tion of base contained in the aliquots from kinetic runs. The reagent is stable for several days. One milliliter of the DNPH reagent was pipetted into each of 25-ml volumetric flasks. An aliquot of the aldehyde containing solution (for amounts, see kinetic procedure) was added and the solution was allowed to stand for 1 day before dilution with 1:1 95% ethanol–water by volume. The absorbance of the solution at 374 mμ was determined with 1 ml of the DNPH reagent diluted to 25 ml as above serving as the blank solution with a Beckman Model DU spectrophotometer. A small decrease in the absorbance with time occurs; however, if a constant time interval passes from addition of the aldehyde solution until determination of the absorbance, the ratio of aldehyde concentrations in different samples is the same as the corresponding absorbance ratios.

Kinetic Procedure.—Ten milliliters (20 ml for runs listed in last two rows of Table I) of the appropriate dabco solution was pipetted into a polypropylene tube containing the glycinatobis(ethylenediamine)cobalt(III) chloride monohydrate and the resulting solution was equilibrated at 35.00 ± 0.01°. Cold acetaldehyde was transferred by a micropipet to 10 ml of cold dabco solution. One milliliter of this was added to the above equilibrated solution. After 15–20 min of further equilibration, a 1-ml aliquot (2 ml for runs listed in last two rows of Table I) of the reaction mixture was pipetted into a 25-ml volumetric flask containing 1 ml of DNPH reagent and the time was taken as zero time. Aliquots were then taken periodically and added to the DNPH reagent in volumetric flasks, and the absorbance was determined as described above.

Observed "infinity" absorbances were within experimental error of those calculated from the spectra of the complex ions involved. The visible spectrum is changed only slightly when glycine is replaced by threonine;[15,16] since the $(Coen_2gly)^{2+}$ is in large excess to the aldehyde under the reaction conditions, the difference is negligible. Calculated infinity values[17] were used to determine rate constants. The pseudo-first-order rate constants were calculated from the following equation: $\log (A - A_\infty) = -k_1t/2.303 + \text{constant}$. The slope was calculated by the method of least squares. The reaction was followed to two-thirds complete reaction.

The stability of the reactants under the reaction conditions was tested as follows. Acetaldehyde (*ca.* 2.9×10^{-3} *M*) in 0.96 *M* dabco solution was sampled periodically as described above (except 0.5-ml aliquots were used); an 8% decrease in absorbance occurred after 5 hr. Glycinatobis(ethylenediamine)cobalt(III) chloride monohydrate (0.190 *M*) in 1.36 *M* dabco was held at 35° for 3 days. The visible spectrum of a 1-ml aliquot diluted to 25 ml was identical with that of authentic material.

Registry No.—Acetaldehyde, 75-07-0; glycinatobis(ethylenediamine)cobalt(III) chloride, 14408-57-2.

(15) C. T. Liu and B. E. Douglas, *Inorg. Chem.*, **3**, 1356 (1964).
(16) S. K. Hall and B. E. Douglas, *ibid.*, **8**, 372 (1969).
(17) Determined from spectra obtained by use of a Cary Model 14 spectrophotometer.

Pyrimidines. IX. A New Synthesis of 8-Azapurines and v-Triazolo[4,5-b]pyridines[1]

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The 5-nitropyrimidines **1–5** and the 5-nitropyridines **6** react with sodium azide to furnish the 8-azapurines **14–18** and the *v*-triazolo[4,5-*b*]pyridines **19**, respectively. The first step of this new reaction leading to *v*-triazoles is probably attack of azide ion at position 6 of the 5-nitropyrimidines and -pyridines followed by cyclization and subsequent elimination of the nitro function as nitrous acid. With hydroxide, deuteroxide, and ethoxide ions as the nucleophiles, N-1 substituted derivatives of some of these nitroheterocycles form stable Meisenheimer-type adducts by reaction at position 6. A reaction with deuterium oxide in DMSO-d_6/D_2O concurrent with adduct formation is H–D exchange at position 6 of the N-1 substituted 5-nitro-2-oxo-pyrimidines and -pyridines, **1–3** and **6**. A carbanion mechanism is postulated for these H–D exchange reactions.

The chemistry of *v*-triazolo[4,5-*d*]pyrimidines[2] (8-azapurines) has developed in conjunction with biological studies on the antimetabolite activity of analogs of the nucleic acid purines.[3] Such compounds have been prepared previously by the action of nitrous acid on 4,5-diaminopyrimidines[4,5] and from substituted *v*-triazoles.[6,7] This report describes a new and facile synthesis of some 8-azapurines and 5-oxo-*v*-triazolo[4,5-*b*]-pyridines. The procedure consists of the treatment of certain 5-nitrooxopyrimidines and -pyridines with sodium azide, which results, overall, in the addition of the three-nitrogen fragment of the *v*-triazole ring to the 5,6 positions of the nitropyrimidine or -pyridine followed by elimination of the nitro function as nitrous acid. A preliminary report[8] on this reaction has appeared. The extent and mechanism of this process as well as its practical value are now further elaborated.

Results

The reaction with azide ion was achieved with the following types of compounds (Scheme I): 5-nitrouracils (**1**), 5-nitrocytosines (**2**, Y = NR_2), 4-ethoxy-1-methyl-2-oxo-5-nitropyrimidine (**2h**), 2-oxo-5-nitropyrimidines (**3**), 4-oxo-5-nitropyrimidine (**4**), 2-amino-4-oxo-5-nitropyrimidine (**5**), and 2-oxo-5-nitropyridines (**6**). With compounds **1–3** and **6**, which are not alkylated at N-1, only salt formation between these acidic nitro compounds and the reagent is observed. Therefore ammonium chloride (in slight molar excess relative to the sodium azide) was added to these reaction

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant CA 08748).

(2) For recent reviews on the chemistry of *v*-triazolo[4,5-*d*]pyrimidines, see (a) J. Gut, *Advan. Heterocycl. Chem.*, **1**, 238 (1963); (b) R. K. Robins in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 434.

(3) For leading references on the antimicrobial and antitumor activity by 8-azapurines, see (a) R. E. Handschumacher and A. D. Welch in "The Nucleic Acids," Vol. 3, E. Chargaff and J. N. Davidson, Ed., Academic Press, New York, N. Y., 1960, p 453; (b) H. G. Mandel, *Pharmacol. Rev.*, **11**, 743 (1959); (c) A. Albert and K. Tratt, *J. Chem. Soc., C*, 344 (1968).

(4) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, *J. Amer. Chem. Soc.*, **67**, 290 (1945).

(5) S. Gabriel and J. Coleman, *Chem. Ber.*, **34**, 1234 (1901); W. Traube, *Justus Liebigs Ann. Chem.*, **432**, 292 (1923).

(6) A. Albert and K. Tratt, *J. Chem. Soc., C*, 244 (1968); A. Albert, *ibid.*, 2076 (1968).

(7) A. Albert, *ibid.*, 152 (1969).

(8) H. U. Blank and J. J. Fox, *J. Amer. Chem. Soc.*, **90**, 7175 (1968).

TABLE I

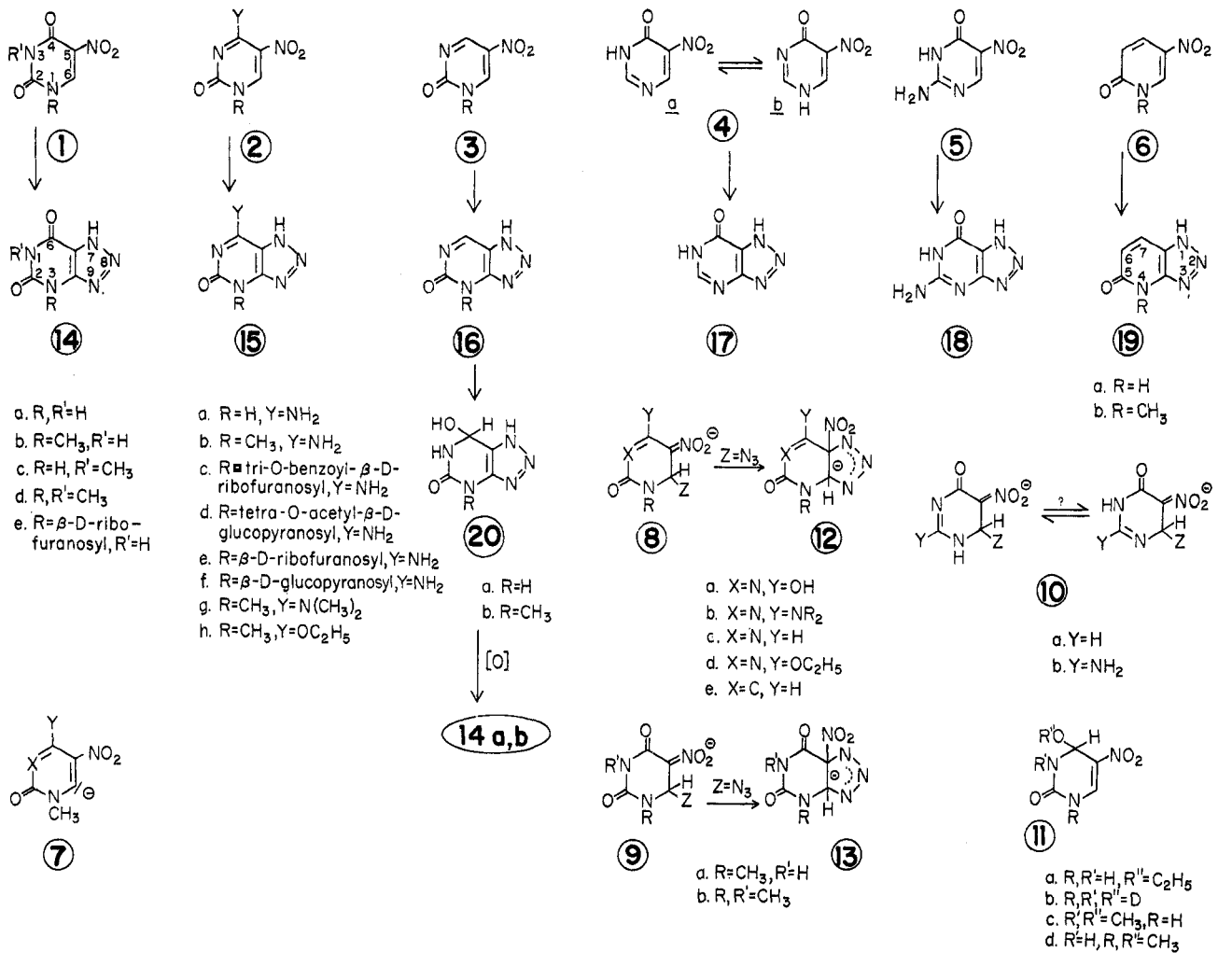
Starting material	Reaction to *v*-triazolo compounds: Equiv NaN_3 (solvent)	Temp, °C	Time, hr	Yield, %	Products of reaction with NaN_3[a]	Mp, °C (solvent of recrystn)	pK_a[b]	Uv (in H_2O): λ_{max}, mμ	ϵ_{max}	pH	Ionic species[c]
5-Nitrouracil (1a)	4 (DMF)	70	144	86	8-Azaxanthine[d] (14a)	>320 (H_2O)	4.66	263	6,450	2	0
							9.79	265	8,510	7	−
								(235)	(2,360)	13	2−
								285	6,450		
1-Methyl-5-nitrouracil (1b)	1.1 (EtOH)	78	16	86	3-Methyl-8-azaxanthine[d] (14b)	316 dec (50% EtOH) [lit. 313 (H_2O)]	4.42	270	5,370	2	0
							11.37	268	7,080	7	−
								245	8,710	14	2−
								271	10,715		
3-Methyl-5-nitrouracil (1c)	2.6 (DMF)	90	72	44	1-Methyl-8-azaxanthine[d] (14c)	261 (H_2O) [lit. 262 (H_2O)]	4.67	(230)	(4,175)	2	0
							9.85	263	6,310		
								(230)	(3,715)	7	−
								265	8,130		
								(235)	(4,890)	13	2−
								285	6,025		
1,3-Dimethyl-5-nitrouracil (1d)	1.2 (EtOH)	78	14	95	1,3-Dimethyl-8-azaxanthine[d] (14d)	258–260 (H_2O) [lit. 260 (H_2O)]	4.47	(230)	(3,980)	2	0
	1.3 (DMF)	24	16	83				271	6,310		
	1.3 (CH_3CN)	82	72	94				(230)	(4,170)	7	−
	1.4 (HMPT)	60	0.7	85				269	8,510		
5-Nitrouridine[e] (1e)	1.3 (DMF)	24	16	81	3-β-D-Ribofuranosyl-8-azaxanthine (14e) ($C_9H_{11}N_5O_6 \cdot H_2O$)	164–166 dec (H_2O)	4.13	263	7,510	0.3	0
							10.31	264	9,820	6	−
								242.5	10,230	12	2−
								268	11,170		
5-Nitrocytosine (2a)	2 (DMF)	90	72	50	6-Amino-2-oxo-8-azapurine[f] (15a)	>320 (6 *N* HCl) (lit. no mp)		277	2,330	2	
								250	6,310	6.7	
								277	9,035		
								250	7,450	8.6	
								277	9,375		
1-Methyl-5-nitrocytosine (2b)	2.5 (DMF)	90	3.5	77	6-Amino-3-methyl-2-oxo-8-azapurine (15b) ($C_6H_6N_6O$)	>360 (H_2O)	2.67	(235)	(4,635)	0	+
							5.93	285	7,260		
								(250)	(3,820)	4	0
								284	9,310		
								250	9,150	12	−
								281	10,030		
1-Tri-*O*-benzoyl-β-D-*ribofuranosyl*)-5-nitrocytosine[g] (2c)	2 (DMF)	75	3	62	6-Amino-3-(tri-*O*-benzoyl-β-D-ribofuranosyl)-2-oxo-8-azapurine (15c) ($C_{30}H_{24}N_6O_8$)	219–221 dec (EtOH)					
1-(Tetra-*o*-acetyl-β-D-glucopyranosyl)-5-*nitrocytosine*[g] (2d)	4.5 (DMF)	70	4	75	6-Amino-3-(tetra-*O*-acetyl-β-D-glucopyranosyl)-2-oxo-8-azapurine ((15d) ($C_{18}H_{22}N_6O_{10}$)	230 dec (EtOH)					
5-Nitrocytidine[g] (2e)	2 (DMF)	85	7.5	78	6-Amino-3-β-D-ribofuranosyl-2-oxo-8-azapurine (15e) [$C_9H_{12}N_6O_5 \cdot {}^1/_2H_2O$]	>230 dec (H_2O)	2.65	278	8,210	0	+
							5.26	~340	330		
								(250)	(5,030)	4	0
								282	9,870		
								248	10,760	8	−
								279	10,270		
1-β-D-Glucopyranosyl-5-nitrocytosine[g] (2f)	By deacylation of **2d**			66	6-Amino-3-β-D-glucopyranosyl-2-oxo-8-azapurine (15f) ($C_{16}H_{14}N_6O_6 \cdot 2H_2O$)	>230 dec (H_2O)					
4-Dimethylamino-1-*methyl-5-nitro-2-oxo*-pyrimidine[h] (2g)	3.0 (DMF)	75	3.5	87	6-Dimethylamino-3-methyl-2-oxo-8-azapurine (15g) ($C_7H_{10}N_6O$)	343–344 (H_2O)	2.71	289	9,650	0	+
							5.71	(225)	(8,760)		
								288	12,120	3.8	0
								258	12,760	7	−
								284	13,560		
4-Ethoxy-1-methyl-5-nitro-2-oxopyrimidine[h] (2h)	1.1 (DMF)	85–95	6	68	6-Ethoxy-3-methyl-2-oxo-8-azapurine (15h) ($C_7H_9N_5O_2$)	219–220 (H_2O)		268	8,025	7[i]	
1-Methyl-5-nitro-2-oxo-pyrimidine[j] (3b)	1.7 (DMF)	70–75	22	>50[k]	3-Methyl-2-oxo-8-azapurine (16b) ($C_6H_5N_5O$) *and* 6-hydroxy-3-methyl-2-oxo-1,6-dihydro-8-azapurine (20b) ($C_6H_7N_5O_2$)	311 dec (H_2O)	−1.22	262	3,790	12 *N* HCl	+
	1.2 [HMPT–CH_3CN (1:5)]	Reflux	48	25			5.57[l]	319	6,000		
								245	7,070	2	0
								290	520		
								(270)	(4,740)	7.5	−
								310	9,110		
5-Nitro-4-oxopyrimidine[m] (4)	2.2 (HMPT)	125–140	26	1.7	8-Azahypoxanthine[n] (17)	>305 dec [lit. 308 (exptl)]	5.16	253	8,710	2	0
							10.78	259.5	9,120	8	−
								270	10,230	13	2−
2-Amino-5-nitro-4-oxo-pyrimidine (5)	2.4 (HMPT)	130–150	20	<1	8-Azaguanine[f] (18)		−1.04	247	11,220	3.8	0
							6.54	266	6,760		
								214	21,890	8.8	−
								244	5,760		
								278	6,030		
5-Nitro-2-oxopyridine (6a)	2 (DMF)	100	60	12	5-Oxo-*v*-triazolo[4,5-*b*]pyridine[o] (19a)	280 dec (H_2O) (lit. 280–282 dec)	5.90	235	3,140	0	0
							11.08	(291)	(11,190)		
								305	11,430		
								(262)	(2,200)	7	−
								315	13,850		
								260	3,110	14	2−
								312	10,600		
								~363	755		

TABLE I (*Continued*)

Starting material	Reaction to *v*-triazolo compounds: Equiv NaN_3 (solvent)	Temp, C°	Time, hr	Yield, %	Products of reaction with NaN_3[a]	Mp, °C (solvent of recrystn)	pK_a[b]	Uv (in H_2O) λ_{max}, mμ	ϵ_{max}	pH	Ionic species[c]
1-Methyl-5-nitro-2-oxo-pyridine (**6b**)	1.2 (DMF)	120 then 80	2 24	69	4-Methyl-5-oxo-*v*-triazolo[4,5-*b*]pyridine (**19b**) ($C_6H_6N_4O$)	276–278 dec (H_2O)	5.90	245 305 262.5 314	3,565 10,960 3,050 14,090	0 10 	0 –
	2 (DMSO)	80	96	47							

[a] All new compounds reported herein with formulas gave satisfactory C, H, and N analyses. [b] Values for new compounds were obtained at 23.5 ± 0.5° and are accurate to ±0.05 pH unit except for **19a** and **19b**, for which the spread averaged ±0.1 pH unit. [c] Cationic species (+), neutral (0), anionic (−), dianionic (2−). [d] Alternate synthesis reported: G. Nubel and W. Pfleiderer, *Chem. Ber.*, **98**, 1060 (1965). p*K* values and uv data taken from this reference. [e] I. Wempen, I. L. Doerr, L. Kaplan, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 1624 (1960); K. A. Watanabe and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 109 (1969). [f] Alternate synthesis: L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Amer. Chem. Soc.*, **70**, 3875 (1948). Uv data for **15a** taken from this reference. Uv data for **18** taken from ref 9. [g] J. J. Fox and D. van Praag, *J. Org. Chem.*, **26**, 526 (1961). [h] I. Wempen, D. van Praag, and J. J. Fox, unpublished results. [i] At acidic and basic pH values decomposition occurs, probably by conversion into 3-methyl-8-azaxanthine (**14b**). [j] L. M. Stempel, G. B. Brown, and J. J. Fox, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 14-O. [k] Calculated on the basis of isolated 3-methyl-8-azaxanthine (**14b**) (*cf.* text for the oxidation of **20b** to **14b** by means of iodide). [l] Equilibrium constant; see text. Ionic species data: cation refers to **16b**, neutral species to **20b**, anion to **16b**. [m] See I. Wempen, H. U. Blank, and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 593 (1969). [n] See ref 4 for alternate synthesis. Uv data from ref 3c. [o] H. Graboyes and A. R. Day, *J. Amer. Chem. Soc.*, **79**, 6421 (1957).

SCHEME I



mixtures to favor the neutral, undissociated 5-nitroheterocycles in the lactam form. Under these conditions reaction with azide does take place. No addition reaction with azide occurred with 1,3,6-trimethyl-5-nitrouracil, 2,4-diethoxy-5-nitropyrimidine, 2-ethoxy-5-nitropyrimidine, or 2-ethoxy-3-nitropyridine. Instead, sodium azide acted as a base with traces of water which may have been present in the solvent (DMF) to catalyze the slow hydrolysis of the latter two ethoxy derivatives to the corresponding oxonitroheterocycles.

Good to excellent yields of the 8-azapurine derivatives were obtained in the reaction of azide ion with 5-nitrouracils (**1**), 5-nitrocytosines (**2**), 2-oxopyrimidines (**3**), and even 5-nitro-2-oxopyridines (**6**), the latter of which should be less activated owing to the absence of one ring nitrogen. On the other hand, 5-nitro-4-oxopyrimidine (**4**) yielded only a small amount of

TABLE II

REACTIVITIES OF CERTAIN 5-NITRO-2-OXOPYRIMIDINES AND -PYRIDINES WITH NaN_3[a]

Reaction	Reaction temp, °C	Product formed, % (accuracy ± 4%)	Time, hr	Remarks
1d ⟶ 14d	Room	25	1.6	No decomposition or side reaction observed
	Room	53.5	19.7	
	Room	78	95.3	
	Room	>95	360.0	
3b ⟶ 16b	Room	None	15.0	A constant amount of adduct (*ca.* 10%) is observed in the mixture (see text)
	37	6	1.5	*Ca.* 13% adduct
	37	46	68.6	No adduct; some decomposition
6b ⟶ 19b	60	None	2.0	No decomposition or side reaction detectable
	100	None	0.5	
	120–122	29	1.7	
	120–122	40	4.0	
	120–122	58	9.6	
	120–122	67	18.0	

[a] The reactions were monitored by nmr spectroscopy in DMSO-d_6 (0.3 ml). Each reaction solution contained 0.11 mmol of reactants. The relative insolubility of sodium azide in DMSO precluded the use of an excess of this reagent.

8-azahypoxanthine, and from compound **5** only a trace amount of 8-azaguanine was detected. Moreover, the N-1 alkylated derivatives of **1–3** and **6** usually afforded better yields of the corresponding 8-azapurines or *v*-triazolopyridines than did those without an alkyl substituent at N-1.

The formation of 8-azaguanine (**18**) from 5-nitrocytosine (**5**) was demonstrated by paper chromatography in four different solvent systems using for a comparison a commercial sample of **18**. Only traces of **18** could be detected in the very complex reaction mixture. No attempt was made to isolate **18** from this reaction mixture.

3-Methyl-2-oxo-8-azapurine (**16b**) formed a covalent hydrate (**20b**) across the 1,6 double bond by addition of water. Albert[9] had shown that 2-oxo-8-azapurine itself also forms the same type of hydrate. Attempts to crystallize pure **20b** from a mixture of **16b** and **20b** under varying conditions of pH were unsuccessful. The structure of **16b** was proved by uv and nmr spectroscopy[8] and by measurement of the equilibrium constant (5.57 ± 0.05) for the anion of **16b** ⇌ adduct **20b**. This value is in fair agreement with that determined by Albert[9] for **16a**. Conclusive proof of the structure **16b** ⇌ **20b** was obtained by oxidation of this mixture with iodine at pH 8 to the known 3-methyl-8-azaxanthine (**14b**).

The reactions with azide ion described herein were run in a variety of solvents, such as ethanol, acetonitrile, DMF, DMSO, and hexamethylphosphorotriamide (HMPT), as shown in Table I, along with other reaction conditions. The reactions were monitored by paper chromatography and by uv spectroscopy. From these data, as well as from practical considerations, DMF is the most convenient solvent.

A semiquantitative nmr study was done to compare the reactivities of 1,3-dimethyl-5-nitrouracil (**1d**) and 1-methyl-5-nitro-2-oxopyrimidine and -pyridine (**3b** and **6b**) with azide ion to their corresponding *v*-triazoles (**14d**, **16b**, and **19b**), as shown in Table II. Only for the reaction of **3b** to **16b** was an intermediate detected by a signal at δ 5.83. The structure of this intermediate will be discussed below. In the case of **1d** and **6b**, the nmr spectrum showed only the signals for the end products (**14d** and **19b**). These signals appeared at the same rate at which those for starting materials disappeared. The reaction was followed by observing the decrease of the H-6 signal. In the cases of **3b** and **6b** one observes also alteration in chemical shifts and a lowering in multiplicity as H-4 of **3b** and H-3 and H-4 of **6b** are converted into H-6 of **16b** and H-6 and H-7 of **19b**.

Intermediacy of Adducts.—During the reaction of **3b** to **16b** a compound which differed from starting material or end product in having a proton signal at δ 5.83 (*cf.* Table II) was detected by nmr spectroscopy. This signal is best explained by compound **8c** (Z = N_3), which is the sodium azide adduct of **3b**. That **8c** is the correct structure for this intermediate is based first on the existence of the analogous adducts of type **8** and **9** (Z = OH, OD, OEt),[10] as discussed below, and secondly on the fact that the H-6 signals of these stable adducts are all in the same region of δ 5.69–5.92 (see Table III). Evidence that adducts of type **8** and **9** (Z = OH, OD, OEt) are easily formed in solution and are sometimes isolable in crystalline form is as follows:

(A) Compound **9b** (Z = OC_2H_5) had been isolated as a stable sodium salt by Pfleiderer and Mosthof,[12] and this is probably one of the first examples of a crystalline Meisenheimer-type[13] adduct in the heterocyclic series.[14] In addition, evidence for the existence of **9b** (Z = OH) as a stable compound in alkaline solution is derived from the following fact. A "pK_a

(9) A. Albert, *J. Chem. Soc., B*, 427 (1966).

(10) In addition to hydroxide, deuteroxide, or ethoxide ion, other nucleophilic agents also attack at position 6 of some of these 5-nitroheterocycles. For example, treatment of 1,3-dimethyl-5-nitrouracil (**1d**) with some amines furnished compounds **9b** (Z = NH_2, $HNCH_2C_6H_5$, $HNNH_2$) as shown by nmr and uv spectroscopy.[11] These amine adducts are very labile, and hydrolyze easily with traces of water back to the starting material.

(11) H. U. Blank and J. J. Fox, unpublished results.

(12) W. Pfleiderer and H. Mosthof, *Chem. Ber.*, **90**, 728 (1957).

(13) For information about Meisenheimer adducts and related compounds, see R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(14) Recently, it was shown that 2- and 4-methoxy-3,5-dinitropyridines and 2- and 4-methoxy-5-nitropyrimidines also form Meisenheimer-type compounds both at methoxyl- and hydrogen-bearing ring positions.[15]

(15) G. Illuminati and F. Stegel, *Tetrahedron Lett.*, 4169 (1968).

TABLE III
REACTIONS WITH NaOR[a]

Starting material	Conditions[b]	$t_{1/2}$ for H-6 → D-6	Adduct[c] in mixture (%)	Nmr signals of adducts[d] (starting materials), δ ppm
1b	A		**9a**, Z = OD (10)	H-6, 5.80 (9.24) CH_3, 2.90 (3.41)
1d	A	~3 days	**9b**, Z = OD (75)	H-6, 5.82 (9.28) CH_3, 3.00, 2.94 (3.48, 3.21)
	C		**9b**, Z = OEt (100)	H-6, 5.86 (9.28) CH_3, 2.99 (3.48, 3.21)
1e	B		Type **9a** Z = OD (20)	H-6, 5.86 (9.58)
2b	B	~60 min	**8b**, Z = OD (55)	H-6, 5.69 (9.25) CH_3, 2.90 (3.43)
2g	B	~60 min	**8b**, Z = OD (50)	H-6, 5.92 (9.01)
2h	B	>90% exchange in 25 min	**8d**, Z = OD (75)	H-6, 5.73 (9.32) CH_3, 2.87 (3.49)
3b	B	Slow dec	**8c**, Z = OD (>98)	H-4, 8.24 (9.17) H-6, 5.79 (9.49) CH_3, 2.93 (3.59) $J_{4,6}$ = 1.3 (3.5) Hz
	D		**11d**[b] (35)	H-6, 8.52 (9.49) H-4, 5.63, 5.57 (9.17) $J_{4,6}$ = 1.3 (3.5) Hz
6b	B	~3 min	**8e**, Z = OD (>95)	H-3, 5.13 (6.49) H-4, 7.34 (8.16) H-6, 5.89 (9.17) CH_3, 2.92 (3.57) $J_{3,4}$ = 9.5 (10) Hz $J_{4,6}$ <2 (3.2) Hz

[a] Qualitative data are given for the H–D exchange at position C-6 of some of these compounds and for the formation of some Meisenheimer-type adducts together with nmr data for these adducts. [b] Conditions were as follows. (A, B) The 5-nitroheterocycle (15 mg) was dissolved in DMSO-d_6 (0.5 ml). Two drops of 10% NaOD (A) or 20% NaOD (B) were then added to this solution. The data in columns 3–5 were obtained from the nmr spectrum of the resulting mixture of starting material and adduct. (C) The solid sodium ethylate adduct of **1d** (15 mg) was dissolved in DMSO-d_6 (0.5 ml). (D) Recrystallization of **3b** from methanol furnished a mixture of **3b** and a covalent methanol adduct to which structure **11d** is ascribed by analogy to the ethanol adduct **11a**. Footnote *m*, Table I. Another possible structure could be **11c**. The spectrum was taken in DMSO-d_6. [c] The percentage of Meisenheimer-type adduct given is calculated mainly from the intensity of the methyl signals of adduct and nonadduct and including material which may already have deuterium at position C-6 (*cf.* Scheme II). [d] The δ values given refer to TMS as internal standard. The δ values given in parentheses refer to the respective starting materials. Coupling constants (J) are expressed in hertz. In all cases nmr spectroscopy was done by adding 2 drops of 10% or 20% NaOD to a solution of **1–3** or **6** in DMSO-d_6.

value" (9.01 ± 0.04) was found[16] for 1,3-dimethyl-5-nitrouracil (**1d**) which is really an equilibrium constant for the reversible addition of water to the 5,6 double bond of **1d** in alkaline solution, resulting directly in **9b** (Z = OH).[16] The structure of compound **9b** (Z = OEt and Z = OD) has been proved unambiguously by nmr spectroscopy in DMSO-d_6. The value for H-6 in **1d** of δ 9.28 drops to δ 5.86 in **9b** (Z = OEt) and δ 5.82 in **9b** (Z = OD).

(B) Recently, a related type of adduct has been described, namely, the ethanol and the D_2O adducts of 2-oxo-5-nitropyrimidine (**3a**), formulated as **11a** and **11b**.[17]

(C) Nmr spectroscopy directly proves the formation of **9a** (Z = OD) (or **8a**),[18] **8b** [R = CH_3, Z = OD, Y = NH_2 or $N(CH_3)_2$], **8c** (R = CH_3, Z = OD), **8d** (R = CH_3, Z = OD), and **8e** (R = CH_3, Z = OD) starting from the appropriate compounds **1**, **2**, **3**, and **6**, respectively. The initial spectrum of these compounds in DMSO-d_6 changed drastically by addition of base, leading to a mixture of starting material together with varying proportions of the corresponding base adducts **8** or **9**. The observed chemical shifts for H-6 of the neutral nitropyrimidines and -pyridines and of their base adducts (**8** or **9**) are given in Table III together with a rough estimate of the relative composition of the mixtures.[19]

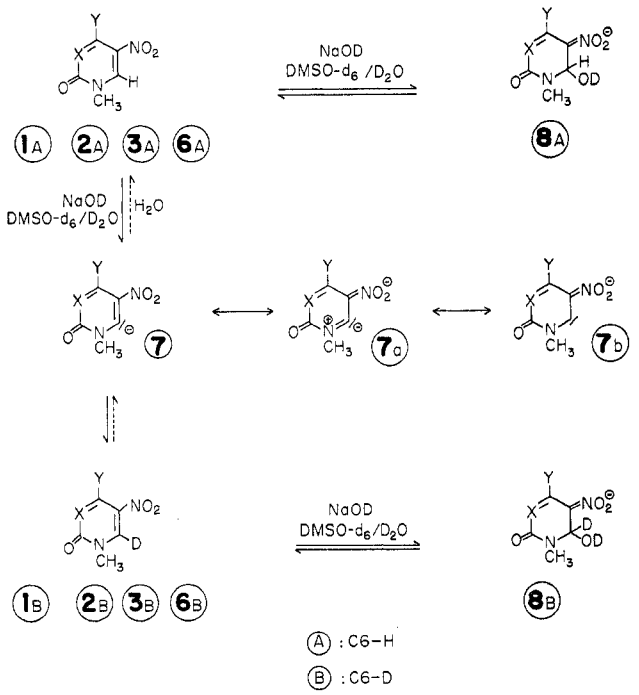
(D) The formation of **8b** (R = CH_3, Y = NH_2, Z = OH) and **8b** (R = CH_3, Y = $N(CH_3)_2$, Z = OH) is also proved and can be quantitatively measured by "pK" determination: 3-methyl-5-nitrocytosine (**2b**) and 5-nitrocytidine (**2e**) give, in the alkaline region, spectral shifts which were attributed to an acidic dissociation.[20,21] Brown[20] estimated this "acidic pK_a value" of 1-methyl-5-nitrocytosine (**2b**) to be 10.57 ± 0.03 and attributed this pK_a to dissociation of the 4-amino group. However, 1-methyl-4-dimethylamino-5-nitro-2-oxopyrimidine (**2g**) also had a "pK_a" value of 9.04 ± 0.05,[22] which is of the same magnitude as that of 1,3-dimethyl-5-nitrouracil. These data, together with the nmr evidence previously discussed, make it clear that, in aqueous base, nucleophilic attack at C-6 generally occurs with compounds **2** to furnish

(16) W. Pfleiderer and H. Braun, personal communication, from University of Konstanz, Germany.
(17) I. Wempen, H. U. Blank, and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 593 (1969).
(18) Compounds **8a** and **9a** are different tautomeric forms of the same compound, probably **9a** being slightly favored.
(19) In some cases these mixtures slowly decomposed with time.
(20) D. J. Brown, *J. Appl. Chem.*, **9**, 203 (1959).
(21) J. J. Fox and D. van Praag, *J. Org. Chem.*, **26**, 526 (1961).
(22) J. J. Fox, I. Wempen, and D. van Praag, unpublished results.

anions **8b** (Z = OH). As described previously in the case of 1,3-dimethyl-5-nitrouracil (**1d**), the "pK_a" values for **2b**, **2e**, and **2g** represent the equilibrium constant for the reversible addition of water across the 5,6 double bond, leading to "acinitro" anions of type **8b** (Z = OH).

H–D Exchange at Position C-6.—Concomitant with the attack of the deuteroxide ion at position 6 of compounds **1–3** and **6** in DMSO-d_6 leading to **8** and **9**, a competitive reaction is observed (Scheme II): all

SCHEME II



these compounds more or less readily exchange the proton at C-6. This H–D exchange could occur starting from adducts **8A** or from **1A–3A**, and **6A**, respectively. Both types of compounds are present in the exchanging medium. The acidity of H-6 in the adducts of type **8** and **9** should be considerably less than that for H-6 of the respective starting materials **1A–3A** and **6A** for two reasons: first, the adducts are negatively charged; and secondly, the C-6–H bonds of the adduct have lower s character than the C-6–H bonds of the neutral starting materials. For these reasons we suggest the mechanism outlined in Scheme II, with **1A–3A** and **6A** being the reactive species involved in the H–D exchange reaction. (For **9b** a similar scheme can be written.) This mechanism postulates carbanions **7** as intermediates. Scheme II also offers a plausible explanation for the fact that H–D exchange is greatly depressed in certain cases such as **1d** and **3d** (*cf.* Table III). Thus strong mesomeric effects favor a high rate of formation and a high stability of the addition compounds **8** and **9**, thereby suppressing the H–D exchange reactions in certain cases. A similar explanation is given by Buncel, *et al.*,[23] to rationalize the fact that the base-catalyzed H–D exchange in 1,3,5-trinitrobenzene is more difficult than in 1,3-dinitrobenzene. A carbanion mechanism is also preferred by other workers in the case of base-catalyzed H–D exchange reactions. Thus the base-catalyzed H–D exchange of nitro aromatics[23,24] and of some heterocycles like pyridine N-oxides, N-methyl-2- and -4-pyridones, N-methylpyrimidones, and pyridinium salts,[25] which exchange most rapidly at the positions adjacent to the activating substituents or to the ring nitrogen, is believed to proceed by a carbanion mechanism.

In general, the reactions of **1–3** and **6** with base seem to be the result of two types of activation: for the direct attack at C-6, furnishing the Meisenheimer-type adducts, *mesomeric effects* of the substituents in *ortho* and *para* positions are most important for the rate of formation and for the stability of these adducts. In the case of H–D exchange, where attack is on hydrogen, mesomeric effects become much less important than *inductive effects*.[26] The activating inductive effect on C-6–H by N-1 and 5-NO_2 should be roughly in the same order of magnitude for all these compounds, whereas the activating mesomeric effect at C-6 shows greater variation.

Discussion

The experimental facts presented strongly support our postulated reaction mechanism[8] for the conversion of the 5-nitropyrimidines **1–3** and 5-nitropyridines **6** to *v*-triazolo compounds. Thus the first and most important step is the nucleophilic attack by azide ion on position 6 of these compounds, which would lead initially to intermediates **8** and **9**. These would then cyclize easily to the unstable intermediates **12** and **13**, respectively. Finally, these unstable intermediates then eliminate HNO_2, irreversibly, leading to the anions of the *v*-triazolo[4,5-*d*]pyrimidines **14–16** and to the *v*-triazolo[4,5-*b*]pyridines **19**. For the reaction of **4** and **5** with sodium azide, which afforded **17** and **18**, the conclusion is drawn by analogy that compounds **10a** and **10b**, respectively, are intermediates. This ionic mechanism is based first on analogies between the reactions of **1–3** and **6** with azide ion and with hydroxide, deuteroxide, and ethoxide: only compounds which easily form the stable Meisenheimer-type adducts **8** and **9** (Z = OH, OD, OEt) give good yields of 8-azapurines in the azide reaction. Second, the observed intermediate with the C–H signal at δ 5.83 should have structure **8c** as described above and not the alternative structure **12c**. Finally, certain trinitrobenzene derivatives react with azide ion to form stable addition complexes[27] analogous to Meisenheimer-type compounds.

An alternative mechanism would be a concerted reaction. This possibility is considered unlikely. In addition to the facts discussed above concerning the electrophilic reactivity of position 6 of these nitroheterocycles, the reactivity of azide ion itself points toward a nucleophilic reaction of azide *ion* in the first step of this reaction. To our best knowledge, no

(23) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.* (London), **22**, 123 (1968).

(24) E. Buncel and A. W. Zabel, *J. Amer. Chem. Soc.*, **89**, 3082 (1967).

(25) (a) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967); (b) J. A. Zoltweicz, G. M. Kauffman, and C. L. Smith, *J. Amer. Chem. Soc.*, **90**, 5939 (1968); (c) P. Beak and J. Bonham, *ibid.*, **87**, 3365 (1965); P. Beak and E. Monroe, *J. Org. Chem.*, **34**, 589 (1969).

(26) A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 41 (1965), and leading references therein.

(27) P. Caveng and H. Zollinger, *Helv. Chim. Acta*, **50**, 861 (1967).

concerted reactions of this strong nucleophile, azide *ion*, are known.[28]

Another reaction leading to *v*-triazolo derivatives is worthy of mention. Meek and Fowler[29] showed that reaction of sodium azide with 1,2-di-*p*-toluenesulfonylethylene yielded 4(5)-tosyl-*v*-triazole. Their reaction proceeds first by *substitution* of tosyl by azide followed by *cyclization* and tautomerism to a *v*-triazole, whereas in our case the first step is a nucleophilic *addition* followed by a *cyclization*, etc. Their reaction therefore is quite different. It should also be noted that Rembarz, *et al.*,[30] and Callaghan, *et al.*,[31] have observed the elimination of nitrous acid from certain *v*-triazolines to form *v*-triazoles.

Brief mention should be made of the scope and limitations of the reaction of 5-nitroheterocycles with azide ion. Since most of the starting materials used in this study are commercially available or can be prepared easily,[32] this method should be more economical and facile for the syntheses of some known *v*-triazolo derivatives. Moreover, by this procedure some interesting new compounds have been prepared (see Table I), especially compounds **14e** and **15e**, which are new nucleoside analogs. These latter compounds may be viewed either as 5,6-disubstituted pyrimidine nucleosides or as 3-glycosyl-8-azapurines.

From experimental observations, it appears that in both the 5-nitropyrimidine and -pyridine series an oxo[33] substituent in the 2 or 4 positions must be present in the starting material for reaction with azide ion. Such a substituent functions as an additional activating group and prevents cyclic delocalization of the π-electron system in these compounds. The 5,6 double bond in the reactive compounds therefore can be characterized as being localized and highly activated by both a nitro and an oxo group, and also by the fact that in all cases except **5**, the mesomeric system, which causes that activation, ends at position 6. In the excepted compound **5**, in which the proton probably resides on N-3 and not on N-1, the mesomeric system extends to C-2. In the case of 5-nitro-4-oxopyrimidine (**4**), both tautomeric forms, **4a** and **4b**,[34] should be present in the reaction mixture, with **4b** probably being the more reactive species in the reaction with azide ion. Experimentally the importance of the final above-mentioned point became apparent. All compounds with a 2-oxo substituent furnished 8-azapurines in good yields, whereas 2-amino-, 2-ethoxy-, or 2-unsubstituted 5-nitropyrimidines or -pyridines gave only poor yields or did not react to form 8-azapurines at all. On the other hand, 4-ethoxy-1-methyl-2-oxo-5-nitropyrimidine (**2h**) reacted with relative ease with sodium azide to afford the 8-azapurine derivative (**15h**). This latter example demonstrates that in this case attack of azide ion at position 6 is favored over substitution at C-4. Theoretically, an alternative reaction might have been a reversible nucleophilic attack at position 4 of **2h** with subsequent substitution of the ethoxide group by azido; however, this substitution reaction was not observed experimentally.

The structures of all known compounds synthesized herein were established by comparison of their ultraviolet spectral characteristics or other physical data with reported values (see Table I). The 3-ribosyl derivative of 8-azaxanthine (**14e**) was established by the similarity of its uv spectrum as a function of pH with that for 3-methyl-8-azaxanthine (**1b**).[36] For compounds **15b** and **15g**, the uv data of Cavalieri, *et al.*,[37] on 8-azaisoguanine (**15a**) was used for comparison. In addition, the structures were confirmed by pK_a data (spectrophotometrically determined) and by nmr analyses. Some of these data are included in Table I.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are corrected. The nmr spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The uv spectra were determined on a Cary Model 15 spectrometer; the apparent pK_a values were determined spectrophotometrically using buffers and techniques previously described.[38] Paper chromatography was performed on Schleicher and Schuell paper No. 597 in the following systems: (A) 4% sodium citrate solution (descending); (B) 3% ammonium chloride solution (descending); (C) acetonitrile–water–concentrated ammonium hydroxide (7:2:1, ascending); (D) *t*-butyl alcohol–methyl ethyl ketone–50% formic acid (40:30:30, ascending). The compounds were visualized on the developed chromatograms under uv light. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedure.—The nitroheterocycle (0.001 mol) and finely powdered sodium azide (0.0015–0.003 mol) were suspended in 10–15 ml of DMF. (In the case of starting compounds which were unsubstituted at N-1, ammonium chloride, in slight molar excess over the sodium azide, was added.) The mixture was stirred and heated where necessary. The progress of the reaction was monitored spectrophotometrically by adjusting the pH of an aliquot to *ca.* 12 and observing the disappearance of the uv maximum in the 330–370-mμ region and the rise of a new maximum in the 270–320-mμ region. After the reaction was complete, the DMF was removed by evaporation *in vacuo*. The dry residue was dissolved in hot water and acidified to pH 3–4 with HCl or acetic acid. In many cases, the precipitated product was chromatographically pure. Recrystallization or fractional crystallization from H_2O or ethanol was necessitated with impure products. The purity of all products was established by paper chromatography in four systems. In Table I data are presented regarding reaction temperatures and times, solvents used, yields obtained, and solvents of recrystallization together with physical values for compounds shown in Scheme I.

Registry No.—Adduct **8b** of **2b** (Z = OD), 12407-92-0; adduct **8c** of **3b** (Z = OD), 12407-95-3; adduct **8d** of **2h** (Z = OD), 12407-91-9; adduct **8e** of **6b** (Z =

(28) Concerted reaction mechanisms have been demonstrated for *neutral* azides, RNs. See R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565, 633 (1963), for a review.

(29) J. S. Meek and J. S. Fowler, *J. Amer. Chem. Soc.*, **89**, 1967 (1967).

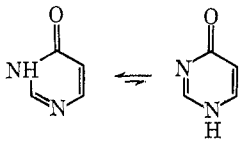
(30) G. Rembarz, B. Kirchhoff, and G. Dongowski, *J. Prakt. Chem.*, **33**, 199 (1966).

(31) P. D. Callaghan and M. S. Gibson, *Chem. Commun.*, 918 (1967).

(32) During the course of these studies an improved synthesis of 3-alkyl-5-nitrouracils by *direct* alkylation of 5-nitrouracils at N-3 was developed in our laboratory: H. U. Blank and J. J. Fox, *J. Heterocycl. Chem.*, in press.

(33) Though thiono analogs of the oxopyrimidines discussed herein have not been studied, it is possible that they, too, would serve in this reaction.

(34) For pyrimidone-4 the equilibrium is roughly known: log $K_{o,p}$ = 0.18 calculated by the pK method and 0.40 as determined from uv data.[35]



(35) See A. R. Katritzky and J. O. Lagawski, *Advan. Heterocycl. Chem.*, **1**, 341 (1963), and leading references therein.

(36) G. Nübel and W. Pfleiderer, *Chem. Ber.*, **98**, 1060 (1965).

(37) L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Amer. Chem. Soc.*, **70**, 3875 (1948).

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OD), 12407-89-5; adduct **9a** of **1b** (Z = OD), 12407-88-4; adduct **9a** of **1e** (Z = OD), 12407-94-2; adduct **9b** of **1d** (Z = OD), 12407-90-8; adduct **9b** of **1d** (Z = OEt), 12407-93-1; **11d**, 23430-66-2; **14a**, 1468-26-4; **14b**, 2083-04-7; **14c**, 2083-05-8; **14d**, 2278-15-1; **14e**, 22855-06-7; **15a**, 4730-46-5; **15b**, 23430-72-0; **15c**, 23110-95-4; **15d**, 22855-07-8; **15e**, 22855-08-9; **15f**, 22855-09-0; **15g**, 23465-14-7; **15h**, 23430-73-1; **16b**, 22699-23-6; **17**, 2683-90-1; **18**, 134-58-7; **19a**, 23431-04-1; **19b**, 22699-22-5; **20b**, 22699-24-7.

Pyridazines. XXXIII. Valence Isomerizations of Some Tetrazolo[1,5-*b*]pyridazines

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Several examples of valence isomerizations of fused tetrazolo rings of different tetrazolo[1,5-*b*]pyridazines and related systems into azido functions are presented. Valence isomerization could be induced by forming a new fused five- or six-membered hetero ring or by N oxidation.

Recently, we were able to show that fusion of an azolo ring, involving a pyridazine ring nitrogen at the bridgehead of the bicyclic system, caused spontaneous valence isomerization of tetrazolo[1,5-*b*]pyridazines into the corresponding azidopyridazines.[1-3]

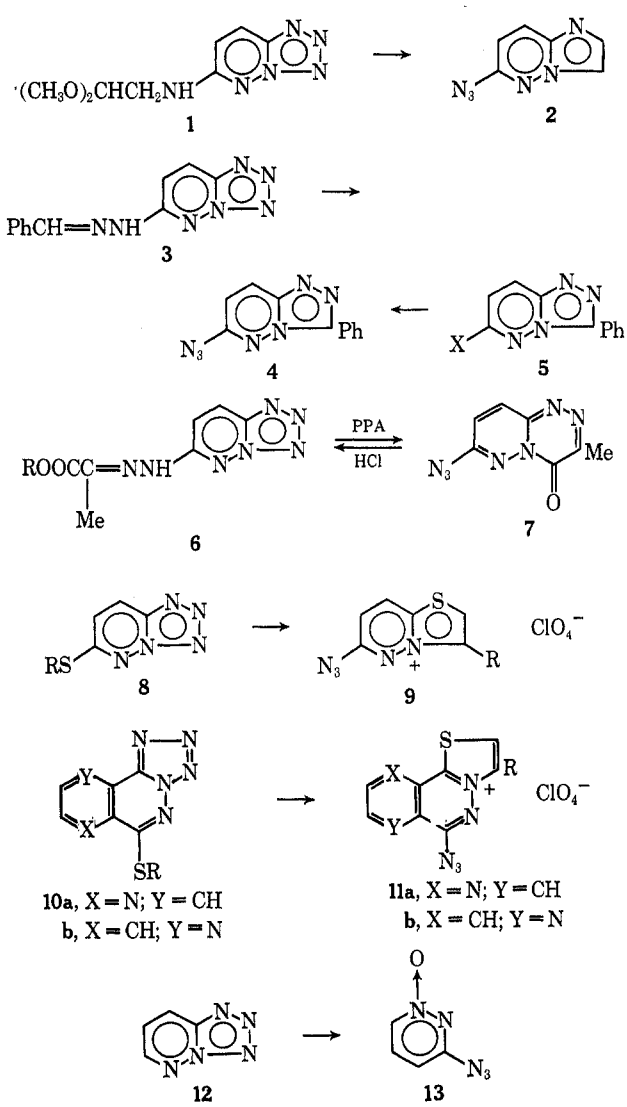
In order to test the generality of such valence isomerizations in the tetrazolopyridazine series, further experiments have been performed which include the formation of a fused azole or azine ring, a sulfur-containing five-membered ring, or an introduction of a N-oxide function.

Since earlier attempts[1] toward simultaneous formation of a fused imidazole ring were not successful, another approach to such conversion has been attempted. It was now possible to convert 6-dimethoxyethylaminotetrazolo[1,5-*b*]pyridazine (**1**) with polyphosphoric acid into the corresponding 6-azidoimidazo[1,2-*b*]pyridazine (**2**) (see Scheme I) and thus induce a complete elimination of the fused tetrazolo ring as is evident from infrared and nmr spectra. The presence of the tetrazolo isomer in a solution of deuteriochloroform could not be detected.

Similarly, the formation of a fused *s*-triazolo ring could be now extended by employing procedures designed previously for syntheses of simple *s*-triazolo[4,3-*b*]pyridazines[4] or *s*-triazolo[4,3-*a*]-1,3,5-triazines.[5] In this manner, the hydrazone **3** could be transformed into the bicyclic compound **4** by employing either the lead tetraacetate technique or by means of bromine. Here again, valence isomerization was discernible from spectral data and, in addition, from chemical transformations of compounds **5** (R = $NHNH_2$) with nitrous acid or (**5**, R = Cl) by means of sodium azide. As anticipated, in both cases no ring closure to a fused tetrazolo heterocycle occurred and only an azide group was formed (**4**).

A fused six-membered ring could be generated in the reaction of **6** (R = Et) with polyphosphoric acid, and once more the tetrazolo ring was isomerized to the azido group. The obtained bicyclic compound **7**, a representative of the newly discovered pyridazino[6,1-*c*]*as*-triazine system,[6] is susceptible to acid hydrolysis and as soon as the fused *as*-triazine ring was opened this resulted in immediate generation of the fused tetrazolo ring (**6**, R = H) from the azido group present in the starting compound.

SCHEME I



(1) A. Kovačič, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, **5**, 351 (1968).
(2) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969).
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