The major product has a proton nmr pattern identical with that of the product obtained from bis(trifluoromethylthio)mercury and *n*-butyl iodide and must, therefore, be trifluoromethyl *n*-butyl sulfide.

Anal. Calcd for $C_5H_9F_3S$: C, 38.0; H, 5.7; F, 36.0; S, 20.3. Found: C, 38.3; H, 5.9; F, 36.5; S, 20.7.

C. **Trifluoromethyl Isobutyl Sulfide.**—A mixture of 15.4 g (0.275 mole) of isobutylene and 32 g (0.313 mole) of trifluoromethanethiol was irradiated for 5 min. Upon distillation of the reaction mixture through a small spinning-band still, there was obtained 34.10 g (78%) of trifluoromethyl isobutyl sulfide distilling at 85°, n^{25}D 1.3647–1.3649.

Anal. Calcd for $C_5H_9F_3S$: C, 38.0; H, 5.7; S, 20.3. Found: C, 37.6; H, 5.9; S, 20.1.

D. **Trifluoromethyl Cyclohexyl Sulfide.**—A mixture of 45 g (0.493 mole) of cyclohexene and 52 g (0.508 mole) of trifluoromethanethiol was irradiated for 5 hr. Upon distillation of the reaction mixture through a large spinning-band still, there was obtained 64.5 g (69%) of trifluoromethyl cyclohexyl sulfide distilling at 72° (60 mm), n^{25}D 1.4180.

Anal. Calcd for $C_7H_{11}F_3S$: C, 45.6; H, 6.0; S, 17.4. Found: C, 45.9; H, 6.3; S, 17.2.

E. **Trifluoromethyl Benzyl Sulfide.**—This procedure is similar to that described by Man, *et al.*[17]

A mixture of 30 g (0.0744 mole) of bis(trifluoromethylthio)mercury was placed in a flask fitted with an addition funnel and a reflux condenser, and heated by an oil bath. The bath was heated to 95°, and then 25 g (0.146 mole) of benzyl bromide was added dropwise. A precipitate formed immediately. The heating was continued for 1 hr after the addition was completed, and then the mixture was worked up as described in B, 1. Upon distillation through a small spinning-band still, there was obtained 18.3 g (65%) of benzyl trifluoromethyl sulfide distilling at 56° (8 mm), n^{25}D 1.4709.

Studies on the Azidoazomethine–Tetrazole Equilibrium. IV. Azidopurines[1]

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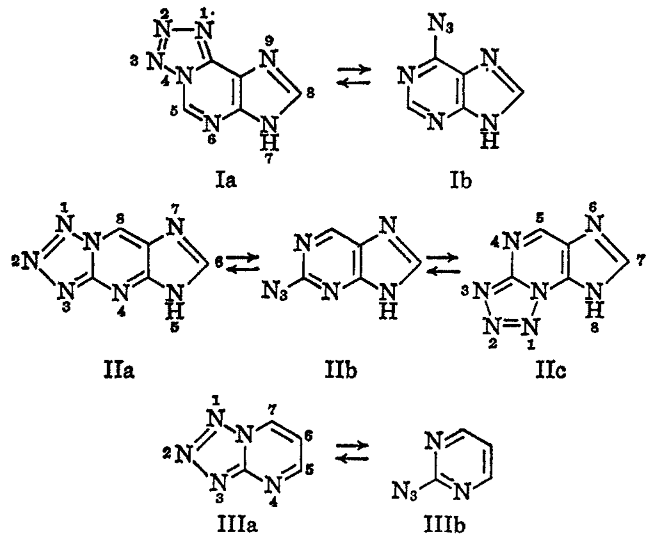
The azidoazomethine–tetrazole equilibrium for the systems tetrazolo[5,1-*i*]purine (Ia)–6-azidopurine (Ib) and tetrazolo[1,5-*a*]purine (IIa)–2-azidopurine (IIb)–tetrazolo[5,1-*b*]purine (IIc) has been examined by means of infrared and proton magnetic resonance spectrometry. II is the first example in which all three tautomers (IIa, b, and c) have been detected in a single medium. Tetrazole stabilization is shown to be greater in Ia than in IIa and IIc. The heats of tautomerization of IIa–IIb and IIc–IIb, respectively, are found to be +4.7 ± 0.2 and +2.7 ± 0.2 kcal/mole. In addition, the magnitude of the heat of tautomerization of tetrazolo[1,5-*a*]pyrimidine (IIIa) to 2-azidopyrimidine (IIIb), +5.1 ± 0.1 kcal/mole, is the same as that of IIa–IIb. An increase in entropy is observed in each case on going from the tetrazolo tautomer to the azido, as expected, and in the temperature range studied the entropy effects compete with the enthalpy effects in controlling the position of equilibrium.

In previous papers we have reported on the azidoazomethine–tetrazole equilibrium in pyrimidines,[2] and we now report some observations on the analogous equilibrium in purines. The preparations of both 6- and 2-azidopurines (Ib and IIb) have been claimed,[3,4] but for I evidence was later presented in favor of the tricyclic structure, tetrazolo[5,1-*i*]purine (Ia).[4,5] Recently, the preparations of some mono-, di-, and triazidopurines have been reported[6,7] in which one of the main considerations in assigning the structures has been the presence of one or more azido infrared absorption bands in the 2200–2100-cm.$^{-1}$ region. Our results indicate that the presence of an azido absorption band in the infrared spectrum of a sample does not preclude the possibility that the tetrazole tautomer is also present.

In this paper the effects of solvent and temperature on the equilibria between tetrazolo[5,1-*i*]purine (Ia) and 6-azidopurine (Ib) and among tetrazolo[1,5-*a*]purine (IIa), 2-azidopurine (IIb), and tetrazolo[5,1-*b*]purine (IIc) are examined. In addition to infrared and proton magnetic resonance (pmr) spectra, support for the assignment of tautomers in system II of Scheme I was provided by data on the equilibrium between tetrazolo[1,5-*a*]pyrimidine (IIIa) and 2-azidopyrimidine (IIIb).[2c]

Scheme I



Experimental Section

I,[3] II,[4] and III[8] were prepared by the nitrosation of the corresponding hydrazino derivatives. The infrared spectra were

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[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] (a) C. Temple, Jr., W. C. Coburn, Jr., M. C. Thorpe, and J. A. Montgomery, *J. Org. Chem.*, **30**, 2395 (1965); (b) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *ibid.*, **30**, 829 (1965); (c) C. Temple, Jr., and J. A. Montgomery, *ibid.*, **30**, 826 (1965).

[3] 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.

[4] J. A. Johnson, Jr., H. J. Thomas, and H. J. Schaeffer, *J. Am. Chem. Soc.*, **80**, 699 (1958).

[5] J. P. Glusker, D. van der Helm, and W. E. Love, Abstracts, Meeting of the American Crystallographic Association, Aug 1961, p 47.

[6] N. B. Smirnova and I. Y. Postovskii, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva*, **9**, 711 (1964).

[7] T. Itai and G. Ito, *Chem. Pharm. Bull.* (Tokyo), **10**, 1141 (1962).

[8] K. Shirakawa, Japanese Patent 777 (Feb 6, 1957); *Chem. Abstr.*, **52**, 4699*h* (1958).

TABLE I

EQUILIBRIUM CONSTANTS AND INFRARED AND PMR SPECTRAL ASSIGNMENTS

				Chemical shift, τ (ppm)			
				Tetrazolo tautomer		Azido tautomer[a]	
				Ia		Ib	
Solvent[b]	Concn, % (w/v)	K_T[c] (34°)	ν, cm^{-1}[d]	5-H	8-H	2-H	8-H
D_2O	<2.5	...	...	5.13[e]	3.87[e]	...	...
DMSO-d_6	10	...	*f*	−0.02	1.38	...	...
CF_3COOH	10	...	2200	...	...	0.87	0.87
DMSO-d_6–CF_3COOH (1:1 v/v)	10	0.37	...	0.12	0.96	0.75	1.07
CH_3COOH	<5	0.33	2145	0.20	1.26	1.26	1.41
0.5 *N* NaOD	<4	...	...	9.40[g]	8.11[g]	...	...
				IIa		IIb	
				8-H	6-H	6-H	8-H
DMSO-d_6	5	0.44,[h] 3.5[i]	2135	−0.26	1.08	0.97	1.42
CF_3COOH	10	...	2180	...	...	0.45	0.65
DMSO-d_6–CF_3COOH (2:1 v/v)	3	2.0[h,j]	...	−0.10	1.13	0.63	0.75
CH_3COOH	<5	...	2145	...	...	0.90	1.42

[a] We suggest these assignments for these pairs of protons on the basis of previous work.[17] [b] DMSO-d_6 = dimethyl-d_6 sulfoxide. [c] 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 ±5%. [d] Wavenumber of the infrared absorption band assigned to the antisymmetric stretching vibration of the azido group. [e] In parts per million measured downfield from HOD as internal reference. [f] No azido band detected. [g] Shift in parts per million downfield from the methyl absorption of sodium 3-trimethylsilylpropane-1-sulfonate used as internal reference. [h] IIb/IIa. [i] IIb/IIc. Tetrazolo[5,1-*b*]purine (IIc) gave peaks at τ (H_5) = 0.55 and τ (H_7) = 1.22 ppm. [j] IIc was not detected.

determined with a Perkin-Elmer Model 521 spectrophotometer. The spectra of the solids were run in pressed potassium bromide disks, while spectra of solutions were run in fixed-thickness cells equipped with windows of Irtran-2 for solutions in dimethyl sulfoxide (DMSO) or CF_3COOH, and with windows of silver chloride for solutions in CH_3COOH.

The pmr spectra were obtained on a Varian A-60 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.

Results and Discussion

The results at 34° for systems I and II are summarized in Table I. Corresponding data for system III (Scheme I) have been reported.[2c] In Table I, column three shows the equilibrium constants at 34° for those systems in which more than one form was detectable in the pmr spectra.

The infrared spectrum of solid I exhibits a weak, but distinct, absorption band at 2145 cm^{-1}, indicating the presence of some azido form, Ib, in the solid state.[9,10] Examination of the pmr spectra of I in a variety of solvent systems shows that the major form observed is determined by the nature of the solvent. In a trifluoroacetic acid solution of I only the azido form (probably protonated) is detected, indicated by the observance of peaks for only one form in the pmr spectrum and the presence of an azido absorption band at 2200 cm^{-1} in the infrared spectrum. In contrast, only the tetrazole tautomer is found in DMSO and DMSO-d_6 solutions of I as indicated by the absence of azido absorption bands in the 2200–2100-cm^{-1} region of the infrared spectrum (DMSO), and by the presence of only one tautomer in the pmr spectrum (DMSO-d_6). Similarly only the tetrazole form was observed in the pmr spectrum in D_2O and in 0.5 *N* NaOD (anion of Ia) solutions of I. In the DMSO-d_6 solution of I, none of the azido tautomer (Ib) was detected in the pmr spectrum over the temperature range 34–150°, showing the great stability of Ia in this polar medium.[11] The pmr spectrum of I in 1:1 (v/v) DMSO-d_6–CF_3COOH showed both the tetrazolo and azido forms in the ratio 3:1. In this solution we could not obtain data at higher temperatures because the compound decomposes, as evidenced by new peaks in the spectrum. Finally, both the tetrazolo and azido forms (ratio 3:1) were found in an acetic acid solution of I. Comparison of the pmr spectrum of the two forms in this medium with those of the tetrazolo form in DMSO-d_6 and of the azido form in CF_3COOH (see Table I) indicates that tetrazole destabilization is mainly a result of the lower dielectric constant of CH_3COOH as compared with that of DMSO-d_6,[13] rather than to protonation as in CF_3COOH. The relative amount of the azido form appeared to increase slightly as the temperature was raised, but the low solubility of I in CH_3COOH precluded accurate measurement of the equilibrium constant as a function of temperature.

The infrared spectrum of solid II showed multiple azido absorption bands near 2150 cm^{-1} and was practically transparent between 1100 and 1000 cm^{-1}, a region in which tetrazoles may exhibit up to four bands.[14] This spectrum provides support for the previous assignment of this product as 2-azidopurine (IIb).[4] Taken together, the infrared and pmr spectra indicated that CF_3COOH and CH_3COOH solutions of II contained only the azido form. However, the pmr spectrum of a solution of II in 2:1 (v/v) DMSO-d_6–CF_3COOH showed both IIa and IIb in the ratio 3:7 but did not show IIc (*vide infra*), possibly because the low solubility of II in this medium precluded its observation. Finally, the infrared spectrum of II in DMSO also showed a strong azido absorption band, but the pmr

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(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 1st ed, John Wiley and Sons, Inc., New York, N. Y., 1954, p 223.

(10) I. Ya. Postovskii and I. N. Goncharova [*Zh. Obshch. Khim.*, **33**, 2334 (1963)] have observed the tautomerization of a tetrazole to the azido derivative in the crystalline state.

(11) At 130° and higher but not at 100° the signal from the 2-proton of Ia broadened, probably caused by the quadrupole moment of the adjacent nitrogens. See ref 12.

(12) J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 80–83.

(13) Y. N. Sheinker, I. Ya. Postovskii, N. P. Bednyagina, L. B. Senyavina, and L. F. Lipatova, *Dokl. Akad. Nauk SSSR*, **141**, 1388 (1961).

(14) E. Lieber, D. Levering, and L. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

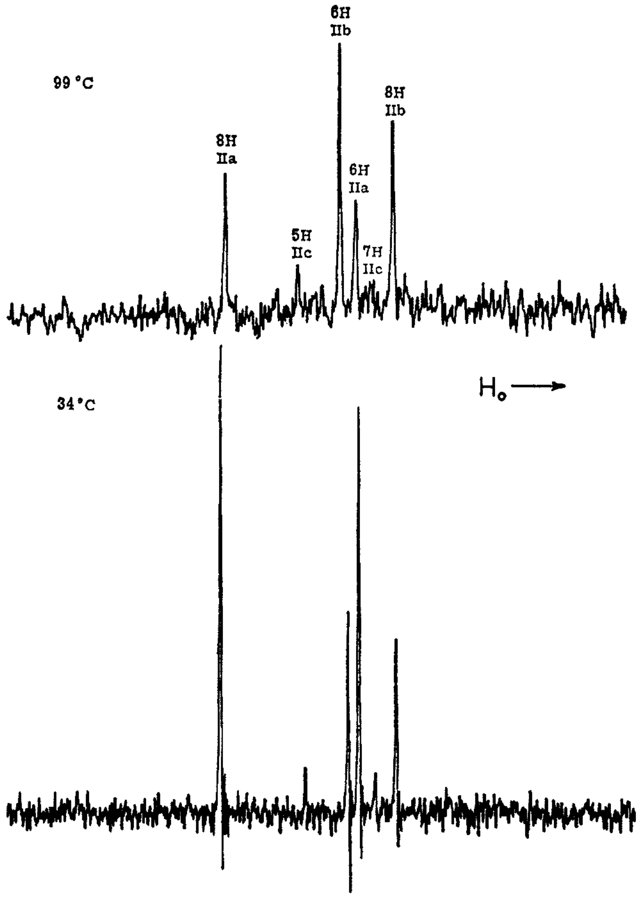

Figure 1.—Pmr spectrum of II in DMSO-d_6 measured at 60 Mc/sec^{-1} and at two temperatures.

spectrum in DMSO-d_6 showed the presence of IIa, IIb, and IIc in the ratio 6:3:1.

The assignment of this pmr spectrum, shown in Figure 1, is based mainly upon the difference in effect of the electron-withdrawing tetrazole ring and of the electron-donating azido group on the chemical shifts of nearby protons.[15] These effects are readily demonstrated by considering system III (Scheme I) in DMSO-d_6 in which the absorptions of the two forms can be unequivocally assigned. In the azido tautomer, IIIb, the 4- and 6-protons (τ = 1.18 ppm) are equivalent, and this peak is identified by comparison of its relative intensity with that of the 5-proton (τ = 2.57 ppm). In the tetrazolo form, IIIa, the 5- and 7-protons (τ = 0.70 and 0.15 ppm) are nonequivalent and their peaks are shifted downfield from the corresponding protons in the azido tautomer (IIIb) by 0.48 and 1.03 ppm. The 6-proton (τ = 2.23 ppm) of IIIa also occurs downfield from the 5-proton of IIIb, but the shift (0.34 ppm) is less. This deshielding effect is attributed to the electron-withdrawing effect of the tetrazole ring and is greater for the 7-proton adjacent to the tetrazole ring than for the 5-proton.

In the spectrum of II the peak height of a high-field proton of a pair is lower, perhaps because of a broadening effect of the quadrupole moments of the two adjacent imidazole ring nitrogens.[12] However, the six peaks observed are easily divided into three pairs by means of their relative intensities. The lowest-field absorption at τ = -0.26 ppm is assigned to the 8-proton of IIa, which leaves the next lowest peak at τ = 0.55 ppm for assignment to the 5-proton of IIc. Both the 6-proton of IIa and the 7-proton of IIc, easily identifiable by matching their relative peak intensities with those of the absorptions already assigned, are less deshielded by the tetrazole ring. The fact that more IIa is present than IIc is consistent with the observation that 1-ethylpurine is more stable than 3-ethylpurine.[16]

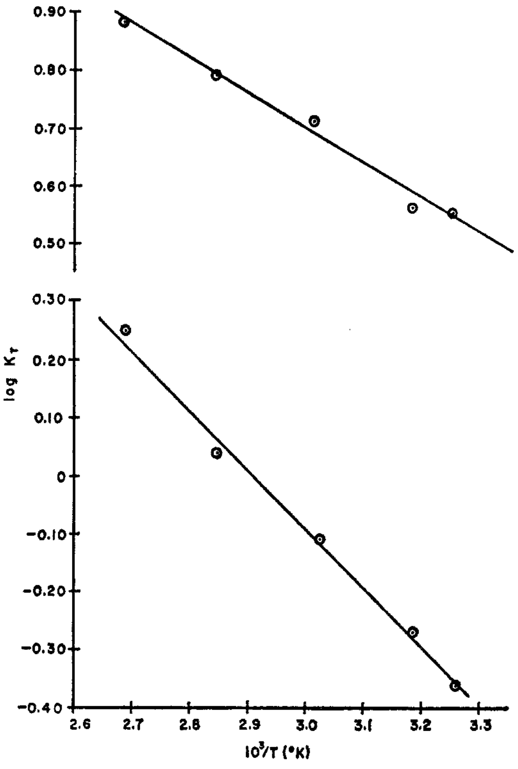

Figure 2.—Effect of temperature on the equilibrium constant for IIa $\rightleftarrows$ IIb (bottom) and IIc $\rightleftarrows$ IIb (top) in dimethyl-d_6 sulfoxide (5% w/v).

The remaining pair of intermediate intensity at τ = 0.97 and 1.42 ppm is at the highest field of the three and is assigned to the 6- and 8-protons of the azido form, IIb. This assignment is consistent with the report that the azido group is electron donating.[15] The corresponding shifts in DMSO-d_6 of purine itself, τ (H_6) = 0.81 ppm and τ (H_8) = 1.32 ppm, and of 2-aminopurine, τ (H_6) = 1.35 ppm and τ (H_8) = 1.92 ppm, indicate that the azido group is only slightly electron donating in this system.[17]

With increasing temperature the relative amount of IIb increased at the expense of that of IIa while the relative amount of IIc remained approximately constant, as shown in Figure 1. In Table II the equilibrium constants for IIb/IIa and IIb/IIc are given for various temperatures. In Figure 2 the variations of the equilibrium constants with temperature show that both tautomerizations to the azido form are endothermic: ΔH(IIb/IIa) = $+4.7 \pm 0.2$ kcal/mole and ΔH(IIb/IIc) = $+2.7 \pm 0.2$ kcal/mole, from the slopes of the corresponding least-squares lines. For comparison with II the temperature variation of the equilibrium involving the related tetrazolo[1,5-*a*]pyrimidine (IIIa) and 2-azidopyrimidine (IIIb) in

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[15] J. H. Boyer and E. J. Miller, Jr., *J. Am. Chem. Soc.*, **81**, 4671 (1959).

[16] R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).

[17] W. C. Coburn, Jr., M. C. Thorpe, J. A. Montgomery, and K. Hewson, *ibid.*, **30**, 1110, 1114 (1965).

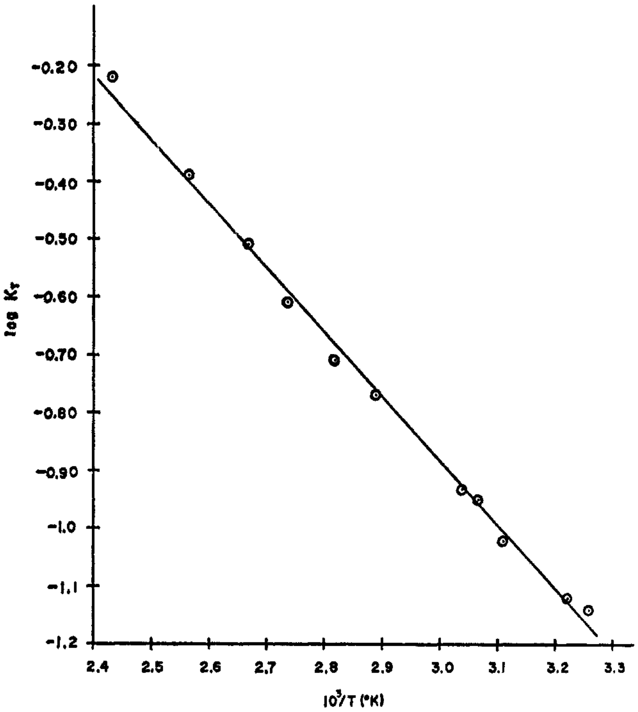

Figure 3.—Effect of temperature on the equilibrium constant for III in dimethyl-d_6 sulfoxide (32% w/v).

DMSO-d_6 was studied. In Table II and Figure 3, the equilibrium constants and the variation of the equilibrium constant with temperature are given for the tautomerization of IIIa to IIIb. The value of the heat of tautomerization, +5.1 ± 0.1 kcal/mole, is of the same magnitude as that found for the tautomerization of IIa to IIb.

TABLE II

VARIATION OF K_T WITH TEMPERATURE IN DMSO-d_6

Temp, °C	K_T,[a,b] IIb/IIa	K_T,[a,b] IIb/IIc	Temp, °C	K_T,[b] IIIb/IIIa	Temp, °C	K_T,[b] IIIb/IIIa
34	0.44	3.5	34	0.07	82	0.20
41	0.54	3.6	38	0.08	93	0.25
58	0.77	5.0	49	0.10	102	0.31
78	1.09	6.0	53	0.11	117	0.41
99	1.79	7.4	56	0.12	139	0.60
			73	0.17		

[a] In the calculation of these equilibrium constants the low solubility of II necessitated the use of peak heights rather than integrated intensities. [b] The relative deviation in K_T was ±5%.

Table III shows the calculated thermodynamic quantities at 298 and 373°K for systems II and III (Scheme I). These data show that in each case where the tetrazole ring opens to form the less constrained azido tautomer there is a significant increase in entropy. In fact, in the case of IIc ⇄ IIb, even at room temperature the entropy contribution, $T\Delta S°$, is greater than the enthalpy change, so that the azido form is more predominant over the entire temperature range investigated. At 373°K the azido tautomer, IIb, is more stable than either of the tetrazolo tautomers; that is, the position of equilibrium is entropy controlled. Although Schleyer, Blanchard, and Woody[18] have pointed out the novelty of entropy-governed equilibria, Leffler and Grunwald[19] have pointed out that in some reactions it is possible, by a moderate change of temperature, to change from an enthalpy-controlled to an entropy-controlled situation, and that in a ring-opening reaction $\Delta S°$ should be positive. The entropy changes observed here thus serve to confirm further the assignment of the pmr peaks to the respective tetrazolo and azido tautomers in systems II and III.

TABLE III

THERMODYNAMIC QUANTITIES

Equilibrium	T, °K	$\Delta G°$, cal/mole	$\Delta S°$, gibbs/mole	$\Delta H°$, cal/mole	$-T\Delta S°$, cal/mole
IIa ⇄ IIb	298	+600	+13.7	+4700	−4100
	373	−400	+13.7	+4700	−5100
IIc ⇄ IIb	298	−600	+11.2	+2700	−3300
	373	−1500	+11.2	+2700	−4200
IIa ⇄ IIc	298	+1250	+2.5	+2000	−750
	373	+1070	+2.5	+2000	−930
IIIa ⇄ IIIb	298	+1700	+11.3	+5100	−3400
	373	+900	+11.3	+5100	−4200

Acknowledgment.—The authors are indebted to Mr. C. L. Kussner for assistance in preparing the compounds and to Dr. W. J. Barrett and the members of the Analytical Chemistry Section of Southern Research Institute for the spectral determinations.

(18) P. von R. Schleyer, K. R. Blanchard, and C. D. Woody, *J. Am. Chem. Soc.*, **85**, 1358 (1963).

(19) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, Chapter 3.