intensity) 161 (100) B + 2H, 163 (34) B + 2H.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_5$: C, 43.41; H, 4.74. Found: C, 43.64; H, 4.89.

3,4-Dimethoxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one (**33**).

The nucleoside **29** (1 g, 1.93 mmoles) was dissolved in a mixture of methanol (30 ml) and tetrahydrofuran (30 ml). Sodium methoxide (1.5 g) was added and the mixture was heated at reflux for 1.5 hours. Methanol (25 ml) was added and the mixture was heated at reflux for an additional 24 hours. The mixture was cooled to 0°, and Amberlite IR-120 resin (H^+ form, 6 g) was added. The mixture was stirred for 15 minutes and then filtered. The filtrate was coevaporated with 2 g of silica gel and applied to the top of an open-bed silica gel column (4.5 × 21 cm). The column was eluted with methanol/chloroform (1:19). Concentration of the fractions containing the product gave **33** as a white powder, yield 460 mg (1.69 mmoles, 88%) mp 158-159°.

Anal. Calcd. for $C_{11}H_{16}N_2O_6$: C, 48.53; H, 5.92; N, 10.29. Found: C, 48.28; H, 6.03; N, 9.96.

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