98-9; **3a** (R′, R″ = OAc), 29246-51-3; **3a** (R′ = H; R″ = Ac), 29162-99-0; **3b** (R = Et; R′, R″ = Ac), 29163-00-6; **3c** (R = Et; R′, R″ = Ac), 29163-01-7; **3c** (R, R′, R″ = Ac), 29163-02-8; **3f** (R = Et; R′, R″ = Ac), 29246-52-4; **3f** (R = Et; R′ = H; R″ = Ac), 29163-03-9; **3f** (R = Et; R′, R″ = H), 29163-04-0; **3f** (R, R′, R″ = H), 29163-05-1; **3f** (R, R′ = H; R″ = Ac), 29163-06-2; **3f** (R, R″ = Ac; R′ = H), 29163-07-3; **3g** (R′ = H; R″ = Ac), 29163-08-4; **3g** (R′, R″ = Ac), 29163-09-5; **4f** (R = Et), 29163-10-8; **4f** (R = Ac), 29163-11-9; **4f** (R = H), 29163-12-0; **4f** (R = $SiMe_3$), 29163-13-1; **4i** (Z = β-OH, H), 29163-14-2; **5** (R = Et), 29163-15-3; **5** (R = $SiMe_3$), 29163-16-4; **6** (R = Et), 29163-17-5; **6** (R = H), 29246-53-5; **6** (R = Ac), 29163-18-6; **7** (R = Et), 29163-19-7; **7** (R = Ac), 29163-20-0; **8**, 29163-21-1; 3,-17-diketo-17-methyl-16,17-secoandrost-4-en-16-oic acid, 29163-22-2; 3β-formyloxyandrost-5-en-17-one, 29163-23-3; 3β,5α-dihydroxyandrostan-17-one 3-formate, 29246-54-6.

Acknowledgment.—The competent technical assistance of Mrs. B. Tucker and Mr. R. Reuter is gratefully acknowledged.

A New Approach to the Synthesis of Nucleosides of 8-Azapurines (3-Glycosyl-*v*-triazolo[4,5-*d*]pyrimidines)[1]

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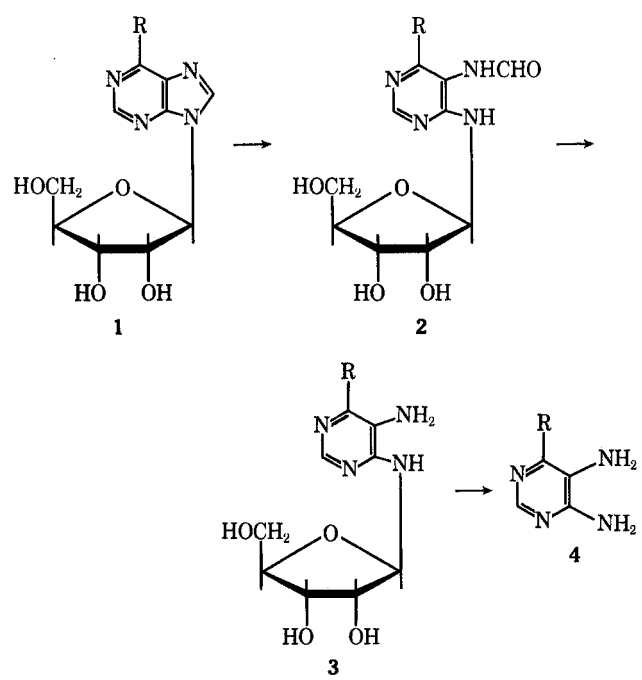
The four isomeric ribosyl derivatives of 8-azahypoxanthine (*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one) have been prepared from appropriately protected derivatives of 6-chloro-9-β-D-ribofuranosylpurine by means of basic cleavage of the imidazole ring of the nucleosides followed by removal of the formyl group from the 5-amino group, closure of the triazole ring with nitrous acid, and then removal of the sugar-protecting groups.

It has been known for some time that certain purines suffer attack by aqueous base at C_2 or C_8, resulting in opening of the pyrimidine[2] or imidazole[3] ring. It appeared to us that these reactions might have synthetic utility, especially in the preparation of 2-[4] and/or 8-azapurine (imidazo[4,5-*d*]-*v*-triazine and *v*-triazolo-[4,5-*d*]pyrimidine) nucleosides difficult to prepare by other methods. For example, the synthesis of 8-azainosine *via* 8-azaadenosine by conventional procedures[6,7] presents difficulties, particularly in the preparation of large amounts of material. One approach to this problem might be to open the imidazole ring of an appropriately substituted purine nucleoside and cyclize the resultant 5-amino-4-glycosylaminopyrimidine with nitrous acid. The possibilities of this route were therefore surveyed.

Inosine (**1**, R = OH), a likely candidate for this route, is quite stable to base,[8] and, although it can be labilized by alkylation at N_7,[9] this approach did not appear promising.[10] Adenosine (**1**, R = NH_2) is completely converted to other compounds in 2 hr by aqueous base at 100°.[11] The only ring-opened product that could be isolated, however, was 4,5,6-triaminopyrimidine (**4**, R = NH_2).[8] Brown and coworkers found that purine ribonucleoside (**1**, R = H)[3] and purine ribonucleotide[12] are extremely sensitive to base, giving rise to sugar-containing pyrimidines that are converted finally to 4,5-diaminopyrimidine (**4**, R = H) (Scheme I). In-

SCHEME I



vestigations in this laboratory[13] and by Brown and coworkers[3] showed that, although 6-chloropurine reacts with aqueous base to give hypoxanthine,[14] nucleosides of 6-chloropurine undergo ring opening under milder

(1) This work, was supported by funds from the C. F. Kettering Foundation and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51. A preliminary account of this work has appeared: J. A. Montgomery and H. J. Thomas, *Chem. Commun.*, 265 (1970).

(2) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).

(3) M. P. Gordon, V. S. Weliky, and G. B. Brown, *J. Amer. Chem. Soc.*, **79**, 3245 (1957).

(4) A synthesis of 2-azaadenosine using this approach has recently been described.[5]

(5) J. A. Montgomery and H. J. Thomas, *Chem. Commun.*, 458 (1969).

(6) J. Davoll, *J. Chem. Soc.*, 1593 (1958).

(7) W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind. (London)*, 2007 (1963).

(8) A. S. Jones, A. M. Mian, and R. T. Walker, *J. Chem. Soc.*, 692 (1966).

(9) K. H. Scheit and A. Holy, *Tetrahedron Lett.*, 4303 (1966).

(10) J. A. Montgomery and H. J. Thomas, unpublished data.

(11) J. A. Montgomery and H. J. Thomas, *J. Amer. Chem. Soc.*, **87**, 5442 (1965).

(12) D. I. Magrath and G. B. Brown, *ibid.*, **79**, 3252 (1957).

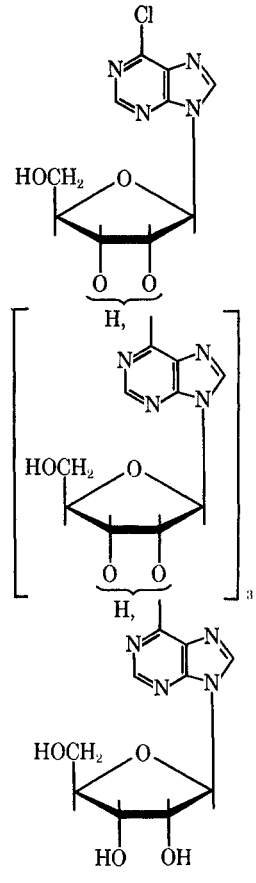
(13) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(14) A. Bendich, P. J. Russell, and J. J. Fox, *J. Amer. Chem. Soc.*, **76**, 6073 (1954).

conditions than those required for chloro displacement to give compounds tentatively identified on the basis of their ultraviolet spectra as 5-amino-4-chloro-6-glycosylaminopyrimidines, such as **3**.[15] In neither case were the products actually isolated and identified. In the related case referred to above, Brown and coworkers[3] found that purine ribonucleoside is facilely cleaved by base primarily to two 5-amino-4-ribosylaminopyrimidines as judged by chromatography and ultraviolet spectroscopy, but the nature of the ribosyl moiety was not determined.

In relevant synthetic work, Todd and coworkers[17] found that they could prepare adenosine by the basic ring closure of 4-amino-6-[(2,3-di-*O*-acetyl-5-*O*-benzyl-D-ribofuranosyl)amino]-5-thioformamido-2-(methylthio)pyrimidine followed by the reductive removal of the 5′-*O*-benzyl and the 2-methylthio group. None of the α anomer of adenosine was detected. A similar synthesis of 9-D-ribopyranosyladenine gave the β anomer, and it was concluded that the intermediate 4-D-ribopyranosylaminopyrimidines also had the β configuration.[18,19]

We decided to study the effect of aqueous base on 6-methoxypurine ribonucleoside (**1**, R = OCH_3) and 6-(methylthio)purine ribonucleoside (**1**, R = SCH_3), in addition to 6-chloropurine ribonucleoside (**1**, R = Cl). The 6-methoxypurine ribonucleoside (**1**, R = OCH_3) was completely converted to inosine (**1**, R = OH), and no ring cleavage resulted. The 6-(methylthio)purine ribonucleoside (**1**, R = SCH_3) did undergo ring cleavage but much more slowly than 6-chloropurine ribonucleoside (**1**, R = Cl), and the conditions necessarily employed caused rupture of the glycosyl linkage so that the major product of the reaction was 4,5-diamino-6-(methylthio)pyrimidine (**4**, R = SCH_3). These results caused us to concentrate our attention on the reaction of 6-chloropurine ribonucleoside (**1**, R = Cl) with base. The alkaline hydrolysis of **1** (R = Cl) described above[3] was carried out in very dilute solution. When we increased the concentration of substrate, a quite different result obtained: a very insoluble white solid precipitated from solution. The ultraviolet spectrum of this material was similar to that of 6-methoxypurine, but little could be concluded from its pmr spectrum. More vigorous treatment of this material with base gave inosine (**1**, R = OH). It is, therefore, apparent that 6-chloropurine ribonucleoside (**1**, R = Cl) polymerized by attack of the anion of one of the sugar hydroxyls on C_6. The polymeric material failed to give the typical metaperiodate–Schiff test for cis hydroxyls[20] and, thus, either the 2′- or 3′-hydroxyl must be involved. Since, in other cases, attack is known to occur at the 2′-hydroxyl of **1** (R = Cl),[21] we believe the linkage is between C_6 and C_2'. Elemental analyses indicated that the polymer is likely a pentamer (**5**). A variety of conditions gave the same material.



5

Because this difficulty could obviously be circumvented by protecting the sugar moiety with a base-stable group, we next studied the effect of base on 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**6**). Hydrolysis of **6** with 0.5 *N* sodium hydroxide in dioxane–water (1:1) at room temperature for 45 min gave a 7.6% yield of 2′,3′-*O*-isopropylideneinosine (**7**), a quite unexpected product (hypoxanthine nucleosides were undetected by previous workers), and a 47% yield of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (**8**) (Scheme II). Although the ultraviolet spectra of the reaction mixtures obtained by the previous investigators led them to conclude that the products were the 5-amino-4-chloro-6-glycosylaminopyrimidines,[3,13] we found no compound of this type. In truth, however, this earlier data[3,13] is not really consistent with that for either structure (see Table I), due no doubt to the fact that the reaction gave at least three products (see below). An examination of the pmr spectrum of the formylaminopyrimidine **8**, in conjunction with that of **17** (see Experimental Section), established that the sugar had retained its β-D-ribofuranosyl configuration.

It was now necessary to remove the formyl group in order to effect ring closure to the triazolo[4,5-*d*]pyrimidine ribonucleoside. We were unable to find conditions under which we could, by means of aqueous base, remove the formyl group from **8** without also rupturing the glycosyl linkage giving 4,5-diamino-6-chloropyrimidine (**4**, R = Cl). These results, along with the ultraviolet spectra of all the compounds involved (Table I),

(15) In contrast to the nucleosides, 9-ethyl-6-chloropurine was converted to 9-ethylhypoxanthine by aqueous base,[16] indicating that substitution at N-9 is not the determining factor but that the nature of the substituent is.

(16) J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **79**, 5238 (1957).

(17) G. W. Kenner, C. W. Taylor, and A. B. Todd, *J. Chem. Soc.*, 1620 (1949).

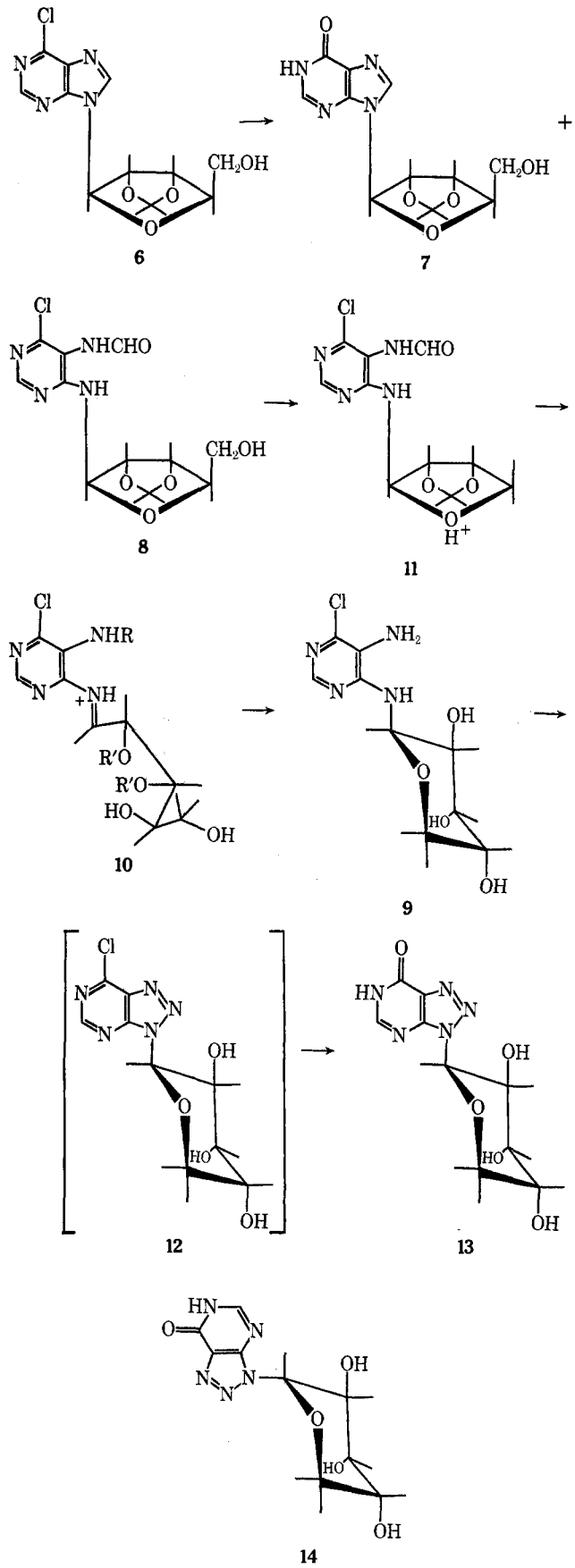
(18) G. A. Howard, G. W. Kenner, B. Lythgoe, and A. R. Todd, *ibid.*, 855 (1946).

(19) G. W. Kenner, H. J. Rodd, and A. R. Todd, *ibid.*, 1613 (1949).

(20) Although trans-vicinal hydroxyls also give a positive test, the rate of oxidation is much slower and the intensity of the color developed is less.

(21) T. A. Khwaja and R. K. Robins, *J. Amer. Chem. Soc.*, **88**, 3640 (1966).

SCHEME II



indicate that Brown and coworkers[3] probably obtained a mixture of inosine (**1**, R = OH), 4-chloro-5-formylamino-6-(β-D-ribofuranosyl)aminopyrimidine (**2**, R = Cl), and 4,5-diamino-6-chloropyrimidine (**4**, R = Cl), but none of the 5-amino-4-chloro-5-(β-D-ribofuranosyl)-aminopyrimidine (**3**, R = Cl) that we desired.

Treatment of **8** with hydrochloric acid readily removed the formyl and isopropylidene groups, but the resultant product was shown by chromatography to be a mixture of two compounds, which were not separated but were treated with sodium nitrite in the aqueous acid. This treatment resulted in closure to the *v*-triazolo[4,5-*d*]pyrimidine **12**, followed by hydrolysis of the now labile chlorine of **12**[22] to give **13**. The major product isolated from this reaction was identified on the basis of its spectra (*vide infra*) and elemental analyses as 9-β-D-ribopyranosyl-8-azahypoxanthine (**13**); the minor component was identified in the same way as the α anomer **14**. The acid treatment[23] obviously opened the furanose ring to give a structure such as **10**,[25] which then reclosed to the pyranose **9**.[27] The nature of the sugar moiety of **9** should be determined by the relative stabilities of the possible isomers. The pyranoses are in general more stable than the furanoses.[28] The most stable isomer of the final product (and hence of **9**) should be the β-pyranose in the normal (*N*) conformation (**13**).[29,30] In this conformation the $C_{1'}$ and $C_{2'}$ protons would be trans diaxial. The coupling constant $J_{1'2'}$ of **13** is 9.5 Hz (see Table II), which indicates[31] that, indeed, this compound is the β anomer and, therefore, that ring closure of **9** gave primarily the β anomer **12**, which exists principally in the *N* conformation. The $C_{1'}$ and $C_{2'}$ protons of the α-pyranose (**14**) would be cis axial–equatorial in either the *N* or the *A* conformation and, therefore, the coupling constant $J_{1'2'}$ cannot be used to distinguish between the two conformers. Both of these conformers have instability factors.[32] In the *N* conformation the bulky 8-azapurine moiety is axial, and it would seem that under conditions of the ring closure the anomeric effect[33] might not be significant. On the other hand, the *A* conformation would have 1,3-diaxial hydroxyls, and the Δ2 effect[34] would be operative. The chemical shift of the $C_{1'}$ proton of **14** would support, but not establish, the *N* conformation since the absorption band is downfield from that of the β-pyranose **13**.[35]

In order to prevent this furanose–pyranose isomerization, we sought a blocking group for the 5′-hydroxyl that would withstand both the basic ring cleavage and the acidic amide hydrolysis steps, but which could later be removed from the 8-azapurine ribonucleoside. The

(22) Y. F. Shealy, J. D. Clayton, C. A. O'Dell, and J. A. Montgomery, *J. Org. Chem.*, **27**, 4518 (1962).

(23) Under conditions similar to those used originally for the amide hydrolysis, *i.e.*, methanolic hydrochloric acid, Bishop and Cooper[24] found that the equilibrium mixture of *O*-methyl glycosides formed from ribose consisted of 65.8% β-pyranose, 17.4% β-furanose, 11.6% α-pyranose, and 5.2% α-furanose.

(24) C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, **41**, 2743 (1963).

(25) This reaction is similar to the first step in the acid-catalyzed hydrolysis of *N*-arylglycosylamines.[26]

(26) B. Capon and B. E. Connett, *Tetrahedron Lett.*, 1395 (1964).

(27) It is not known whether the isopropylidene group, which might well influence this reaction, comes off before or after reclosure.

(28) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1956, p 378.

(29) Z. Samek and J. Farkas, *Collect. Czech. Chem. Commun.*, **30**, 2149 (1965).

(30) Y. H. Pan, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 246 (1967).

(31) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

(32) Reference 28, p 371.

(33) Reference 28, p 375.

(34) Reference 28, p 377.

(35) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966).

TABLE I

ULTRAVIOLET SPECTRAL DATA

Compd	0.1 N HCl: Max, nm (ε × 10⁻³)	0.1 N HCl: Min, nm	pH 7 buffer: Max, nm (ε × 10⁻³)	pH 7 buffer: Min, nm	0.1 N NaOH: Max, nm (ε × 10⁻³)	0.1 N NaOH: Min, nm
8	240 (12.9)	<225	239 (12.8)	<225	258 (sh) (9.24)	232
	273 (5.7)	264	273 (5.5)	263	280 (9.68)	265
Reaction mixture[a]	250.5	*Ca.* 230			254	*Ca.* 232
	292	*Ca.* 275			290	274
Reaction mixture[b]	*Ca.* 260					
	307					
9	*Ca.* 275 (sh)	244	255	229	256	230
	302		291	270	291	270
4, R = Cl	269	237	254	228	253	230
	307	280	290	269	290	269
4-Amino-6-chloro-5-formylaminopyrimidine[c]	237 (8.2)	220	237 (9.6)	219	256.5 (7.0)	231
	278 (4.5)	260	278.5 (4.0)	258	283.5 (7.0)	270
13	254 (9.83)	224	255 (8.68)	226	275 (10.5)	229
14	254 (9.10)	227	255 (8.04)	228	275 (9.94)	230
α-21	254 (8.82)	228	256 (8.58)	230	275 (9.82)	232
β-21	255 (9.8)	228	255 (8.85)	228	276 (10.9)	232

[a] See ref 3. [b] See ref 13. [c] J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **26**, 4469 (1961).

TABLE II

PMR SPECTRAL DATA

Compd	$C_{1'}$ H, δ in ppm	$J_{1'2'}$, Hz	CH_2OH, δ in ppm
13	5.86	9.8	
14	6.07	2.2	
β-21	6.11	5.0	3.55
β-22	6.25	2.0	3.48
α-21	6.56	6.2	3.50
α-22	6.60	5.0	3.66

urethane group was selected and 6-chloro-9-[2,3-*O*-isopropylidene-5-*O*-(*m*-chlorophenylcarbamoyl)-β-D-ribofuranosyl]purine (**15**) was prepared by the reaction of **6** with *m*-chlorophenyl isocyanate (Scheme III). Treatment of **15** with aqueous base gave results similar to those obtained with **6**; a 44% yield of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-5-*O*-(*m*-chlorophenylcarbamoyl)-β-D-ribofuranosyl)amino]pyrimidine (**17**) was obtained. This compound, on treatment with methanolic hydrochloric acid, gave four products, two of which had retained the isopropylidene group (**19**) and two of which had not (**18**), as judged by the metaperiodate–Schiff test and their chromatographic behavior. Treatment of **18** with aqueous nitrous acid followed by methanolic methoxide gave 8-azainosine (**β-21**)[6] and its α anomer (**α-21**), resulting from ring closure of **18** followed by hydrolysis of the chloro group and then cleavage of the urethane **20**. Treatment of **19** in the same way gave the isopropylidene derivatives of 8-azainosine and its α anomer (**α-** and **β-22**). Acid hydrolysis converted **22** into **α-** and **β-21**.

An examination of the pmr spectra of these compounds (Table II) confirms their identity. Of particular interest are the coupling constants for $C_{1'}$ H and $C_{2'}$ H of the anomeric pair **α-** and **β-22**. The presence of the isopropylidene group lowers the coupling constant $J_{1'2'}$ of the β anomer from 5.0 Hz to 2.0 Hz in agreement with findings of previous workers.[36,37] The pmr spectra of few isopropylidene derivatives of α-ribonucleosides have been examined. In the case of **α-22** the coupling constant $J_{1'2'}$ is only lowered from 6.0 to 5.0 Hz, indicating a dihedral angle of 37.5° (Karplus equation), easily accommodated by the cis protons of the α anomer. In addition, the bands due to the $C_{1'}$ H of the α anomers are downfield from those of the β anomers.[38,39] No exceptions to this empirically satisfactory rule have yet been found.

The yield of **α-21** was slightly higher than that of **β-21**, indicating no great difference in the stability of **α-** and **β-18** or of **α-** and **β-19**, in contrast to the pyranoses. Even the presence of the isopropylidene group of **19** does not appear to favor closure to the β anomer.

Thus, by the use of appropriate blocking groups, we have been able to prepare all four isomeric ribonucleosides of 8-azahypoxanthine (**13**, **14**, and **α-** and **β-20**) from 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**6**). The stability of 8-azainosine (**β-21**) and its pyranose isomer (**13**) to both acid and base was examined. The furanose isomer **β-20** is more labile to both, and in each case the nucleoside is cleaved to 8-azahypoxanthine.

Experimental Section

The melting points reported were determined with a Mel-Temp apparatus and are not corrected. The optical rotations were determined in the solvents specified with a Rudolph Model 80 polarimeter. The uv spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer. The ir spectra of the compounds were determined in pressed KBr disks with a Perkin-Elmer Model 521 spectrophotometer but are not reported. The pmr spectra (Table II) were determined in DMSO-d_6 containing TMS as internal reference with a Varian A-60A spectrometer. Chromatographic analyses were carried out on thin layer plates of silica gel H (Brinkmann). The plates were developed in mixtures of $CHCl_3$ and MeOH in various proportions. The spots were detected by uv light after spraying the plates with Ultraphor (WT, highly concentrated) (BASF Colors & Chemicals, Inc., Charlotte, N. C.). Most of the chromatographic purifications were carried out on Mallinckrodt SilicAR-7 with the solvents indicated. The analytical samples were dried over P_2O_5 at 0.07 mm for 16–20 hr at the temperatures given.

Polymer of 6-Chloro-9-β-D-ribofuranosylpurine (5).—A solution of 6-chloro-9-β-D-ribofuranosylpurine (574 mg, 2.00 mmol) in

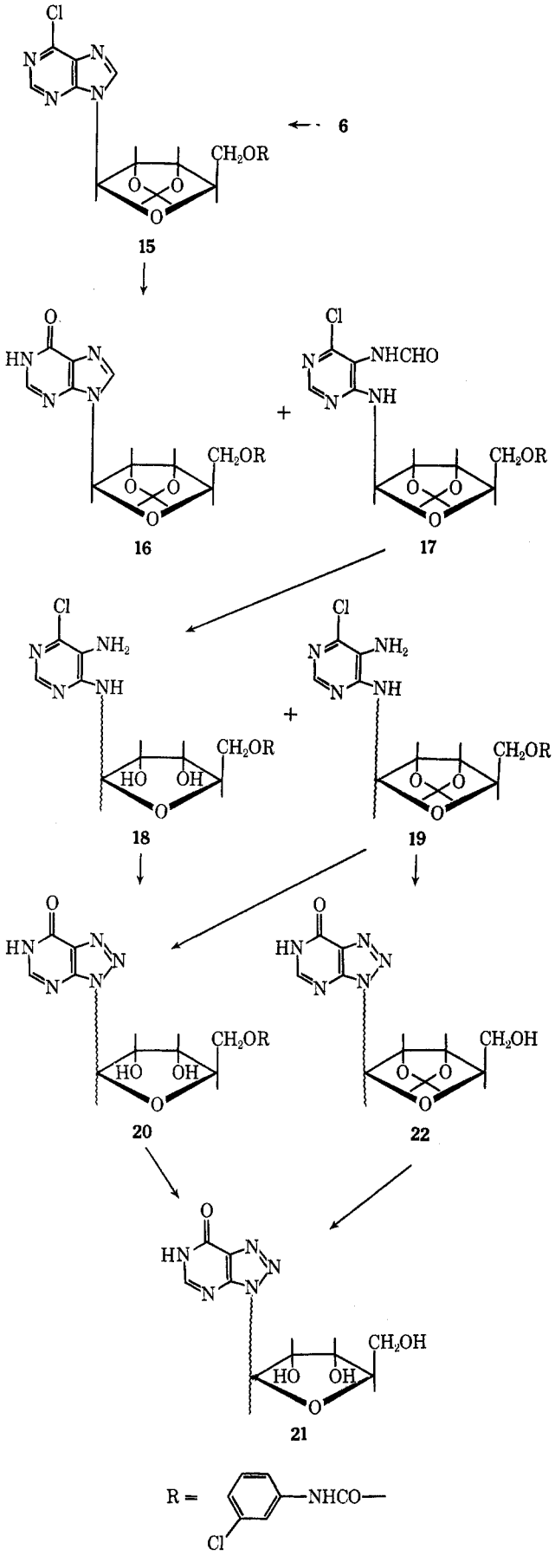
(36) N. J. Leonard and R. A. Laursen, *J. Amer. Chem. Soc.*, **85**, 2026 (1963).

(37) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **34**, 2646 (1969).

(38) J. A. Montgomery and H. J. Thomas, *J. Amer. Chem. Soc.*, **87**, 5402 (1965).

(39) T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.*, **13**, 803 (1965).

SCHEME III



0.1 *N* KOH (40 ml) was heated at 50° for 1 hr. The precipitate that formed was collected by filtration and washed with H_2O, yield 320 mg (61%).

The analytical sample was obtained by precipitation from DMF–EtOH. It was dried at 100°: λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl 254 (49.2); pH 7 254 (49.1); 0.1 *N* NaOH 253 (50.8).

Anal. Calcd for $C_{50}H_{51}ClN_{20}O_{20} \cdot 2H_2O$: C, 45.37; H, 4.19; N, 21.16; Cl, 2.75. Found: C, 45.50; H, 4.20; N, 21.13; Cl, 2.43.

4-Chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (8).—To a cold solution of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (6.00 g, 18.4 mmol) (6) in dioxane (110 ml) was added cold 1 *N* NaOH solution (110 ml). The resulting solution was kept at room temperature for 45 min, stirred with Amberlite IR-120 (H) ion exchange resin until a pH of 4–5 was obtained, filtered to remove the resin, basified to pH 8 with concentrated NH_4OH, and then evaporated to dryness *in vacuo*. During the evaporation, *n*-BuOH was added at intervals to prevent foaming. The residue crystallized from methanol, yield 2.06 g.

The residue from evaporation of the mother liquor was purified by preparative tlc, $CHCl_3$–MeOH (95.5). This treatment gave another 900 mg of product 8 (total yield, 47%) and 215 mg (7.6%) of 2′,3′-*O*-isopropylideneinosine (7).

The analytical sample of the product was obtained by recrystallization from MeOH. It was dried at 78°: mp 180–181°; δ 1.3 and 1.5 (2 s, CH_3), 3.5 (m, $C_{5'}$ H_2), 4.8 (m, $O_{5'}$ H, $C_{2'}$ H, and $C_{3'}$ H), 6.0 (m, $C_{1'}$ H), 6.5 (m, N_6 H), 8.4 (m, C_2 H and CHO), 9.8 ppm (broad, N_5 H). Addition of D_2O to the DMSO-d_6 solution replaced the NH and OH protons by deuterium, and this resulted in collapse of the multiplet at 6.0 ppm to a triplet rather than the expected doublet, apparently due to virtual coupling between $C_{1'}$ H and $C_{3'}$ H. The small coupling constants of this triplet (2 Hz) confirm that 8 is a β-*N*-glycoside.

Anal. Calcd for $C_{13}H_{17}ClN_4O_5$: C, 45.29; H, 4.97; N, 16.25. Found: C, 45.12; H, 4.98; N, 16.17.

9-β- and -α-D-Ribopyranosyl-8-azahypoxanthine (13 and 14). A.—A solution of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (910 mg, 2.65 mmol) (8) in MeOH (90 ml) was treated with MeOH (26.3 ml) containing concentrated HCl (0.22 ml), and the resulting solution was refluxed 30 min, neutralized to pH 5 with a concentrated NH_4OH solution, and then evaporated to dryness *in vacuo*. The white glass that was obtained was shown by tlc to be a mixture of two major products.

A solution of this mixture in H_2O (50 ml) was chilled in an ice bath and acidified with glacial HOAc (1 ml). To the resulting solution was added dropwise a solution of $NaNO_2$ (730 mg, 10.6 mmol) in H_2O (4.0 ml). The reaction solution was kept in the ice bath for 10 min and then left at room temperature for 20 hr. It was then basified to pH 10 with a concentrated NH_4OH solution, and a solution of $Pb(OAc)_2 \cdot 3H_2O$ (1.53 g, 4.05 mmol) in H_2O (10 ml) was added. The resulting precipitate was collected by filtration and dissolved in 20% HOAc (v/v) (10 ml). Treatment of the solution with H_2S for 2 min gave a precipitate of PbS that was removed by filtration. Evaporation of the filtrate to dryness gave a mixture of the α- and β-D-ribopyranoses of 8-azahypoxanthine as a white glass. The β anomer crystallized from a solution of the mixture in 80% EtOH, yield 80 mg.

The analytical sample (13) was obtained by recrystallization from 80% EtOH. It was dried at 78°: mp 266–267° dec; $[\alpha]^{24}D$ −44.6 ± 1.2° (*c* 0.52, H_2O).

Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.01. Found: C, 40.11; H, 4.13; N, 25.95.

Evaporation of the mother liquor gave a residue that was purified by preparative tlc using $CHCl_3$–MeOH (9:1) as the developing solvent. The two major bands obtained were eluted with boiling MeOH. The faster-moving material was more of the β anomer, yield 95 mg (total yield 24%). The slower-moving material was the α anomer, yield 135 mg (19%).

The analytical sample of the α anomer 14 was obtained by purification through the lead salt as a white solid. It was dried at 100°: melting point indefinite; $[\alpha]^{24}D$ −52.4 ± 1.5° (*c* 0.90, H_2O).

Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.01. Found: C, 40.26; H, 4.11; N, 25.81.

B.—A solution of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (1.19 g, 3.45 mmol) (8) in 0.1 *N* HCl (70 ml) was left at room temperture for 20 hr and then chilled in an ice bath. The cold solution was then stirred while a solution of $NaNO_2$ (953 mg, 13.8 mmol) in H_2O (5 ml) was slowly added. The resulting solution was stirred for 10 min, refrigerated for 24 hr, then taken to pH 10 with concentrated

NH_4OH, and treated with $Pb(OAc)_2 \cdot 3H_2O$ (2.01 g, 5.3 mmol) in H_2O (10 ml). The precipitate that formed was collected by filtration and washed thoroughly with H_2O. A solution of the resulting solid in 20% aqueous HOAc (25 ml) was treated with H_2S until there was no longer a precipitate of PbS. The black precipitate was filtered and washed thoroughly with H_2O. The combined filtrate and wash was evaporated to dryness *in vacuo*. From an aqueous solution of the residue there was obtained the β anomer as a crystalline solid, yield 85 mg. Purification of the filtrate by preparative tlc gave another 186 mg of β anomer (total yield 271 mg, 29%) and 170 mg (18%) of α anomer.

6-Chloro-9-[5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]purine (15).—A solution of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (1.96 g, 6.0 mmol) (**6**), triethylamine (0.84 ml, 6.0 mmol), and 3-chlorophenyl isocyanate (1.46 ml, 12.0 mmol) in DMF (35 ml) was held for 20 hr at room temperature and then evaporated to dryness *in vacuo*. A solution of the residue in ether yielded 729 mg (2.5 mmol) of crystalline 3,3′-dichlorocarbanilide. The filtrate was evaporated to dryness *in vacuo*. The residue thus obtained crystallized from MeOH, yield 2.42 g (88%).

A small sample was recrystallized from MeOH for analysis. It was dried at 78°: mp 96–100°; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl 238 (15.3), 265 (7.34); pH 7 238 (15.1), 265 (7.28); 0.1 *N* NaOH 239 (14.8), 264 (8.50).

Anal. Calcd for $C_{20}H_{19}Cl_2N_5O_5$: C, 50.01; H, 3.99; N, 14.58. Found: C, 50.21; H, 3.96; N, 14.64.

4-Chloro-5-formylamino-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (17).—To a solution of 6-chloro-9-[5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]purine (480 mg, 1.00 mmol) (**15**) in dioxane (6 ml) was added 1 *N* NaOH (6 ml). The resulting cloudy suspension became clear after stirring 10 min at room temperature. The clear solution was held an additional 45 min. It was then chilled in an ice bath and slowly neutralized with concentrated HCl. The mixture was evaporated to dryness *in vacuo*, and the residue was partitioned between $CHCl_3$ and H_2O (100 ml each). The $CHCl_3$ layer was dried over $MgSO_4$ and then evaporated to dryness. The residue crystallized from EtOH, yield 220 mg (44%). Addition of D_2O to the DMSO-d_6 solution replaced the NH protons by deuterium, and this resulted in collapse of the doublet of doublets at 6.0 ppm to the expected doublet with a coupling constant of 4 Hz.

The analytical sample was obtained by recrystallization from EtOH. It was dried at 78°: mp 169°; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl 237 (24.8), 273 (6.20); pH 7 237 (24.8), 273 (6.00); 0.1 *N* NaOH 239 (16.8), 275 (sh) (10.8); δ 1.4 and 1.5 (2 s, CH_3), 4.2 (m, C_4' H and C_5' H_2), 4.9 (m, C_2' H and C_3' H), 6.0 (m, C_1' H), 6.6 (d, N_6 H), 7.1, 7.3, and 7.6 (m, phenyl H), 8.4 (s, C_2H and CHO), 9.9 ppm (s, broad, 2 H of NHCO).

Anal. Calcd for $C_{20}H_{21}Cl_2N_5O_6$: C, 48.21; H, 4.25; N, 14.05; Cl, 14.23. Found: C, 48.47; H, 4.20; N, 14.14; Cl, 14.26.

In another run a 3% yield of 5′-*O*-(*m*-chlorophenylcarbamoyl)-2′,3′-*O*-isopropylideneinosine (**16**) was isolated by thin layer chromatography.

Deformylation of 4-Chloro-5-formylamino-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine.—A solution of 4-chloro-5-formylamino-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (999 mg, 2.00 mmol) in 0.017 *N* methanolic HCl (120 ml) was refluxed for 30 min, neutralized to pH 5 with concentrated NH_4OH, and then evaporated to dryness *in vacuo*. Trituration of the residue with H_2O produced a solid weighing 867 mg. Purification by preparative tlc using $CHCl_3$–MeOH (95:5) as the developing solvent gave three major bands. Each band was eluted with boiling MeOH. Evaporation of the MeOH solutions gave the following products: 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-α- and -β-D-ribofuranosyl)-amino]pyrimidine (**18**), 310 mg (36%); 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene)-α- and -β-D-ribofuranosyl)amino]pyrimidine (**19**), 284 mg (30%); and starting material **17**, 129 mg (13%).

8-Azainosine (β-21).—A solution of 2′,3′-*O*-isopropylidene-8-azainosine (β-**22**) in 0.1 *N* H_2SO_4 (20 ml) was kept at room temperature for 3 days, neutralized with $Ba(OH)_2$ solution, filtered to remove the precipitate of $BaSO_4$, and evaporated to dryness *in vacuo*. The residue crystallized from 80% aqueous EtOH, yield 14 mg (41%). The uv and ir spectra of this material were identical with that of an authentic sample of 8-azainosine.[6]

9-α-D-Ribofuranosyl-8-azahypoxanthine (α-21).—A solution of the α anomer of 2′,3′-*O*-isopropylidene-8-azainosine (70 mg, 0.23 mmol) (α-**22**) in 0.1 *N* H_2SO_4 (40 ml) was left for 24 hr at room temperature, neutralized with $Ba(OH)_2$ solution, filtered to remove the precipitate of $BaSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in H_2O (2 ml), and the solution made basic (pH 10) with concentrated NH_4OH. A solution of $Pb(OAc)_2 \cdot 3H_2O$ (349 mg, 0.92 mmol) in H_2O (3 ml) was added. The precipitate that formed was collected by filtration (55 mg). A solution of the lead salt in 20% HOAc (v/v) (20 ml) was treated with H_2S for 2 min, filtered to remove the precipitate of PbS, and evaporated to dryness *in vacuo*. A white solid was obtained. It was dried at 100°: yield 20 mg (29%); $[\alpha]^{24}D$ $+119.6 \pm 1.2°$ (*c* 0.53, H_2O).

Anal. Calcd for $C_9H_{11}N_5O_5 \cdot {}^1/_3H_2O$: C, 39.28; H, 4.27; N, 25.44. Found: C, 39.22; H, 4.30; N, 25.32.

8-Azainosine (β-21) and Its α Anomer (α-21).—A solution of 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-α- and -β-D-ribofuranosyl)amino]pyrimidine (267 mg, 0.62 mmol) (**18**) in H_2O (5 ml) and glacial HOAc (2 ml) was chilled in an ice bath while a solution of $NaNO_2$ (172 mg, 2.49 mmol) in H_2O (2 ml) was slowly added. The cloudy solution that resulted cleared on addition of another 2 ml of HOAc. After being stirred in the cold for 15 min, it was refrigerated 20 hr, and then evaporated to dryness. After trituration with H_2O and then ether, the residue became a solid, yield 140 mg (54%).

A solution of the solid [5′-*O*-(*m*-chlorophenylcarbamoyl)-8-azainosine and its α anomer] (121 mg, 0.28 mmol) (**20**) in 0.1 *N* $NaOCH_3$ in MeOH (10 ml) was refluxed for 4 hr, neutralized with HOAc, and evaporated to dryness *in vacuo*. A solution of the residue in H_2O (10 ml) was made basic (pH 10) with concentrated NH_4OH, and a solution of $Pb(OAc)_2 \cdot 3H_2O$ (190 mg, 0.5 mmol) in H_2O (1 ml) was added. The precipitate that resulted was collected by filtration and dissolved in 20% HOAc (v/v) (10 ml). H_2S was bubbled through the solution for 2 min, and the resulting precipitate of PbS was removed by filtration. Evaporation of the filtrate to dryness gave a hygroscopic solid weighing 43 mg. Purification of this material by preparative tlc, using $CHCl_3$–MeOH (3:1) as the developing solvent, gave a white solid, yield 27 mg (36%). Examination of this material by pmr showed that it was a 1:1 mixture of 8-azainosine (β-**21**) and its α anomer α-**21**.

2′,3′-*O*-Isopropylidene-8-azainosine and Its α Anomer (22).—To a cold solution of 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene)-α- and -β-D-ribofuranosyl)amino]pyrimidine (280 mg, 0.60 mmol) (**19**) in glacial HOAc (2 ml) was added a saturated aqueous solution of $NaNO_2$ (180 mg, 2.61 mmol). A precipitate immediately formed, but the addition of HOAc (2 ml) produced a clear solution, which was left 20 hr at room temperature before it was evaporated to dryness *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O (50 ml each). The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. A yellow glass was obtained: yield 230 mg (85%); λ_{max} nm ($\epsilon \times 10^{-3}$) 0.1 *N* HCl 238 (16.8), 262 (sh) (7.84); pH 7 238 (16.4), 263 (sh) (7.34); 0.1 *N* NaOH 237 (14.2), 276 (9.77).

A solution of this yellow glass [a mixture of 5′-*O*-(*m*-chlorophenylcarbamoyl)-2′,3′-*O*-isopropylidene-8-azainsine and its α anomer] in 0.1 *N* methanolic $NaOCH_3$ (20 ml) was refluxed 1 hr, neutalized with glacial HOAc, and evaporated to dryness *in vacuo*. The residue, a 1:1 mixture of 2′,3′-*O*-isopropylidene-8-azainosine and its α anomer **22**, was separated by preparative tlc, using $CHCl_3$–MeOH (9:1) as the developing solvent. The bands were eluted with boiling MeOH. The slower-moving α anomer was obtained as a white solid, yield 70 mg (45%). The β anomer was also a white solid, yield 40 mg (26%).

Registry No.—**4** (R = Cl), 4316-98-7; **5**, 29351-03-9; **8**, 29168-69-2; **9**, 29168-70-5; **13**, 29168-71-6; **14**, 29168-72-7; **15**, 29168-73-8; **17**, 29168-74-9; α-**21**, 28234-86-8; β-**21**, 4968-68-7; α-**22**, 29246-45-5; β-**22**, 29168-77-2.

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