1,4-dihydronicotinamide of α,α-diphenyl-β-picryl hydrazyl suggests that a free radical mechanism may obtain. This impression is strengthened by the ready reduction of quinone and of malachite green, both of which may form free radicals.[22] The reduction of pyruvic acid by 2,6-dimethyl-3,5-dicarboethoxydihydrolutidine was scarcely conducted under "physiological conditions"; further the nitrogen atom of the dihydropyridine ring had not been alkylated. The reduction of a simple ketone by a 1-alkyl-1,4-dihydronicotinamide has not yet been achieved.

Appendix

In the reduction of malachite green by deuterated 1-benzyl-1,4-dihydronicotinamide, the reducing agent was present only in slight excess over the dye. Since k_H/k_D is significantly greater than unity, the concentration of deuterium in the reducing agent changes as the reaction proceeds, and the calculation of the k_H/k_D ratio from the deuterium content of the product is not obvious. However, the evaluation can be made as follows: Assume the reducing agent consists of a mixture of dihydro compound (XH_2) and monodeutero compound (XHD), with the latter at concentration A. This mixture reacts with malachite green, present at a concentration B.

$$XH_2 + \underset{(B)}{M} \xrightarrow{2k_H} MH + XH \qquad (5)$$

$$\underset{(A)}{XHD} + \underset{(B)}{M} \xrightarrow{k_H} MH + \underset{(K)}{XD} \qquad (6)$$

$$\xrightarrow[k_D]{} \underset{(J)}{MD} + XH \qquad (7)$$

(22) L. Michaelis, *Chem. Revs.*, **16**, 243 (1935); J. B. Conant and N. M. Bigelow, THIS JOURNAL, **53**, 676 (1931); E. Weitz, L. Müller and K. Dinges, *Ber.*, **85**, 878 (1952).

Here MH is leucomalachite green, MD is deuterated leuco malachite green at a concentration (J), XH is I (R = $CH_2C_6H_5$) and XD is deutero I (R = $CH_2C_6H_5$), the latter at a concentration K. Now

$$d(K)/dt = k_H(A)(B) \text{ and } d(J)/dt = k_D(A)(B) \qquad (8)$$

Therefore, regardless of the stage of the reaction, or of the k_H/k_D ratio

$$d(K)/d(J) = k_H/k_D, \text{ and } (K)/(J) = k_H/k_D \qquad (9)$$

Line 4, Table II, corresponds to an experiment with isotopically pure XHD, and therefore the data give directly (J) and (K) for completion of the reaction; k_H/k_D can be calculated from eq. 9. With isotopically impure material (line 1) (K) is not known accurately; it can, however, be estimated at the end of the reaction by assuming the stoichiometry of eq. 2. Then

$$(K)_{final} = (A)_{initial} - (J)_{final} \qquad (10)$$

Combining equations 9 and 10

$$k_H/k_D + 1 = (A)_{initial}/(J)_{final} \qquad (11)$$

A parallel development to that for equation 11 yields an equation suitable for calculating k_H/k_D when a mixture of mono and dideutero compounds is used as reducing agent (as in line 5, Table II). From this equation, from equations 9 and 11, and from the data of Table II, the average value of 4.5 $\pm$ 0.5 for k_H/k_D was found.

Acknowledgment.—The authors wish to thank Dr. F. A. Loewus for his generous assistance with the deuterium analyses here reported. The funds for the purchase of the mass-spectrometer used in this research were supplied by the Atomic Energy Commission under contract No. At(11-1)-92. One of us (D. M.) gratefully acknowledges support of a N. S. F. Fellowship.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE CHEMISTRY DIVISION, RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE TEST STATION]

Kinetics of the Isomerization of Substituted 5-Aminotetrazoles

BY RONALD A. HENRY, WILLIAM G. FINNEGAN AND EUGENE LIEBER

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The kinetics of the equilibrium reaction shown in Table I, where R is 4-ClC_6H_4, C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, or C_2H_5, were studied in the range 116–137°. In the initial stages of the isomerization, the first-order rate law was obeyed. For the forward reaction, the rates (k_1) decreased along the indicated series, the energies of activation increased from about 32,500 to 37,000 cal. per mole and the heats of reaction varied from 4300 cal. per mole (evolved) to 1350 cal. per mole (absorbed). For the aryl substituted aminotetrazoles there was a good correlation between the logarithm of the rates of isomerization and Hammett's sigma values for groups. There was a reasonable agreement both in magnitude and sign between heats of reaction calculated from the temperature coefficients of the equilibrium constants, and the differences in the heats of combustion of isomeric pairs. The kinetics of the cyclizations of guanyl and nitroguanyl azides to the respective tetrazoles were also investigated in a preliminary manner. When 1-phenyl-5-aminotetrazole was heated in aqueous alkali, a rapid, hydrolytic decomposition occurred to yield aniline, ammonia, carbonate and azide ion.

1-Substituted-5-aminotetrazoles and 5-substituted aminotetrazoles are thermally unstable and can be isomerized without appreciable decomposition in ethylene glycol or undisturbed melts at 180–200° to equilibrium mixtures of both isomers.[1,2] The present work is concerned with the kinetics of this isomerization. Since one of the steps in the proposed mechanism involves the cyclization of a guanyl azide, this reaction was also examined kinetically.

(1) W. G. Finnegan, R. A. Henry and Eugene Lieber, *J. Org. Chem.*, **18**, 779 (1953).

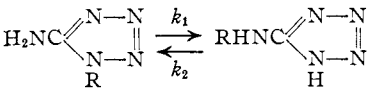
(2) R. A. Henry, W. G. Finnegan and Eugene Lieber, THIS JOURNAL, **76**, 88 (1954).

Experimental

Materials.—The 1-substituted 5-aminotetrazoles were prepared by the diazotization of substituted aminoguanidines and cyclization of the resulting guanyl azides in aqueous basic solution. The 5-arylaminotetrazoles were made by isomerizing 1-aryl-5-aminotetrazoles under non-equilib-

TABLE I

RATES OF ISOMERIZATION OF SUBSTITUTED 5-AMINOTETRAZOLES



R	Temp., °K.	Forward reaction: k_1, min.$^{-1}$ × 10^3	Forward reaction: Energy of activation, cal./mole	Forward reaction: Entropy of activation, cal./degree	Reverse reaction: k_2, min.$^{-1}$ × 10^3	Reverse reaction: Energy of activation, cal./mole	Reverse reaction: Entropy of activation, cal./degree
C_2H_5	390.1				0.589		+11.4
	399.5				1.74		+11.3
	409.8				5.64	36,400	+11.3
C_6H_5	389.3	0.936		+3.2			
	389.8	..			0.359		+10.2
	390.1	1.02		+3.2			
	397.8	2.39		+3.2			
	410.3	8.17	32,800	+3.1	3.73	36,300	+10.1
4-$CH_3OC_6H_4$	390.0	0.381		+5.8			
	399.5	1.04		+5.7			
	410.0	3.50	34,600	+5.7			
	410.3				5.43		
4-$CH_3C_6H_4$	390.2	0.588		+4.4			
	399.9	1.69		+4.3			
	410.5	5.04	33,700	+4.3			
4-ClC_6H_4	390.3	2.28		+4.0			
	399.9	6.33		+4.0			
	410.3	17.58	32,500	+3.9			
3-$CH_3C_6H_4$	410.3	7.08					

rium conditions.[1,2] The 5-ethylaminotetrazole was synthesized either by the catalytic debenzylation of 5-benzylethylaminotetrazole,[1] or by the catalytic hydrogenation of the triethylamine salt of ethylidine 5-aminotetrazole.[3]

Nitroguanyl azide was made by the method of Lieber, *et al.*[4] Guanyl azide was prepared by the diazotization of aminoguanidinium nitrate in absolute ethanol with dinitrogen trioxide.[5] The ethylene glycol (Eimer and Amend, C.P.) was used without purification and a small correction was made for any acidity.

Kinetic Measurements. A. Isomerizations.—The apparatus used for the isomerizations consisted of a double walled flask. The removable inner flask of 50-ml. capacity, which contained the solution of substituted 5-aminotetrazole in ethylene glycol, was maintained at an appropriate temperature by the vapors of a refluxing solvent in the outer flask. Boiling *n*-butanol, methyl *n*-butyl ketone, *m*-xylene, anisole or ethylene glycol enabled temperatures of about 117, 127, 138, 154 or 195° to be maintained. The actual temperature in the ethylene glycol solution was measured by a thermometer, which was inserted through the stopper closing the inner flask. During any one experiment, the temperature did not vary more than ±0.1°.

The substituted 5-aminotetrazole was accurately weighed into the inner flask and the flask was brought to temperature in the vapor bath. A weighed amount of ethylene glycol, preheated to the desired temperature, was then added and the mixture was stirred with the thermometer to ensure rapid attainment of both temperature equilibrium and a homogeneous solution. The concentrations of substituted 5-aminotetrazoles were about 0.35 × 10^{-3} mole per gram of solution (*ca.* 0.4 molal) with the exception of 1-(4-chlorophenyl)-5-aminotetrazole whose solubility limited the concentration to about 0.15 × 10^{-3} mole per gram of solution. Sampling with a preheated pipet commenced as soon as the temperature was constant and was continued at appropriate time intervals. The sample size was varied to allow for the increase or decrease in the concentration of acidic 5-substituted aminotetrazole during the isomerization. Each sample was placed in a tared flask, chilled rapidly to quench the reaction, weighed, diluted with neutral 95% ethanol and titrated to the phenolphthalein end-point with standard sodium hydroxide solution. The concentration of the acidic 5-substituted aminotetrazole was calculated from this titer in terms of moles per gram of solution. Only the data for the first 10 to 15% of reaction were used in each case and the effect due to the reverse reaction was neglected. Representative data are plotted in Fig. 1; the specific reaction rate constants were calculated from the data by the method of least squares rather than by graphical means. Figure 2 shows typical Arrhenius plots of log k *vs.* $1/T$ for the examples studied. The energies of activation were calculated from these latter data by the method of least squares. The results are summarized in Table I.

B. Cyclizations of Guanyl Azides.—Guanyl and nitroguanyl azides cyclize rapidly in aqueous solutions of *p*H greater than about 7 to yield 5-amino- and 5-nitroaminotetrazoles, which are acidic. Addition of base is required to maintain a constant *p*H as the cyclization progresses. In order to avoid any buffering action due to sodium 5-aminotetrazole, a *p*H of 9 was employed for the cyclization of guanyl azide. The cyclization of nitroguanyl azide was performed at *p*H 8 since sodium 5-nitroaminotetrazole does not buffer the solution and the cyclization proceeds at a more easily measured rate.

A mixture of 50 ml. of 0.0418 *N* guanyl azide nitrate solution and 25 ml. of ethanol was precooled to the desired temperature and 25 ml. of 0.0418 *N* sodium hydroxide solution, cooled to slightly below the desired operating temperature, was added very rapidly with mechanical stirring. A standard solution of sodium hydroxide (0.2089 *N*) was then added from a 10-ml. buret at a rate designed to maintain the *p*H (*ca.* 9); the rate of addition was recorded as a function of time. The reaction vessel was immersed in an ice or salt–ice-bath of appropriate temperature and the actual temperature of the reaction solution was continuously recorded with a platinum–platinum rhodium thermocouple. The *p*H of the solution was measured with Beckman Model G *p*H meter using a general purpose glass electrode against a standard calomel electrode. Although these electrodes were designed for operation to −5°, they were used at lower temperatures with reasonable success in several instances even though the response became increasingly sluggish. The solution was agitated vigorously throughout the experiment. The kinetic measurements of the nitroguanyl azide cycliza-

(3) R. A. Henry and W. G. Finnegan, THIS JOURNAL, **76**, 926 (1954).

(4) E. Lieber, R. Sherman, R. A. Henry and J. Cohen, *ibid.*, **73**, 2327 (1951).

(5) K. A. Hoffman, H. Hock and R. Roth, *Ann.*, **380**, 135 (1911).

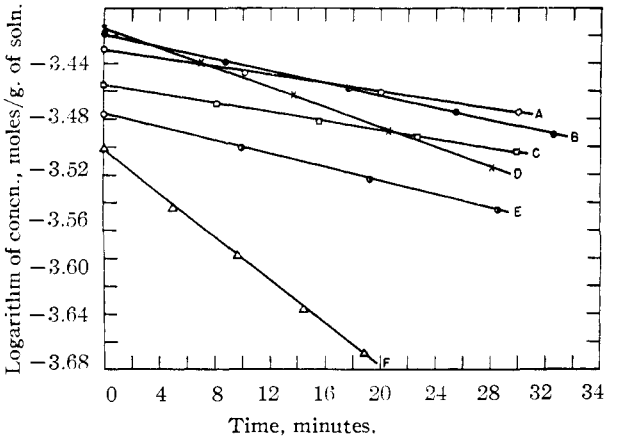


Fig. 1.—Rates of isomerization of substituted 5-aminotetrazoles at 137°: A, 1-(4-anisyl)-5-aminotetrazole; B, 1-(4-tolyl)-5-aminotetrazole; C, 5-(phenylamino)-tetrazole; D, 1-phenyl-5-aminotetrazole; E, 5-(4-anisylamino)-tetrazole; F, 1-(4-chlorophenyl)-5-aminotetrazole.

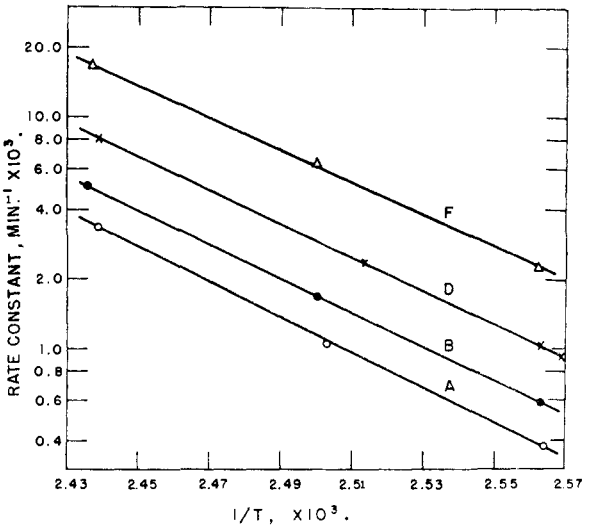


Fig. 2.—Effect of temperature on the rates of isomerization of substituted 5-aminotetrazoles.

tion were made similarly except that the precooled solutions consisting of 50 ml. of 0.0418 *N* nitroguanyl azide solution, 25 ml. of ethanol and 20 ml. of distilled water were adjusted to *ca.* *p*H 8 by the addition of 5 ml. of cold 0.0418 *N* sodium hydroxide solution.

The amount of standard sodium hydroxide solution required to maintain a constant *p*H during the reaction as a function of time can be related to the rate of decrease in the concentration of guanyl or nitroguanyl azides. Since the reaction is essentially irreversible, data for the first half of the cyclization could be used in several cases; the cyclization obeys the first order rate law since a straight line relationship is obtained in plots of log *c* *vs.* *t*. The specific rate constants were calculated from the logarithms of the concentrations *versus* time data using the method of least squares. The results are summarized in Table II.

TABLE II

RATES OF CYCLIZATION OF GUANYL AZIDES

$$RNHC(NH)N_3 \xrightarrow{k} RNHC\begin{matrix}N{-}N\\ \|\\ N{-}N\\ H\end{matrix}$$

R	*p*H	Temp., °K.	k, min.$^{-1}$ × 10²	Energy of activation, cal./mole
H	8.8–9.3	263.6	9.19	
		266.8	12.64	
		268.0	16.81	
		268.9	17.14	
		272.0	25.65	
		273.9	30.91	
		274.2	35.08	17,780
NO_2	7.9–8.2	266.6	5.73	
		269.4	9.53	
		270.1	10.71	
		271.5	12.14	
		273.9	16.97	21,240

Attempts to prepare phenylguanyl azide for a kinetic study of its cyclization to 1-phenyl-5-aminotetrazole were not successful. When 1-phenyl-3-aminoguanidinium nitrate was diazotized in 1 *N* nitric acid, 1-phenyl-5-aminotetrazole invariably was isolated.

Determination of Equilibrium Constants.—These constants were determined in the same apparatus used for the isomerization studies. Weighed samples (0.5–1.0 g.) of the substituted aminotetrazole were allowed to equilibrate in 10 ml. of ethylene glycol at various temperatures. This frequently required several days at the lower temperatures. When the heating was completed, the solution was cooled rapidly to freeze the equilibrium, diluted with neutral 95% ethanol and titrated with standard sodium hydroxide solution to the phenolphthalein end-point. After a small correction had been applied to this titer for the original acidity of the ethylene glycol, the amount of 5-substituted aminotetrazole was calculated. The equilibrium constant was the ratio of 5-substituted aminotetrazole to 1-substituted-5-aminotetrazole. Heats of reaction were calculated from the logarithms of the equilibrium constants *versus* the reciprocals of the absolute temperature using the method of least squares. These results are summarized in Table III.

TABLE III

EFFECT OF TEMPERATURE ON EQUILIBRIUM CONSTANTS

$$H_2NC\begin{matrix}N{-}N\\ \|\\ N{-}N\\ R\end{matrix} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} RHNC\begin{matrix}N{-}N\\ \|\\ N{-}N\\ H\end{matrix}$$

A B

R	Temp., °K.	$K_{eq} = \frac{k_1}{k_2} = \frac{B}{A}$	Heat of reaction, cal./mole
CH_3	426.0	0.0377	
	468.5	0.0470	+2060
C_2H_5	410.0	0.0488	
	425.9	0.0528	
	468.8	0.0604	+1350
C_6H_5	390.2	2.11, 2.13	
	410.1	1.87	
	410.6	1.94	
	410.7	1.85	
	426.1	1.69	
	467.2	1.32	−2230
4-$CH_3OC_6H_4$	410.0	0.589	
	410.2	0.585	
	427.1	0.573	
	467.0	0.526	− 740
4-$CH_3C_6H_4$	410.0	0.975	
	427.0	0.887	
	467.2	0.749	
	468.6	0.752	−1700
4-ClC_6H_4	390.0	6.47	
	410.3	4.96	
	427.1	3.73	
	467.2	2.62	−4290
3-$CH_3C_6H_4$	410.4	1.61	
	467.2	1.02	−1850

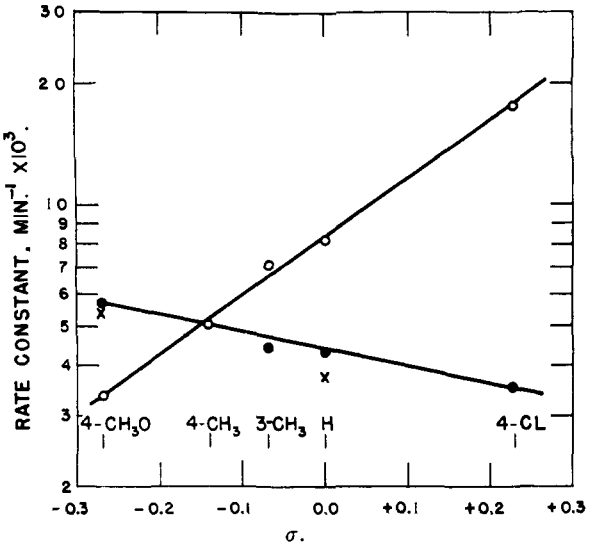


Fig. 3.—Correlation between the rates of isomerization at 137° with Hammett's sigma values for groups: O, 1-substituted aryl-5-aminotetrazoles; experimentally determined rates (k_1); ●, 5-(substituted aryl)-aminotetrazoles; calculated from experimentally determined equilibrium constants and k_1: ($k_2 = k_1/K_1$); ×, 5-(substituted aryl)-aminotetrazoles; experimentally determined rates (k_2).

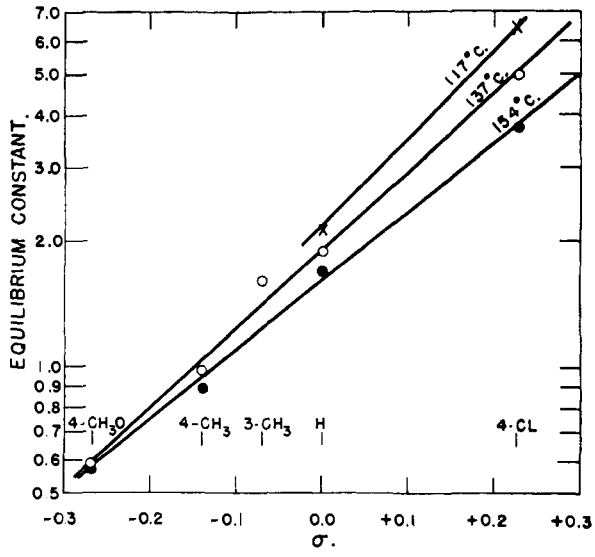


Fig. 4.—Correlation between equilibrium constants and Hammett's sigma values for groups.

Decomposition of 1-Phenyl-5-aminotetrazole in Basic Medium.—A solution of 10.00 g. (0.0620 mole) of 1-phenyl-5-aminotetrazole in 200 ml. of 1 *N* sodium hydroxide was refluxed for 61.5 hours in a system which was protected from atmospheric carbon dioxide and which permitted the collection of evolved gases. Ammonia was absorbed in a saturated solution of boric acid and determined by titration. The aniline produced in the decomposition was removed from the reaction mixture by steam distillation and converted to benzanilide, which was washed, dried and weighed. An aliquot of the remaining alkaline mother liquor was analyzed for carbonate and azide ions by acidifying with an excess of dilute sulfuric acid, distilling and collecting the evolved carbon dioxide and hydrazoic acid in a known volume of 1.1962 *N* barium hydroxide solution. The precipitate of barium carbonate was removed by filtration, washed with cold water, dried at 110° and weighed. The filtrate and washings from the carbonate determination were then back titrated to the phenolphthalein end-point with standard acid to determine the total base neutralized. The equivalents of barium hydroxide neutralized minus the equivalents of barium carbonate obtained corresponded to the equivalents of azide ion in the aliquot. The results expressed in terms, percentage of theory, are as follows: aniline, 83.3%; ammonia, 73.5%; carbonate, 67.6, 66.6, 72.7%; azide, 83.9, 82.6, 81.9%. The azide ion was qualitatively confirmed by a test with ferric ion and further confirmed by a polarographic oxidation study. The low and variable carbonate determinations are probably due to an inefficient absorption system.

Sixteen hours refluxing in a 0.2 *N* sodium hydroxide solution also resulted in extensive hydrolysis of 1-phenyl-5-aminotetrazole.

An attempt to decompose sodium 5-anilinotetrazole in a refluxing 0.1 *N* solution of sodium hydroxide was not successful. No ammonia or aniline was produced and the 5-anilinotetrazole was recovered.

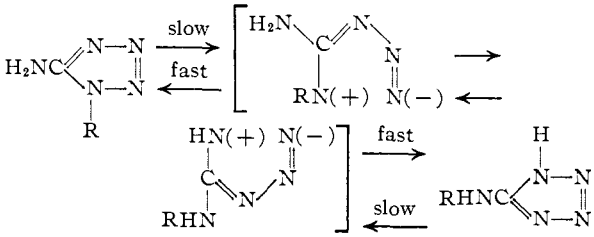
Influence of Solvent and *p*H on Isomerization.—The rates of isomerization of 5-methylaminotetrazole in water at 97.4 ± 0.20° (*ca.* 1.4% × 10^{-3} per minute) and of 1-methyl-5-aminotetrazole in a 0.2 *N* solution of sodium hydroxide at 98° (0.17% × 10^{-3} per minute) are in reasonable agreement with the expected values obtained by extrapolating the data for 5-ethylamino- and 1-ethyl-5-aminotetrazoles in ethylene glycol to lower temperatures. Because the rates of isomerization are so slow, the changes in concentration are very small and subject to considerable experimental error. In contrast to the behavior of 1-phenyl-5-aminotetrazole in a refluxing 1 *N* solution of sodium hydroxide, the 1-methyl compound undergoes only a negligible amount of hydrolytic decomposition during 86 hours at 98° in the 0.2 *N* base solution.

Neither the rate of isomerization of 1-methyl-5-aminotetrazole nor the position of equilibrium appears to be markedly different when this compound is refluxed in pyridine ($k = 0.46 \times 10^{-5}$ min.$^{-1}$ and $K_{eq} = 0.0475$).

Discussion

The isomerization of substituted 5-aminotetrazoles follows the first-order rate law since a straight line relationship is obtained in a plot of log *c* against time for the examples studied (Fig. 1). Inspection of the experimental data reveals several interesting correlations. Figures 3 and 4 show the correlations between Hammett's sigma values for groups[6] and the logarithms of the rates of isomerization, and the logarithms of the equilibrium constants for the aryl aminotetrazoles.

The mechanism previously proposed for this isomerization involved the opening of the tetrazole ring to an activated guanyl azide which, after suitable charge distribution, reclosed in either of two directions to form the equilibrium mixture of substituted 5-aminotetrazoles.[2]

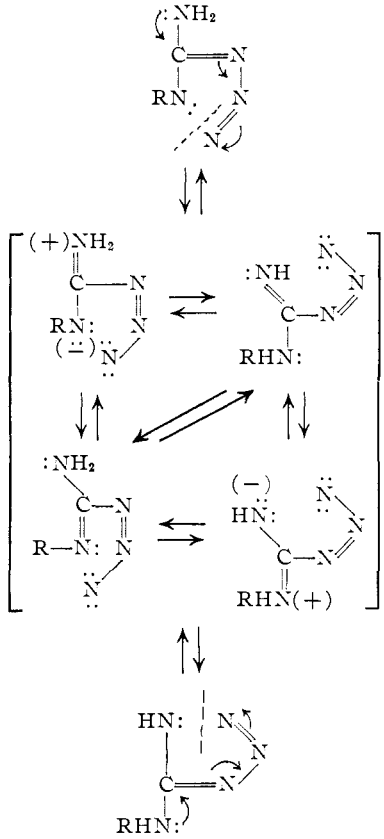


This mechanism adequately accounted for the attainment of equilibrium and for the ratio of products obtained. On the basis of this mechanism, however, one would predict that the rate of the forward reaction would be decreased by electronegative groups in the 1-position, since the heterol-

(6) Since these isomerizations were made in ethylene glycol, a sigma of −0.14 is used for the 4-CH$_3$ group (H. Kloosterziel and H. J. Backer, THIS JOURNAL, **74**, 5806 (1952)).

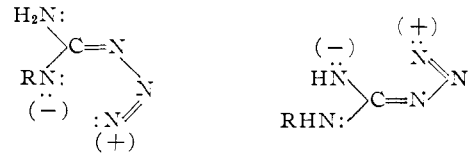
ysis of the bond in the indicated manner would be opposed by the inductive effect of the electronegative substituent. Experimentally, the rate of the forward reaction was found to increase with increasing electronegativity of a 1-substituent, and the rate of the reverse reaction to decrease with increasing electronegativity of a substituent on the 5-amino group (Fig. 3). Consequently, the heterolysis of the nitrogen–nitrogen bond in the ring must occur so as to leave a negative charge in the guanyl azide intermediate on the nitrogen atom originally in the 1-position of the tetrazole ring.

One possible mechanism, consistent with the known properties of substituted 5-aminotetrazoles, is dependent on the shift of electrons from the 5-amino group into the ring. This shift which facilitates the heterolysis of the nitrogen–nitrogen bond is enhanced by either electronegative 1-substituents or electropositive substituents on the 5-amino nitrogen. The rate of isomerization will be increased in proportion to the degree of enhancement. This mechanism is depicted simply as



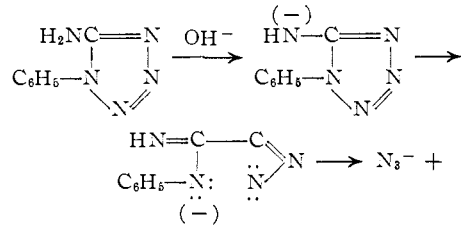
Numerous other tautomeric and resonance structures, including those with the normal, linear azido group, can be written for the intermediate guanyl azide. As a consequence, other routes for the isomerization also can be written.[7] In each, however, the initial transfer of electrons from the 5-amino group into the ring is considered to be a necessary step. The proton shift has been represented as occurring in this intermediate stage after ring opening; this proton migration could equally well occur simultaneously with either the ring opening or closure, or could occur after ring closure.

In order to satisfy the spacial requirement necessary at the moment of ring opening or closing, the azido group in the intermediate must be in the "*cis*" or "boat" form. The terminal nitrogen of the azido group is then within bonding distance of the imino nitrogen. In addition, the azido group must at some stage be free to rotate about the C–N bond if the rearrangement is to occur. Structures such as



although meeting the spacial requirement, would not permit rotation of the azido group.

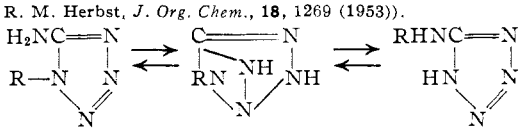
Indirect evidence that the high temperature decomposition reactions of substituted tetrazoles might involve a guanyl azide intermediate was presented previously.[8] More direct evidence for the formation of this type of intermediate has now been obtained. Attempts to measure the rate of isomerization of 1-phenyl-5-aminotetrazole at 98–100° in a 1 *N* solution of sodium hydroxide revealed a rapid decomposition of the starting tetrazole. Aniline, ammonia, carbonate ion and azide ion were formed. These products would be expected from the basic hydrolysis of phenylguanyl azide; this result is similar to that observed by Thiele[9] for the decomposition of guanyl azide in strong base. The rapid decomposition could be due to the removal of a proton from the 5-amino group of 1-phenyl-5-aminotetrazole by hydroxide ion. The resulting negatively charged tetrazolium ion would be expected to undergo a rapid heterolysis to the negatively charged guanyl azide which could stabilize itself by ejecting an azide ion. The remaining phenylcarbodiimide would hydrolyze in the indicated manner.



$$HN{=}C{=}NC_6H_5 \xrightarrow[2OH^-]{H_2O} NH_3 + CO_3^{--} + C_6H_5NH_2.$$

Since 5-anilinotetrazole is not readily hydrolyzed

(7) An alternative mechanism which involves a bicyclic intermediate for the isomerization also has been proposed (W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1269 (1953)).

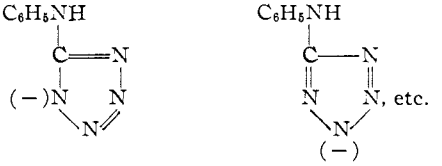


This hypothesis does not adequately account for the influence of R on either the position of equilibrium or the relative rate of isomerization. The high degree of ring strain required by this type of intermediate would make its formation very unlikely.

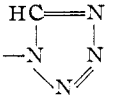
(8) E. Lieber, R. A. Henry and W. G. Finnegan, THIS JOURNAL, **75**, 2023 (1953).

(9) J. Thiele, *Ann.*, **270**, 1 (1892); German Patent 66,806 (1891).

in strong base at 100°, there must be stabilization of the anion through resonance.



There is considerable supporting evidence that the tetrazole ring is electronegative and withdraws electrons from the 5-amino group in substituted 5-aminotetrazoles. For example, 1-alkyl- and 1-aryl-5-aminotetrazoles are exceedingly weak bases[10] which form easily hydrolyzed salts with mineral acids. Increasing electronegativity of the 1-substituent decreases the basicity of the compound. 5-Aminotetrazole and 5-substituted aminotetrazoles are acids comparable to acetic acid in strength[2,11] and the relative acidity of the latter increases with increasing electronegativity of the substituent.[2] The nitration of 5-phenyltetrazole yields principally 5-(3-nitrophenyl)-tetrazole.[12] Unpublished studies by C. J. Thelen[13] have shown that the 1-tetrazolyl group



is about as electronegative as an acetyl group.[14] Furthermore, the alkylation of 1-alkyl-5-aminotetrazoles[15,16] with dimethyl sulfate or benzyl chloride occurs almost exclusively on ring nitrogen atoms, rather than on the 5-amino nitrogen. The most probable electronic structures of 1-substituted-5-aminotetrazoles and 5-substituted aminotetrazoles are apparently those in which a $+\delta$ charge exists on the 5-amino nitrogen and a $-\delta$ charge is placed in the ring. The mechanism of the isomerization very likely involves this shift of charge since the rates of isomerization correlate with the degree to which the polarization occurs.

The rate of isomerization of the 1-substituted-5-aminotetrazoles increases 600% in the series from 4-$CH_3OC_6H_4$ to 4-ClC_6H_4, whereas the rate for the isomerization of the isomeric 5-substituted aminotetrazoles decreases only 50% (Fig. 3). This effect can be explained by the position of the substituent with respect to the nitrogen–nitrogen bond that breaks. In the 1-substituted-5-aminotetrazoles, the group R is attached to one of the nitrogens involved in the bond and the ease of heterolysis of this bond will be directly influenced by the relative electronegativity of the substituent. The influence of the substituent on the cleavage of the bond would be less for the 5-substituted aminotetrazoles since its effect would have to be transmitted through two additional bonds and there are two equivalent bonds that can break in the symmetrical tetrazole ring.

The entropies of activation, calculated from the Eyring equation,[17] are low and constant within

$$k = \frac{k_b T}{h} e^{-\Delta H^{\ddagger}/RT} e^{\Delta S^{\ddagger}/R}$$

experimental error for the isomerizations of the 1-aryl-5-aminotetrazoles. This constancy within the series is in agreement with previous observations[18] and necessarily follows from the correlation of the reaction rate constants with Hammett's sigma values for groups. The frequency factors calculated from the Arrhenius equation, $k = Ae^{-\Delta H/RT}$ are about 10^{13} sec.$^{-1}$. These entropies of activation and the frequency factors are interpreted to mean that the isomerizations are not complicated by steric requirements or the necessity for oriented energetic collisions.

The heats of combustion of several of the isomeric pairs of substituted 5-aminotetrazoles have been measured.[19] The differences between the heats of combustion of 5-methylamino- and 1-methyl-5-aminotetrazoles and between 5-phenylamino- and 1-phenyl-5-aminotetrazoles are +2400 and −2550 cal., respectively. These values are comparable with the calculated heats of reaction (Table III).

The rates of cyclization of the guanyl azides (Table II) are very rapid compared to the rates of isomerization of the substituted 5-aminotetrazoles. The rate-determining step in this cyclization is probably the transformation of the normal guanyl azide tautomers, with linear azido groups, to activated guanyl azides with azido groups in the "*cis*" or "boat" form. On the other hand, the rate-determining step in the isomerization is probably the ring-opening to the intermediate, activated guanyl azide; again, as indicated previously, the azido group must also be in the "*cis*" or "boat" form. The assumption is logically made, therefore, that this intermediate, activated guanyl azide, is the same in both the isomerization and the cyclization reactions. On the basis of this assumption, the difference in activation energies for the two reactions should be the difference in energy content between the substituted tetrazole and its isomeric guanyl azide. Although a direct comparison of the present data suffers from the objection that the effects of *p*H and solvent on the rate of cyclization have not been thoroughly studied,[20]

(10) P. Rochlin, D. B. Murphy and S. Helf, THIS JOURNAL, **76**, 1451 (1954).

(11) F. B. Benson, *Chem. Revs.*, **41**, No. 1 (1947).

(12) R. A. Henry, unpublished results.

(13) This Laboratory.

(14) On the other hand, the nitration of 1-phenyl-5-aminotetrazole yields 1-(4-nitrophenyl)-5-aminotetrazole (W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.*, **18**, 1014 (1953)). This result indicates that the tetrazole ring is capable of donating electrons to a substituent in the 1-position, on demand, during attack by an electrophilic reagent.

(15) R. A. Henry, W. G. Finnegan and E. Lieber, THIS JOURNAL, **76**, 2894 (1954).

(16) R. M. Herbst and D. F. Percival, *J. Org. Chem.*, **19**, 439 (1954).

(17) S. Glasstone, K. D. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., New York, N. Y. 1941, p. 14.

(18) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 121.

(19) W. S. McEwan and M. Williams, this Laboratory, unpublished results.

(20) The cyclization of substituted guanyl azides will also occur in acidic and neutral solutions and in non-aqueous systems; examples are: the slow cyclization of nitroguanyl azide in the solid state at room temperature (R. A. Henry and W. G. Finnegan, unpublished results), its rapid cyclization in buffered aqueous acetic acid solution,[4] and in boiling chloroform the cyclization of phenylguanyl azide in 1 *N* nitric acid (Experimental); the conversion of guanyl azide hydrochloride to 5-acetaminotetrazole by heating in acetic anhydride; the cyclization of guanyl azide hydrochloride to 5-aminotetrazole either in dry pyridine or in sodium ethoxide–ethanol solution.

it is interesting to note that this difference in activation energies is roughly 13 to 16 kcal. per mole. This range of values agrees with the 15 kcal. per mole (approximately) calculated for the resonance energy of the tetrazole ring from heats of combustion data.[19]

From a consideration of the change of the equilibrium constants with temperature, one concludes that the thermodynamically more stable 5-arylaminotetrazole should predominate at low temperatures. This is further supported by the heats of combustion data for isomeric pairs of aryl substituted aminotetrazoles.[19] Experimentally, the rapid cyclization of an alkylguanyl azide in aqueous system results in the formation of the thermodynamically stable 1-alkyl-5-aminotetrazole. The rapid cyclization of an aryl-substituted guanyl azide in aqueous system, however, yields the less stable 1-aryl-5-aminotetrazole as the major product.[1,12] This phenomenon is similar to that encountered in examples of Diels–Alder reaction, where the unstable *endo* adduct predominates under rate controlled conditions and the thermodynamically more stable *exo* adduct predominates under equilibrium conditions.[21]

Acknowledgments.—The authors wish to express their thanks to LeMoyne Plischke for his assistance in the kinetic measurements and to Robert Boschan for valuable suggestions relative to this work.

CHINA LAKE, CALIF.

(21) R. B. Woodward and H. Baer, THIS JOURNAL, **166**, 645 (1944).

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

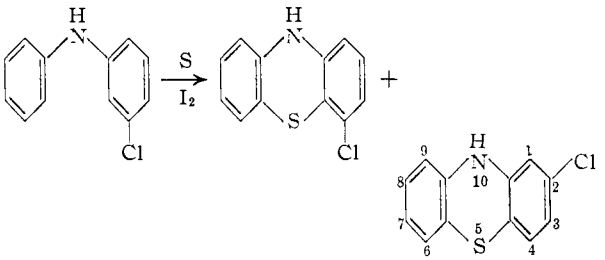
3-Chloro-10-dialkylaminoalkylphenothiazines

BY HARRY L. YALE

RECEIVED NOVEMBER 11, 1954

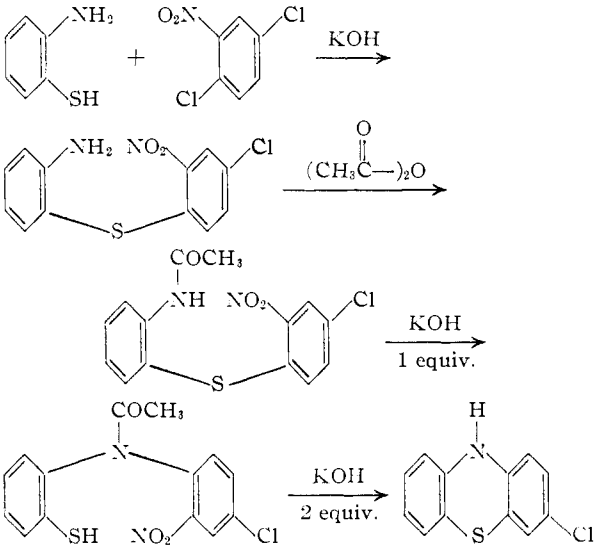
A number of 3-chloro-10-dialkylaminoalkylphenothiazines were prepared by condensing 3-chlorophenothiazine with a variety of dialkylaminoalkyl chlorides in refluxing toluene using sodamide as the condensing agent. These products are oils which can be distilled in high vacuum and form crystalline salts. The preparation of 3-chlorophenothiazine-5-oxide and 3-chlorophenothiazine-5,5-dioxide also is described; the latter compound was condensed with 2-chloro-N,N-dimethylpropylamine to give 3-chloro-10-(2-dimethylamino-1-methylethyl)-phenothiazine-5,5-dioxide.

In recent publications, Charpentier and his associates[1] and Viaud[2] have reported a series of 10-alkylaminoalkyl derivatives of 2- and 4-chlorophenothiazines. The isomeric chlorophenothiazines were obtained as a mixture by the cyclization with sulfur of 3-chlorodiphenylamine and subsequently separated by fractional crystallization.



We have for several years been interested in this class of compounds and wish to report a series of 3-chloro-10-dialkylaminoalkylphenothiazines. One of the compounds described in this paper, 3-chloro-10-(3-dimethylaminopropyl)-phenothiazine was mentioned by Viaud,[2] but no details of the synthesis or the physical properties of the base or its salts were reported.

The classic achievement of Evans and Smiles[3] in affording through the Smiles rearrangement a convenient synthesis of 3-chlorophenothiazine made available to us this nucleus free of any other isomer.



The condensations of 3-chlorophenothiazine with a variety of dialkylaminoalkyl chlorides were carried out in refluxing toluene using sodamide as the condensing agent. The 3-chloro-10-dialkylaminoalkylphenothiazines were obtained as oils which could be distilled in high vacuum without decomposition; they formed crystalline hydrochlorides and acid oxalates.

3-Chlorophenothiazine, by the usual procedures, gave 3-chlorophenothiazine-5-oxide and 3-chlorophenothiazine-5,5-dioxide. The latter compound was condensed with 2-chloro-N,N-dimethylpro-

(1) P. Charpentier, P. Gaillot, R. Jacob, J. Gaudechon and J. Buisson, *Compt. rend.*, **235**, 59 (1952); U. S. Patent 2,645,640 (July 14, 1953).

(2) P. Viaud, *J. Pharm. Pharmacol.*, **6**, 361 (1954).

(3) W. J. Evans and S. Smiles, *J. Chem. Soc.*, **181**, 1263 (1935). The limitations of this synthetic method were implied indirectly by these authors; more recently R. Baltzly, M. Harfenist and F. J. Webb, THIS JOURNAL, **68**, 2673 (1946), have reported two unsuccessful attempts to utilize this rearrangement in the synthesis of related phenothiazines.