The analytical sample was prepared by dissolving a sample of the purified product (85 mg) in acetone, decolorizing the resulting solution with Norit, and crystallizing the pure product from the filtrate by the addition of ether: yield, 59 mg (70%); mp 220°; λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1—274 (sh), 287 (18.5), pH 7—274 (sh), 286 (19.0), pH 13—unstable; σ, in cm^{-1}, 3030, 2960, 2920 (CH), 1625, 1550 (NH, C=C, C=N).

Anal. Calcd for $C_{21}H_{22}BrN_5$: C, 59.44; H, 5.23; N, 16.51. Found: C, 59.51; H, 5.27; N, 16.58.

1-Benzyl-5-benzylaminoimidazole-4-carboxamide (XXIIa).—A suspension of 3,9-dibenzyl-6-dimethylaminopurine bromide (XXI, 1.5 g, 3.5 mmoles) in 0.15 *N* NaOH (4 ml) was refluxed for 6 hr before it was allowed to stand at room temperature overnight. The solid that precipitated was collected by filtration, washed with water, and dried to give 765 mg (71%) of product suitable for use as an intermediate: mp 152°.

The analytical sample was obtained by recrystallizing a sample of the purified product (110 mg) from 50% aqueous ethanol (10 ml): yield, 60 mg (55%); mp 153°. A Bratton–Marshall test for diazotizable amino groups was negative. Thin layer chromatography using chloroform–methanol (15:1) showed a single spot: λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1—254 (7.3), pH 7, 13—269 (8.7); σ, in cm^{-1}, 3320, 3140, 3060, 3030 (NH, CH), 2960, 2920, 2860 (aliphatic CH), 1670, 1600, 1590 (C=O, NH); τ, in ppm, 5.74 d (CH_2 of benzylamino), 4.84 (CH_2 of 1-benzyl), 3.83 t (NH of amine), 3.13 (NH_2 of amide), 2.80 (phenyl), and 2.7 (C^2–H). Upon addition of D_2O the doublet at 5.74 ppm became a singlet and NH–D_2O exchange was evident.

Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.54; H, 5.92; N, 18.28. Found: C, 70.37; H, 5.76; N, 18.35.

1-Benzyl-5-(*N*-benzylformamido)imidazole-4-carboxamide (XXIIb). A.—A solution of 1-benzyl-5-benzylaminoimidazole-4-carboxamide (XXIIa, 100 mg, 0.33 mmole) in formic acid (3 ml) was refluxed for 6 hr before it was evaporated to dryness *in vacuo*. The residue was triturated with ethanol and ether and the insoluble solid was collected by filtration to give 85 mg (78%) of essentially pure product: mp 208°. Thin layer chromatography showed the presence of a small amount of 9-benzylhypoxanthine. Recrystallization of a sample of the isolated product (20 mg) from ethanol with Norit treatment gave the pure product: yield, 14 mg (70%); mp 208°. Thin layer chromatography using chloroform–methanol (15:1) as the eluent showed a single spot: λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1,7,13—245 (sh); σ, in cm^{-1}, 3350, 3160, 3100, 3060, 3010, 2930 (NH, CH), 1690, 1670 (amide I), 1600, 1580 (C=C, C=N); τ, in ppm, 5.27 (CH_2 of both benzyl groups), 3.00 (NH), 2.77 (phenyl), 2.29 and 2.17 (C^2–H and formyl).

Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.43; N, 16.76. Found: C, 67.99; H, 5.54; N, 16.82.

B.—A suspension of 1-benzyl-5-benzylaminoimidazole-4-carboxamide (XXIIa, 100 mg, 0.33 mmole) in diethoxymethyl acetate was stirred at room temperature for 2 days. Thin layer chromatography using chloroform–methanol (19:1) as eluent indicated the presence of two products and the absence of starting compound. The reaction mixture was evaporated to dryness and the residue triturated with ethanol–ether. The insoluble solid was collected by filtration, washed with ethanol–ether and dried *in vacuo* to give the crude product, which was purified by preparative thin layer chromatography on silica gel using chloroform–methanol (19:1) as eluent. The two major products that separated were extracted from the chromatographic layer with methanol. Evaporation of the methanol extracts to dryness gave the purified products which were identified as **1-benzyl-5-(*N*-benzylformamido)imidazole-4-carboxamide** (60% of the crude product) and **9-benzylhypoxanthine** (20% of crude product) by comparison of their spectra with those of known compounds.

5-Amino-1,*N*-dibenzylimidazole-4-carboxamide (XXIII).—A solution of 1,9-dibenzylhypoxanthine (IIa, 250 mg, 0.79 mmole), 6 *N* NaOH (1.8 ml), and ethanol (100 ml) was refluxed for 3 hr. The solid that precipitated from the reaction mixture after partial neutralization (to pH 8 with concentrated HCl) was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Trituration of the residue with water gave the crude product (235 mg, 97%). The crude product was recrystallized from ethanol (5 ml) to give the pure material: yield, 167 mg (69%); mp 161°. A Bratton–Marshall test for a diazotizable amino group was positive. Thin layer chromatography using chloroform–methanol (19:1) as the eluent showed a single spot: λ_{max}, in mμ ($\epsilon \times 10^{-3}$), pH 1—243 (10.7), 268 (13.3), pH 7—268 (16.8), pH 13—267.5 (16.6); σ, in cm^{-1}, 3405, 3270, 3210, 3150 (NH), 3015, 2895, 2850 (CH), 1615, 1610, 1580 (NH, C=C, C=N), τ, in ppm, 5.61 d (CH_2 of benzylamide), 4.92 (CH_2 of 1-benzyl), 4.20 (NH_2), 2.83 (C^2–H), 2.75 (phenyl), 2.12 t (amide NH). Upon the addition of D_2O the doublet at 5.61 ppm became a singlet and NH–D_2O exchange was evident.

Anal. Calcd for $C_{18}H_{18}H_4O$: C, 70.56; H, 5.93; N, 18.29. Found: C, 70.28; H, 5.97; N, 18.36.

Acknowledgment.—The authors are indebted to Dr. W. J. Barrett, under whose direction the microanalyses and spectral determinations reported were carried out by members of the Analytical Chemistry Section of Southern Research Institute, to Dr. W. C. Coburn, Jr., and Mrs. M. Thorpe for their help in the interpretation of the proton magnetic resonance spectra, and to Mrs. Imogene L. Baswell for most of the chromatographic analyses.

Studies on the Azidoazomethine–Tetrazole Equilibrium. V. 2- and 6-Azidopurines[1]

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The azidoazomethine–tetrazole equilibrium in seven new 2- and 6-azidopurine systems is examined. Results indicate that this equilibrium is solvent dependent, that the tetrazolo tautomer is stabilized by electron-donating groups, and that the azido tautomer is stabilized by electron-withdrawing groups. In addition, hydrolysis of the azido group or cleavage of the pyrimidine ring were the major reactions resulting from the treatment of the 6-azidopurine systems with aqueous acid or base.

In a recent paper we reported some observations on the azidoazomethine–tetrazole equilibrium for the systems involving 2- and 6-azidopurine.[2] Some substituted systems have now been prepared to examine the effect of solvent and of certain electron-donating and electron-attracting groups on this equilibrium. The results indicate that the azidoazomethine–tetrazole equilibrium is quite mobile, and furthermore that the use of chemical methods to assign either the azido or tetrazolo structure may not always be valid.[3] As in

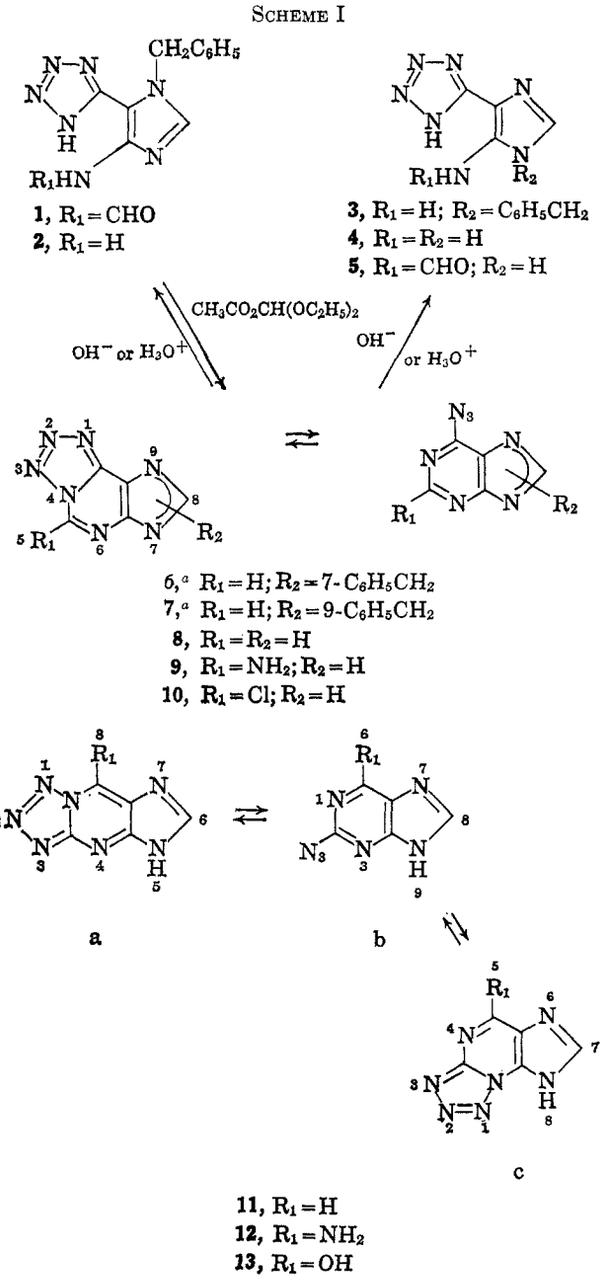
(1) This investigation was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51.

(2) C. Temple, Jr., M. C. Thorpe, W. C. Coburn, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 935 (1966).

(3) (a) T. Itai and G. Ito, *Chem. Pharm. Bull.* (Tokyo), **10**, 1141 (1962); (b) F. R. Benson, L. W. Hartzel, and E. A. Otten, *J. Am. Chem. Soc.*, **76**, 1858 (1954).

previous reports[2] the proton magnetic resonance (pmr) and infrared spectra, taken together, were used to determine the relative amounts of each tautomer in a given solvent. In addition, reaction of the 2-substituted 6-azidopurine systems with hydrochloric acid resulted in hydrolysis of the azido group. In contrast, cleavage of the pyrimidine ring occurred on treatment of those systems unsubstituted in the 2 position with aqueous acid or base. These ring-opening reactions are similar to those recently reported for *s*-triazolopurines[4] (see Scheme I).

SCHEME I



1, R_1 = CHO
2, R_1 = H
3, R_1 = H; R_2 = $C_6H_5CH_2$
4, R_1 = R_2 = H
5, R_1 = CHO; R_2 = H

6,[a] R_1 = H; R_2 = 7-$C_6H_5CH_2$
7,[a] R_1 = H; R_2 = 9-$C_6H_5CH_2$
8, R_1 = R_2 = H
9, R_1 = NH_2; R_2 = H
10, R_1 = Cl; R_2 = H

a b c

11, R_1 = H
12, R_1 = NH_2
13, R_1 = OH

[a] Purine numbering system used.

Relevant information on the preparation of the azidopurine–tetrazolopurine systems are given in Table III and typical procedures are reported in the Experimental Section. All the compounds herein were prepared from a chloropurine, directly by treatment with sodium azide, or indirectly by conversion to the hydrazinopurine followed by nitrosation. Both methods were used in the preparation of the *N*-benzyl systems **6** and **7** from the corresponding 6-chloropurines.[5a] Although the reaction of 2-amino-6-chloropurine with sodium azide failed, the nitrosation of 2-amino-6-hydrazinopurine[5b] provided a good yield of **9**. Similarly, the nitrosation of 2-chloro-6-hydrazinopurine[5b] was used to prepare the chloro system **10**, since it had been reported that 2,6-dichloropurine reacts readily with sodium azide to give 2,6-diazidopurine (**14**, see below).[5c] In addition, 2-hydrazinoadenine[5b] gave **12**, and 2-chlorohypoxanthine[5b] gave the monohydrate of **13**. When the latter was dried at 110°, elemental analyses indicated that some decomposition occurred (see below). Recrystallization of the hydrate from glacial acetic acid, however, yielded the one-half acetate of **13**.

Reaction of **6** with an equivalent amount of aqueous sodium hydroxide at room temperature opened the pyrimidine ring to give *N*-(1-benzyl-5-tetrazol-5-ylimidazol-4-yl)formamide (**1**).[4] Treatment of **6** with excess base not only opened the pyrimidine ring, but also removed the formyl group to give 5-(4-amino-1-benzylimidazol-5-yl)tetrazole (*2*). In addition, the latter was obtained from the action of methanolic hydrogen chloride on **1**. The cyclization of *2* to **6** was effected with diethoxymethyl acetate at 100°, but was more difficult than the cyclization of the related 3-(4-amino-1-benzylimidazol-5-yl)-*s*-triazine.[4] Reaction of **7** with excess base gave 5-(5-amino-1-benzylimidazol-4-yl)tetrazole (**3**); similar treatment of **8** and **10** provided the same product, 5-[5(4)-aminoimidazol-4(5)-yl]tetrazole (**4**). The formyl derivative (**5**) of **4** was obtained when the molar ratio of base to **8** was 1.6. Compound **4** may be the unidentified product previously obtained in the action of base on **8**.[6] In contrast to the ring-opening reactions, **9** was recovered unchanged when it was refluxed in 1 *N* sodium hydroxide for 2 hr.

The action of hot, 1 *N* hydrochloric acid on **8** was reported to give adenine, identified by paper chromatography.[6] Under similar conditions, we have found that the major reaction is cleavage of the pyrimidine ring to give **4**, which also results from the action of concentrated hydrochloric acid on **8** at room temperature. Thin layer chromatography of the crude product, however, indicated that adenine might be present as a trace impurity. Similarly, treatment of **6** and **7** with concentrated hydrochloric acid gave **2** and **3**, respectively. In contrast to the conversion of **8** to **4**, none of the latter was obtained by treatment of **9** and **10** with concentrated hydrochloric acid. Although both **9** and **10** were stable at room temperature in this medium, hydrolysis of the azido group was a major reaction when the solutions were heated. Compound **9** provided guanine, identified by thin layer chromatography and its ultraviolet spectrum. From **10** the major product was identified as xanthine hydrochloride by its elemen-

(4) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **30**, 3601 (1965).

(5) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **82**, 4592 (1960); (b) J. A. Montgomery and L. B. Holum, *ibid.*, **79**, 2185 (1957); (c) N. B. Smirnova and I. Y. Postovskii, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **9**, 711 (1964).

(6) A. Bendich, A. Giner-Sorolla, and J. J. Fox in "Ciba Foundation Symposium on the Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., J. and A. Churchill Ltd., London, 1957, p. 10.

TABLE I

ULTRAVIOLET AND INFRARED SPECTRA

Compd	Ultraviolet absorption spectra,[a] λ_{max}, mμ (ε × 10^{-3}) pH 1	pH 7	pH 13		Infrared absorption spectra,[b] 2300–2100- and 1700–1500-cm^{-1} regions
1	243 (11.8)	238 (10.0)	244 (10.4)		1655, 1620, 1570, 1500
2	243 (7.66)	258 (8.80)	258 (8.80)		1665, 1630, 1590, 1500
	267 (7.66)				
3	246 (9.94)	246 (12.5)	245 (12.7)		1635, 1610, 1570, 1520,
	267 (11.6)				1500
4	245[c]	257[c]	258[c]		1665, 1630, 1610, 1570,
	267[c]				1505
5	247 (15.6)	245 (14.8)	237 (14.4)		1650, 1630, 1585
6	*c*	253 (5.52)	*c*		1660, 1600, 1520
		262 (6.22)			
		287 (6.35)			
7	253 (4.74)	253 (4.74)	*c*		1645, 1540, 1500
	261 (4.78)	261 (4.78)			
	288 (8.47)	288 (8.47)			
9	270 (8.90)	269 (7.70)	275 (6.40)	2140[d]	1685, 1650, 1555
	292 (9.80)	301 (8.40)	317 (7.10)		
10	217 (15.8)	220 (17.4)	228 (19.6)	2145	1605, 1570
	250 (7.03)	289 (13.9)	297 (10.8)		
	287 (15.4)				
12	233 (19.5)	230 (25.6)	234 (28.2)	2130	1670, 1645, 1605, 1590
	271 (11.4)	267 (9.00)	271 (8.12)		1500
	311 (1.51)[e]	310 (3.52)	324 (2.96)		
	321 (1.10)[e]	321 (2.75)[e]			
13[f]	261 (4.20)	266 (4.11)	267 (4.10)		1695, 1585, 1545, 1510
	296 (9.00)	302 (10.3)	315 (8.32)		
14[g]	245 (22.2)	243 (20.5)	242 (20.5)	2220	1640, 1580
	297 (12.6)	300 (11.3)	245 (20.2)[e]	2175	
	305 (11.3)[e]		306 (9.85)	2125	

[a] Determined in aqueous solution with a Cary Model 14 recording spectrophotometer. [b] Determined in pressed potassium bromide disks with a Perkin-Elmer Model 521 spectrophotometer. [c] Unstable. [d] Weak. [e] Shoulder. [f] Monohydrate. [g] See ref 5c.

tal analyses and by comparison of its ultraviolet spectrum and thin layer chromatogram with those of an authentic sample.

The ultraviolet spectra and important bands in the infrared spectra (KBr disk) for the new compounds are presented in Table I.

Results and Discussion

Tautomer assignments and equilibrium constants at 34° are given in Table II. The corresponding data for systems **8** and **11** have been reported.[2] In the 6-azidopurine series the tautomer assignment is straightforward. When only one tautomer is detected in the pmr spectrum, the presence or absence of an azido absorption band in the infrared spectrum identifies the tautomer. When two tautomers are detected in the pmr spectrum, the assignment can usually be made from the chemical shifts. Thus, the ring protons of the azido tautomer are more nearly equivalent and their absorption peaks occur at a higher field than the corresponding protons in the tetrazolo tautomer. This difference in the chemical shift of the ring protons is attributed to the opposing effect of the electron-withdrawing tetrazole ring (deshielding) and the electron-donating azido group (shielding). In systems **6–9** only the tetrazolo tautomer is detected in dimethyl sulfoxide-d_6 (DMSO-d_6). In contrast only the azido form (protonated) is found in trifluoroacetic acid (CF_3COOH) with the exception of **7**, which contains 17% of the tetrazolo form. The difference between **7** and **6** cannot be attributed to the electronic nature of the benzyl group, and therefore must be attributed to the degree of protonation.[7] A similar result has been noted in an *N*-methylpyrimidine system.[8] Both the azido and tetrazolo forms can be observed in solutions of **6**, **7**, and **8** in a 1:1 mixture of DMSO-d_6 and CF_3COOH. These results, when compared with the data in the individual solvents, emphasize the solvent dependent nature of the equilibrium. In system **10** the effect of the electron-withdrawing chloro group on azido stabilization was quite evident as only the azido form was detected in either DMSO-d_6 or CF_3COOH. The strong azido peak in the infrared spectrum (KBr disk) of **10** also indicated that the azido tautomer was the major form in the solid state.

In the 2-azidopurine series one azido and two tetrazolo tautomers are possible, and the tautomer assignment is more difficult than in the 6-azidopurine series. Assignment of the three tautomers (**11a**, **11b**, and **11c**) in a DMSO-d_6 solution of the parent system was based mainly upon the difference in the chemical shifts of the pyrimidine CH proton ($\tau_b > \tau_c > \tau_a$).[2] For those systems containing a 6 substituent (**12** and **13**), the use of the chemical shift of the imidazole CH for the identification of the tetrazolo tautomers was not possible (see Table II). The signal from the imidazole CH of an azido tautomer, however, occurred at a higher field than the corresponding signals of the tetrazolo tautomers.

A solution of the 6-amino-2-azidopurine system, **12**, in CF_3COOH showed only the azido form **12b** (pro-

(7) This statement suggests that the 9 nitrogen is a major point of protonation in **6** and **7**, and that the protonated form of **7** is slightly less stable than the corresponding protonated form of **6**.

(8) C. Temple, Jr., W. C. Coburn, Jr., M. C. Thorpe, and J. A. Montgomery, *J. Org. Chem.*, **30**, 2395 (1965).

(9) At this temperature $K_T([b]/[a]) = 4.6$ and $K_T([b]/[c]) = 2.9$.

TABLE II

EQUILIBRIUM CONSTANTS AND INFRARED AND PMR SPECTRAL ASSIGNMENTS

System	Solvent[a]	Concn, % (w/v)	K_T[b] (34°)	σ (cm^{-1})[c]	Chemical shift, τ (ppm)							
					Tetrazolo tautomer				Azido tautomer			
					5-H	8-H	CH_2	C_6H_5	2-H	8-H	CH_2	C_6H_5
6	A	20		*d*	0.02	1.13	4.15	2.55				
	B	20		2205					0.91[e]	1.15	4.18	2.54
	C	20	0.20		0.28	1.13	4.10	2.57	0.87[e]	1.08	4.23	2.57
7	A	20		*d*	−0.07	1.21	4.30	2.65				
	B	10	4.9	2175	0.02	0.57	4.08	2.51	0.89[e]	0.93	4.24	2.51
	C	10	0.41		0.19	1.16	4.29	2.65	0.78[e]	1.08	4.35	2.65
8	A	10		*d*	−0.02	1.38						
	B	10		2200					0.87[e]	0.87		
	C	10	0.37		0.12	0.96			0.75[e]	1.08		
9	A	10		*d*		1.11						
	B	10		2180						1.15		
	D[f]	<4				2.11[f]						
10	A	10		2155						1.46		
	B	10		2155						0.60		

System	Solvent[a]	Concn, % (w/v)	K_T[b] (34°)	σ (cm^{-1})[c]	Chemical shift, τ (ppm)					
					Tetrazolo tautomer a		Azido tautomer b		Tetrazolo tautomer c	
					8-H	6-H	6-H	8-H	5-H	7-H
11	A	5	0.44,[g] 3.5[h]	2135	−0.26	1.08	0.97[e]	1.42	0.55	1.22
	B	10		2180			0.45[e]	0.65		
12	A	10	2.7,[g] 1.1[h]	2130	0.73[i]	1.63	2.55[i]	1.88	2.10[i]	1.52
	B	10		2195[j]				0.78		
13	A[k]	10	*l*	*d*		1.58				1.80
	B[k]	10	*m*	2190				1.43		1.33
	A[n]	10	0.1,[g] 0.5[h]	*o*		1.53		1.93		1.64
	B[n]	10		2190				1.31		
14[p]	A	10	10.4,[q] 9.2[q]	2135				1.59		
	B	10		2200				0.77		
	E	10		2140				1.58		

[a] A, dimethyl sulfoxide-d_6; B, trifluoroacetic acid; C, 1:1 (v/v) mixture of A and B; D, 0.5 *N* NaOD; E, glacial acetic acid. [b] Ratio of the integrated intensities of the protons from the azido tautomer to that of the tetrazolo tautomer. The estimated mean deviation in K_T was less than ±10%. [c] Wavenumber of the infrared absorption band assigned to the antisymmetric stretching vibration of the azido group. [d] No azido band detected. [e] We suggest these assignments for the ring protons on the basis of previous work: W. C. Coburn, Jr., M. C. Thorpe, J. A. Montgomery, and K. Hewson, *J. Org. Chem.*, **30**, 1110 (1965); **30**, 1114 (1965). [f] Shift in ppm downfield from the methyl absorption of sodium 3-trimethylsilylpropane 1-sulfonate used as internal reference. [g] Ratio of **b**/**a**. [h] Ratio **b**/**c**. [i] Amino group protons. [j] An additional band was observed at 2155 cm^{-1}. [k] Hydrate. [l] Initially only **c** was detected, but after 71 hr the solution contained 80% **c** and 20% **a**. [m] Initially a mixture of **c** and **b** but after 30 min only **b** was detected. [n] One-half acetate [τ (ppm) = 8.07 in A and 8.17 in B]. [o] A weak azido band was observed initially at 2140 cm^{-1}, but not after 24 hr. [p] See ref 5c. [q] Unidentified tetrazolo tautomers showed peaks at τ = 1.30 and 1.47 ppm.

tonated). In a DMSO-d_6 solution of **12**, however, **12a**, **12b**, and **12c** were detected in the ratio 1.0:2.7:2.6. The imidazole CH signal (τ = 1.83 ppm) at the highest field was assigned to the azido tautomer (**12b**), which was confirmed by the increase in its intensity at the expense of the other CH signals when the temperature was raised to 92°. At this temperature the ratio of **12a**:**12b**:**12c** was 1.0:4.6:1.6.[9] One of the tetrazolo CH peaks (τ = 1.63 ppm) is readily paired with an NH_2 peak (τ = 0.73 ppm) by means of their integrated intensities. This pair is assigned to **12a**, based on the large deshielding effect of the tetrazole ring on the chemical shift of the adjacent NH_2 peak.[2,8] The remaining two peaks can then be assigned to the other tetrazolo tautomer, **12c**.

In the 2-azidohypoxanthine system, **13**, the chemical shifts of the ring protons in the pmr spectra of the one-half acetate are slightly different from those of the monohydrate. Although this difference can be attributed to the change in the solvent resulting from the added water or acetic acid, the addition of water to an azomethine linkage of **13** to give a covalent hydrate cannot be excluded.[10] The pmr spectrum of the hydrate in DMSO-d_6 initially shows only one tautomer at τ = 1.80 ppm; however, within 1 hr, a second tautomer is detected at τ = 1.58 ppm. At equilibrium the ratio of the first tautomer to the second is 4:1. The infrared spectrum of the hydrated material in DMSO exhibits two carbonyl bands (1735 and 1690 cm^{-1}), but no azido absorption band. Thus, the two forms are assigned to the tetrazolo tautomers **13a** and **13c**. Based on previous work[8] the carbonyl band at 1735 cm^{-1} can be assigned to **13a** and that at 1690 cm^{-1} to **13c**. The 1690-cm^{-1} band is the more intense, and therefore the main tautomer in this solution and in the solid state is probably **13c**. The pmr spectrum of a trifluoroacetic acid solution of the hydrate is also unusual in that, immediately after dissolution, the main form is **13c**. The intensity of this peak rapidly decreases, so that after 30 min only the azido form **13b** can be detected. Unexpectedly, the pmr spectrum of the one-half acetate of **13** in DMSO-d_6 showed all three tautomers and furthermore, the intensities of the three peaks varied with time. After about 1 hr the ratio of **13a**:**13b**:**13c** was approximately 6:1:3. When equilibrium was attained in about 2 hr, the ratio of **13a**:**13b**:**13c** was 9.5:1.0:2.0. As above, the assignment of the tautomers is based on the infrared spectrum of this material in DMSO. Initially this spectrum shows

(10) The formation of a covalent hydrate in the 2-azidopyrimidine system has been observed: see C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **30**, 829 (1965).

TABLE III

Compds	Reactants	Molar ratio[a]	Reaction Time, hr	Reaction Temp, °C	Recrystn solvent[b]	Yield, %	Mp,[c] °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
					Ring Opening Reactions								
1	6 + 1 *N* NaOH	1.1	18	*d*	A	97	254–257 dec	53.50	4.08	36.45	53.38	4.04	36.30
2	6 + 2 *N* NaOH	6.7	18	*d*	B[e]	76	237–238 dec	54.70	4.56	40.70	54.40	4.48	40.68
	6 + 12 *N* HCl	*f*	60	*d*		83							
	1 + HCl–CH_3OH	*f*	18	*d*		92							
3	7 + 1 *N* NaOH	3.3	18	*d*	B	69	239–240	54.70	4.56	40.70	54.62	4.58	40.50
	7 + 12 *N* HCl	*f*	60	*d*		98							
4	8 + 1 *N* NaOH	5.4	26	*d*	B[e]	55	>264	31.80	3.31	64.90	32.04	3.41	64.48
	8 + 12 *N* HCl	*f*	60	*d*		84							
	10 + 1 *N* NaOH	4.9	3	*d*		60							
5	8 + 1 *N* NaOH	1.6	18	*d*	A	56[g]	>200 dec	33.50	2.79	54.70	33.56	3.15	54.96
					Sodium Azide Reactions								
	Purine												
6	7-Benzyl-6-chloro-	1.9	3	100	C	92	145–146[h]	57.40	3.58	39.00	57.43	3.65	39.11
7	9-Benzyl-6-chloro-	1.9	3	100	C	84	160–161 dec	57.40	3.58	39.00	57.48	3.61	39.14
13	2-Chloro-6-hydroxy-	1.1	1.5	78	B[e]	49[i]	>264	30.75[j]	2.57	50.25	30.49[j]	2.68	51.01
								34.75[j]	2.41	47.30	34.46[j]	2.44	46.68
14	2,6-Dichloro-	2.0	0.2	78	E[k]	60	207–210 dec[l]	29.70	1.00	69.30	30.04	1.42	68.70
					Nitrosation Reactions								
	Purine												
6	7-Benzyl-6-hydrazino-	1.0	60	*d*	C	90	145–146						
7	9-Benzyl-6-hydrazino-[m]	1.0	18	*d*	C	65	159–161 dec						
9	2-Amino-6-hydrazino-	1.0	2	*d*	D[e]	66	>264	34.10	2.27	63.60	33.92	2.34	63.42
10	2-Chloro-6-hydrazino-	1.0	4	*d*	C	64	*n*	30.65	1.02	50.15	30.68	1.24	50.72
12	6-Amino-2-hydrazino-	1.1[o]	60	*d*	B[e]	41	>264	34.10	2.27	63.60	33.97	2.64	63.41

[a] Inorganic/organic. [b] A, precipitated from a basic solution with hydrochloric acid; B, water; C, tetrahydrofuran–petroleum ether (bp 85–105°); D, precipitated from a 2 *N* ammonium hydroxide solution with hydrochloric acid; E, ethanol. [c] Determined on a Kofler Heizbank apparatus and are corrected. [d] Room temperature. [e] Dried *in vacuo* over phosphorus pentoxide at 78°. [f] Large excess. [g] Based on the amount (53%) of **8** that reacted. [h] Solidified and remelted at 158–159° dec. [i] Monohydrate. [j] One-half acetate obtained by recrystallization of monohydrate from glacial acetic acid. [k] Dried *in vacuo* over phosphorus pentoxide at 110°. [l] Reported to decompose 190–200°; see ref 5c. [m] Hydrochloride. [n] Decomposed above 160°. [o] Solvent was 10% acetic acid.

weak absorption bands at 2140 (**13b**) and 1735 cm^{-1} (**13a**), and a strong, broad band at about 1700 cm^{-1} (**13c**). After 24 hr the carbonyl band at 1735 cm^{-1} was stronger than the band now at 1710 cm^{-1}, and the azido band was undetected.

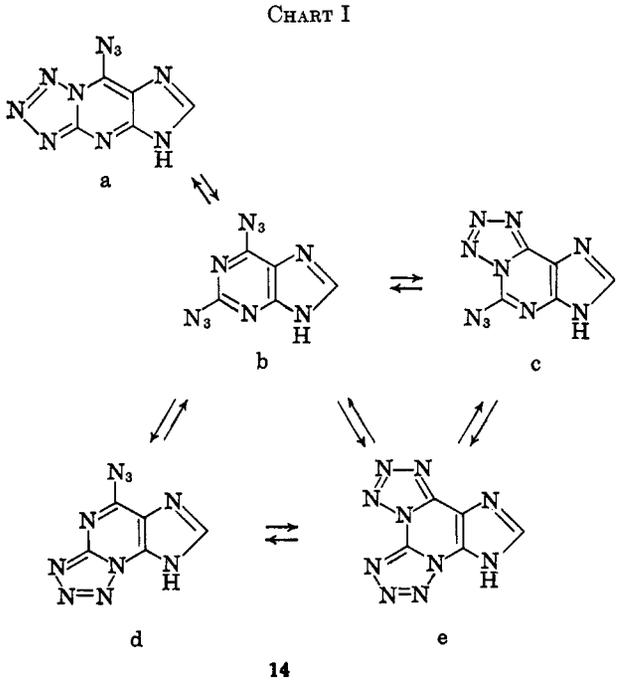
In the 2,6-diazidopurine system, **14**,[5c] five tautomers (**14a–e**) are possible. The infrared and pmr spectra showed that CF_3COOH and CH_3COOH solutions of **14** contained only the diazido form **14b**; however, the pmr spectra of **14** in DMSO-d_6 showed the presence of **14b** and two tetrazolo tautomers in the approximate ratio 8:1:1, respectively. The tetrazole tautomers are most likely **14a** and **14c**, but definite assignments cannot be made from the available evidence. (See Chart I.)

Experimental Section

The infrared spectra were determined with a Perkin-Elmer Model 521 spectrophotometer. The solutions were run in fixed-thickness cells equipped with windows of Irtran-2 for solutions in dimethyl sulfoxide or trifluoroacetic acid, and with windows of silver chloride for solutions in acetic acid. The pmr spectra were obtained on a Varian A-60 or A-60A spectrometer, using tetramethylsilane as an internal reference for the nonaqueous solutions. Temperature was controlled by the Varian V-6057 variable-temperature system. Probe temperatures were obtained from the known temperature dependence of the chemical-shift difference of the two peaks of ethylene glycol.

The reaction conditions, yields, and properties of the new compounds are summarized in Tables II and III. Only typical procedures are reported.

CHART I



N-(**1-Benzyl-5-tetrazol-5-ylimidazol-4-yl)formamide** (1) **and 5-(4-Amino-5-benzylimidazol-5-yl)tetrazole** (2).—A suspension of **6** (0.5 g) in 1 *N* sodium hydroxide (2.1 ml) and water (3 ml) was stirred at room temperature for 18 hr. The resulting solution was filtered, and the filtrate was neutralized with 1.1 *N* hydrochloric acid (2 ml) to give **1**. When **6** (1.5 g) was treated with 2 *N* sodium hydroxide (20 ml) for 18 hr, neutralization of the solution deposited **2**. The latter was also obtained by treatment of **1** with 20% methanolic hydrogen chloride for 18 hr, or **6** with concentrated hydrochloric acid for 60 hr.

Preparation of System 6. A.—A solution of 7-benzyl-6-chloro-7*H*-purine[5a] (2.0 g) in *N*,*N*-dimethylformamide (20 ml) containing sodium azide (1.0 g) was heated at 100° for 3 hr. The mixture was evaporated to dryness under reduced pressure, and the residue was washed with water (40 ml) and recrystallized from tetrahydrofuran–petroleum ether (bp 85–105°).

B.—To a suspension of 7-benzyl-6-hydrazino-7*H*-purine[5a] (1.0 g) in water (10 ml) containing sodium nitrite (300 mg) was added 1 *N* hydrochloric acid (4.3 ml). The mixture was stirred at room temperature for 60 hr; the solid was collected by filtration, washed with water, and recrystallized as above.

C.—A solution of **1** (0.2 g) in diethoxymethyl acetate (20 ml) was heated in an oil bath at 100° for 3 hr and evaporated to dryness *in vacuo*, and the resulting residue was recrystallized as above.

Preparation of System 13.—A suspension of 2-chlorohypoxanthine[5a] (0.9 g) and sodium azide (0.4 g) in 1:1 ethanol–water (20 ml) was refluxed for 1.5 hr. The resulting solution was cooled, and the product was collected and recrystallized from water. This sample darkened but did not lose its water of hydration after drying *in vacuo* at 110°. The one-half acetate was obtained by recrystallization of the hydrate from glacial acetic acid.

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Synthesis of 5-Substituted Pyrimidines[1]

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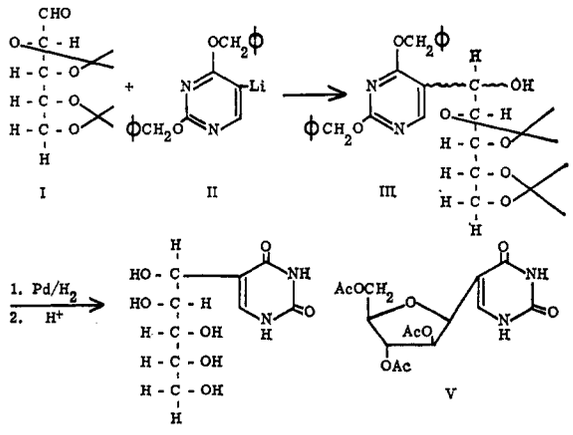
5-Substituted pyrimidine nucleosides were synthesized in practical yields by the reaction of diisopropylidene-*aldehydo*-pentoses with 2,4-dibenzyloxy-5-lithiopyrimidine. Thus, 5-α-D-arabinitoluracil, 5-β-D-xylofuranosyluracil, and 5-α-D-ribitoluracil were obtained. The configuration at the anomeric carbon was determined by optical rotatory dispersion studies.

The study of the chemistry and of the biological significance of pseudouridine has attracted the attention of many investigators. Particularly interesting is the fact that this nucleoside is found in soluble RNA, which is known to be an important factor in protein synthesis.[2,3] The isolation and structure elucidation of pseudouridine[4,5] was followed by its synthesis in low yields.[6] While this work was in progress, an improved procedure for the preparation of this compound was reported.[7]

The search for potential antimetabolites active in amino acid incorporation has led to the preparation of analogs in which a noncarbohydrate moiety was introduced at position 5 of the pyrimidine nucleus.[8] We report here a facile synthesis of pseudouridine analogs containing a five-carbon sugar. Diisopropylidene-*aldehydo*-D-arabinose, diisopropylidene-*aldehydo*-D-xylose, and diisopropylidene-*aldehydo*-D-ribose were condensed with 2,4-dibenzyloxy-5-lithiopyrimidine and the condensation products were converted to the desired compounds.

D-Arabinose was converted to the diethyl dithioacetal derivative.[9] The diisopropylidene diethyl dithioacetal derivative of arabinose was prepared and the mercaptal groups were cleaved by a modification of a known procedure[10,11] to give diisopropylidene-*aldehydo*-D-arabinose (I). 2,4-Dibenzyloxy-5-bromopyrimidine[12] prepared in a manner analogous to that of 2,4-diethoxy-5-bromopyrimidine[13] was converted to the pyrimidyllithium compound[14] (II) at a temperature of −70° by treating it with *n*-butyllithium. The operation was successful only when *n*-butyllithium was precooled to −70° before adding it to the reaction vessel; under this condition the solution became a pale yellow color; an orange color[15] was observed only



5 - α - D - ARABINITOL URACIL

IV

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