781. *The Tautomerism of* 5-*Amino*-1-*aryl*-1 : 2 : 3-*triazoles.*

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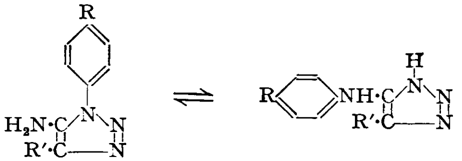
The rates of isomerisation of ethyl 5-amino-1-phenyl-1 : 2 : 3-triazole-4-carboxylate have been measured in ethyl alcohol at 70°. It is found that: (i) at low values of $[H^+]$ ($<10^{-4}$ mole/l.), rate of reaction $= k$[triazole]$[H^+]$; (ii) at all values of $[H^+]$ $>10^{-4}$ mole/l., rate of reaction $= k'$[triazole]; (iii) electron-attracting groups in the *para*-position of the 1-phenyl group increase the rate of the forward reaction and decrease that of the back reaction; electron-repelling substituents have the opposite effect. A mechanism is suggested that is consistent with these observations.

Arrhenius energies, *E*, and *PZ* factors are recorded for a number of 5-amino-1-aryl-1 : 2 : 3-triazoles in ethyl alcohol.

Dimroth (*Annalen*, 1908, **364**, 183) established that 5-amino-1-aryl-1 : 2 : 3-triazoles (I) exist in solution or in a melt in tautomeric equilibrium with 5-anilino-1 : 2 : 3-triazoles (II). He (*ibid.*, 1910, **377**, 127) made a cursory study of the tautomerism of ethyl 5-amino-1-phenyl-1 : 2 : 3-triazole-4-carboxylate in alcohol and in benzene at 60°, and found that there was a slow autocatalytic approach to equilibrium in the absence of added acid, but that in the presence of picric acid (only one concentration investigated) the reaction rate was increased, and a first-order rate law was followed. To elucidate the mechanism of the tautomerism, it seemed desirable to study the kinetics of the autocatalysis and of the apparent acid-catalysis in greater detail, and to determine the effect of substituents in the aryl group.

(I)



(II)

Experimental and Results

Reagents.—Ethyl alcohol was purified by distillation at atmospheric pressure, and had b. p. 78·0°. Picric acid was twice recrystallised from alcohol and obtained as yellow needles, m. p. 123°. The amino-triazoles were prepared according to the general method of Dimroth (*ibid.*, 1908, **364**, 183), recrystallised from water or alcohol, and dried at room temperature in a vacuum.

Preparation of 5-*Amino*-1-*aryl*-1 : 2 : 3-*triazole*-4-*carboxylic Esters. General method.*—A mixture of equivalent quantities of an aromatic azide (about 7 g.) and cyanoacetic ester, with sodium ethoxide (3·5 g.) and alcohol (30 ml.), was heated gently, and then kept at room temperature for about 3 hr. Water was added, and the solid triazole crystallised several times from alcohol. The properties of the compounds prepared in this way are recorded in Table 1.

TABLE 1. *5-Amino-1-aryl-1 : 2 : 3-triazole-4-carboxylic esters* (I; R′ = CO_2Et).

R		Me	NO_2 *	Br †	OMe	CO_2Et
M. p.		147·5 °	156° ‡	166 °	147°	166°
Yield (%)		52	63	81	72	57
Formula		$C_{12}H_{14}O_2N_4$	$C_{11}H_{11}O_4N_5$	$C_{11}H_{11}O_2N_4Br$	$C_{12}H_{14}O_3N_4$	$C_{14}H_{16}O_4N_4$
Found (%) :	C	58·6	47·8	—	55·0	55·3
	H	5·7	4·0	—	4·9	5·3
	N	23·0	25·6	17·5	21·8	18·3
Reqd. (%) :	C	58·4	47·7	—	55·0	55·3
	H	5·9	4·0	—	5·3	5·3
	N	22·8	25·3	17·6	21·4	18·4

* This compound is the acid isomer, ethyl 5-*p*-nitroanilino-1 : 2 : 3-triazole-4-carboxylate. The rate of isomerisation of the neutral isomer is too fast to measure. Crystallisation from alcohol results in complete conversion into the acid isomer. † Found : Br, 25·8. Required : Br, 25·3%.

‡ Yellow; the others are colourless; all are needles.

Method of Analysis.—Dimroth (*ibid.*, 1910, **377**, 211) showed that the acid isomer, ethyl 5-anilino-1 : 2 : 3-triazole-4-carboxylate, could be titrated with alcoholic potassium hydroxide by using phenolphthalien as indicator. This has been confirmed :

Triazole (g.)		0·2472	0·3938
0·0743N-KOH (ml.) :	Found	14·4	22·85
	Calc.	14·35	22·85

Kinetic Measurements.—Solutions of known amounts of the neutral triazole isomers in alcohol (about 4×10^{-2} mole/l.) in presence of known amounts of added acids (picric or perchloric) were kept at constant temperature. Equal portions were withdrawn at known times, and the quantity of acid isomer present was measured by titrating with standard alcoholic potassium hydroxide (titre value x ml. at time t sec.). The mixture was kept at constant temperature until equilibrium had been established, whereupon a further portion was withdrawn and titrated. This equilibrium value (E ml.) was checked by a further titration after several more hours. The sum of the first-order constants for the forward and the back reactions ($k_1 + k_2$) was obtained from the equation $(k_1 + k_2)t = 2{\cdot}303\,[\log_{10} E - \log_{10}(E - x)]$, by plotting $\log_{10}(E - x)$ against t.

Equilibrium Constants $K = C_{\text{acid}}/C_{\text{neutral}}$.—A known weight ($w$) of triazole dissolved in alcohol was kept for about 5 days at the appropriate temperature. The concentration of acid isomer present at equilibrium was determined by titration. Several determinations were made at each temperature. The equilibrium constant as computed involves the titre value (v) in the form $kv/(w - kv)$, where k is a constant; errors in v have the smallest effect on K when K is near unity. This is brought out by the figures quoted below. Very high or very low values of K are less consistent, as shown by the variations in the following typical results (I $\rightleftharpoons$ II; R′ = CO_2Et) for K (at 50°) for the followings R groups : OMe, 0·49, 0·49, 0·61; Me, 1·07, 1·04, 1·05; H, 3·1, 2·8, 2·8; CO_2Et, 62, 47.

Initial Autocatalysis.—Experiments carried out on ethyl 5-amino-1-phenyl-1 : 2 : 3-triazole-4-carboxylate at 70° without the addition of acids showed that the reaction was autocatalytic, but that the first-order rate constant ($k_1 + k_2$) finally attained a constant value (Table 2 and Figs. 1 and 2).

TABLE 2. *Autocatalysis at* 70·0°.

Ethyl 5-amino-1-phenyl-1 : 2 : 3-triazole-4-carboxylate ($4{\cdot}51 \times 10^{-2}$ mole/l.) in ethyl alcohol. 10·0 Ml. withdrawn for each titration.

Run 1 : 0·023N-KOH				Run 2 : 0·026N-KOH			
t (sec.)	Titre (x ml.)	t (sec.)	Titre (x ml.)	t (sec.)	Titre (x ml.)	t (sec.)	Titre (x ml.)
0	0·35	5,700	4·95	0	0·30	5100	3·40
600	0·40	6,600	6·10	600	0·35	5700	4·15
1200	0·60	7,800	7·60	1200	0·50	6300	4·90
1800	0·85	8,400	8·30	1800	0·55	6900	5·70
2400	1·20	9,000	8·95	2400	0·85	7500	6·45
3000	1·80	9,600	9·55	3000	1·25	8100	7·15
3900	2·85	10,200	10·10	3600	1·75	9300	8·35
4500	3·45	∞	17·20	4500	2·70	∞	15·95
5100	4·15						

Since the acid dissociation constant of the acidic isomer is not known accurately in alcohol at 70°, it is not possible to investigate directly the variation of reaction rate with increase of hydrogen-ion concentration during the reaction. However, in the following way it is possible to derive a quantity which is proportional to the average hydrogen-ion concentration over a short period of time $(t_2 - t_1)$ sec. If x_1 and x_2 are the titre values at times t_1 and t_2, and E is the equilibrium titre at t_∞, then

$$(k_1 + k_2) = \frac{1}{(t_2 - t_1)} \cdot \ln \frac{(E - x_1)}{(E - x_2)}$$

For the weak acid isomer TH, we have the dissociation :

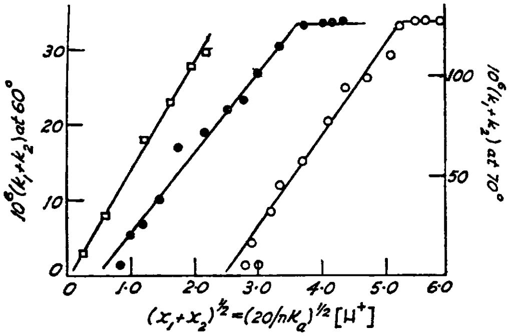
$$\begin{array}{cccc} \mathrm{TH} + \mathrm{EtOH} \rightleftharpoons & \mathrm{T}^- & + \mathrm{EtOH_2}^+ & \\ (A - a) & a & a & \text{mole/l.} \end{array}$$

where a will be small since the dissociation constant, K_a, of the weak acid will be even smaller in alcohol than in water. Whence,

$$K_a = a^2/(A - a), \textit{ i.e.}, [\mathrm{EtOH_2}^+]^2 = K_a(A - a) \quad . \quad . \quad . \quad . \quad (X)$$

The average titre over the short period $(t_2 - t_1)$ is $(x_1 + x_2)/2$, and since a is small, $(A - a) \approx A = n(x_1 + x_2)/20$, if 10·0 ml. are withdrawn and titrated against nN-KOH. Substitution into (X) yields $[\mathrm{EtOH_2}^+] = \sqrt{nK_a/20(x_1 + x_2)}$. A plot of $(k_1 + k_2)$ against $\sqrt{(x_1 + x_2)}$ is therefore equivalent to a plot of $(k_1 + k_2)$ against $[\mathrm{EtOH_2}^+]$. These plots are shown in Fig. 1, and show that the initial rate is proportional to the concentration of hydrogen ion. It will be noticed that Dimroth's results (*ibid.*, p. 160) at the lower temperature of 60° have apparently not reached the " threshold " at which the rate becomes independent of the hydrogen-ion concentration.

FIG. 1.

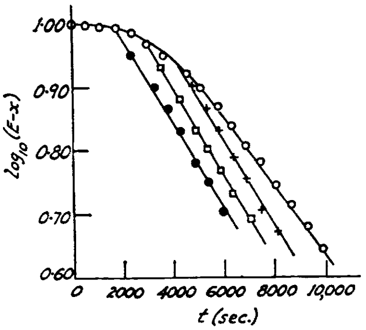


□ *From Dimroth's results at* 60° (*Annalen*, 1910, **377**, 160).

● *Run* 1 *of Table* 2.

○ *Run* 2 *of Table* 2 ($\sqrt{(x_1 + x_2)}$ *axis moved* 2·0 *units*).

FIG. 2.



○ *Autocatalytic run.*
Acid added after : ● 1800 *sec.*; □ 3000 *sec.*; + 4200 *sec.*

Final Rate Independent of Acid Concentration.—The attainment of a constant rate after a certain minimal hydrogen-ion concentration has been reached, which is shown by the limiting value of $(k_1 + k_2)$ reached by our lines in Fig. 1, has also been confirmed by addition of picric acid at various times to autocatalytic runs. The results are shown in Fig. 2.

The rate of isomerisation of ethyl 5-amino-1-phenyl-1 : 2 : 3-triazole-4-carboxylate in presence of various concentrations of acids above the initial minimum of $<10^{-4}$ mole/l., has been found to be independent of the nature and concentration of the added acid. The absence of a salt effect has also been demonstrated for this acid-independent part of the reaction (Table 3).

Substituted 5-*Amino*-1-*phenyltriazoles.*—The rate constants for isomerisation $(k_1 + k_2)$, and the equilibrium constants $(K = k_1/k_2)$ have been measured for some *para*-substituted 5-amino-1-phenyltriazoles in alcohol in the presence of perchloric acid; from these, separate values of k_1 and k_2 were calculated (Tables 4 and 5). Good linear plots are obtained when Hammett's equation is applied to the results recorded in Table 4.

TABLE 3. *Effect of added acid.*

Ethyl 5-amino-1-phenyl-1 : 2 : 3-triazole-4-carboxylate in ethyl alcohol at 70·0°.

Picric acid				*Perchloric acid*		
Mole/l.	$10^4 (k_1 + k_2)$ (sec.$^{-1}$)	Mole/l.	$10^4 (k_1 + k_2)$ (sec.$^{-1}$)	Mole/l.	LiBr (mole/l.)	$10^4 (k_1 + k_2)$
0·00	1·27 (final rate)	0·00500	1·41	0·00290	—	1·43
0·000137	1·31	0·0113	1·33	0·00116	—	1·38
0·000411	1·43	0·0188	1·36	0·00116	0·207	1·42
0·00100	1·33	0·0376	1·41	0·00232	0·423	1·36
0·00200	1·30					

TABLE 4. para-*Substituted 5-amino-1-phenyltriazoles* (I; $R' = CO_2Et$).

$(k_1 + k_2) = PZ \,.\, e^{-E/\boldsymbol{R}T}$

R	$10^4 (k_1 + k_2)$ (sec.$^{-1}$) 50°	60°	70°	E (cal./mole)	$\log_{10} PZ$
OMe	0·098	0·290	0·85	22,800	16·5
Me	0·110	0·370	1·00	22,600	16·5
H	0·150	0·460	1·36	22,500	16·5
Br	0·220	0·710	1·90	22,300	16·5
CO_2Et	0·580	1·90	5·30	22,100	16·8

TABLE 5. *Rates of forward and back reactions.*

para-Substituted 5-amino-1-phenyltriazoles (I; $R' = CO_2Et$).

	50°			60°		
R	K	$10^6 k_1$	$10^6 k_2$	K	$10^6 k_1$	$10^6 k_2$
OMe	0·51	3·3	6·5	0·67	11·5	17·5
Me	1·06	5·7	5·4	1·59	22·7	14·3
H	2·90	11·2	3·8	4·55	37·5	8·5
Br	14	21	1·5	26	69	2·6
CO_2Et	55	57	1·0	83	188	2·3

DISCUSSION

A satisfactory mechanism for the tautomerism must explain the following facts :

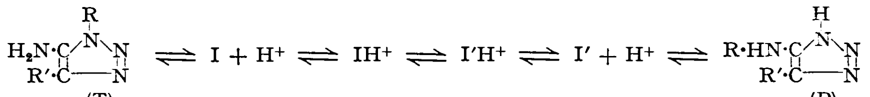
(1) At extremely low values of $[H^+]$ (less than 10^{-4} mole/l.),

rate of reaction $= k[\text{triazole}][H^+]$ . . . . (i)

(2) At all values of $[H^+]$ greater than 10^{-4} mole/l., rate of reaction $= k'[\text{triazole}]$. (ii)

(3) Electron-attracting groups in the *para*-position of the 1-phenyl group increase the rate of the forward reaction and decrease that of the back reaction; electron-repelling substituents have the opposite effect.

Two general mechanisms can be proposed for the reversible isomerism of amino-triazoles : (1) those which involve isomerisation, reaction with a solvated proton, and further isomerisation :



(T) (P)

in which I and I′ are unspecified isomers : and (2) those which involve initial reaction of the triazole with a proton, and rearrangement of the protonated molecule to give the isomer :

$$T + H^+ \rightleftharpoons IH^+ \rightleftharpoons I'H^+ \rightleftharpoons H^+ + P$$

An immediate distinction between those two general mechanisms can be made on the basis of our experimental findings. Application of Christiansen's method (*Z. physikal. Chem.*, 1935, **28**, *B*, 303; 1936, **33**, *B*, 145; 1937, **37**, *B*, 374) for consecutive reactions yields the following different rate equations for the two mechanisms :

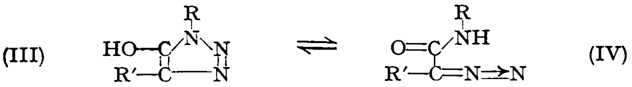
$$\text{Rate of reaction} = \frac{k[H^+]([T] + [P])}{1 + k'[H^+]} \quad . \; . \; . \; . \; . \; . \quad (1)$$

or

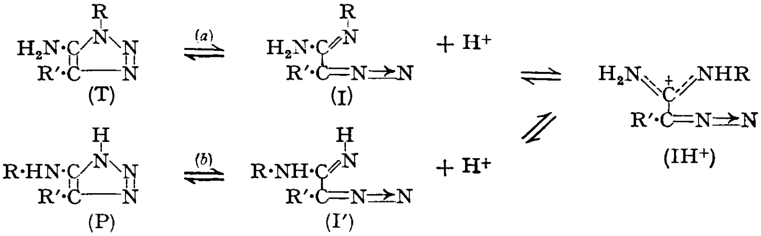
$$\text{Rate of reaction} = k''[H^+]([T] + [P]) \quad . \; . \; . \; . \; . \; . \quad (2)$$

Since we have found (Figs. 1 and 2; Table 2) that the rate is directly proportional to the hydrogen-ion concentration at very low values [equation (i)], but that above a very small minimal concentration no further increase of rate occurs with addition of hydrogen ion [equation (ii)], mechanism (2) is quite inadequate. Furthermore, though, under certain conditions, a mechanism of the type (2) can cause the velocity to increase less rapidly than the hydrogen-ion concentration (Bell, " Acid-Base Catalysis," Oxford Univ. Press, 1941, p. 125), this would be expected to occur at very high hydrogen-ion concentrations (*op. cit.*, p. 126), not, as in this reaction, at remarkably low hydrogen-ion concentrations. Equation (1) predicts the general shape of curve which we have found (Fig. 1), with a rounding off near the threshold hydrogen-ion concentration, which our measurements are presumably not accurate enough to detect. The value of the critical hydrogen-ion concentration for the change from a rate governed by equation (i) to one governed by (ii) cannot at present be predicted, but will depend upon the relative values of k and k' in (1), which reduces to (i) and (ii) for small and large hydrogen-ion concentrations respectively. For the amino-triazole tautomerism the critical hydrogen-ion concentration is exceedingly small.

The structures of the intermediate isomers I and I′ in mechanism (1) cannot be determined directly from our kinetic results, but they can be inferred with reasonable accuracy, since the analogous tautomerism of 1-aryl-5-hydroxy-1 : 2 : 3-triazoles (III) (Dimroth, *Annalen*, 1904, **335**, 1; 1905, **338**, 143; 1910, **373**, 336; 1913, **399**, 91; Brown and Hammick, *J.*, 1947, 1384) is known to involve open-chain aliphatic diazo-compounds (IV).

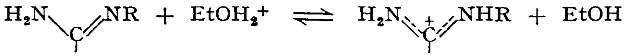


The amino-triazole tautomerism could occur through similar open-chain intermediates, thus avoiding the necessity to postulate migration of a phenyl group from nitrogen to nitrogen. Incorporation of this idea into the mechanism (1) derived from our results yields the following scheme :



An interesting feature of this mechanism is that a single protonated intermediate (IH^+), an amidine cation, is formed from I and I′, so that IH^+ and $I'H^+$ of mechanism (1) are resonating canonical forms of a single structure. Our experimental results on the effect of substituents in R refer to the reaction in presence of excess of acid, when (*a*) is the rate-determining step of the forward reaction, production of the acid isomer, and (*b*) that of the reverse reaction, production of the neutral isomer. Electron-attracting groups in the *para*-position of the phenyl group of the neutral isomers are expected to decrease the resonance energy of the triazole ring, and thus to facilitate formation of the open-chain isomer with a resultant increase of reaction rate. Electron-repelling groups will have the opposite effect. Our experimental results (Table 5) are therefore consistent with the proposed mechanism. The effect of substituents on the rate of the back reaction is not so easily inferred, since, in the acidic isomer, the substituted nitrogen atom is not a part of the triazole ring. The only safe conclusion is that the effect of substituents on the rate-determining step (*b*) will be less than on the step (*a*). The direction of the effect is indeterminate from electronic considerations (cf. Table 5).

The most interesting feature of the kinetics and of the proposed mechanism of the reaction is the dependence of the rate on hydrogen-ion concentration at extremely low values, and the postulation under such conditions of a rate-determining step involving a reaction which might normally be expected to be almost instantaneous, *viz.*, the reaction of an amidine with a solvated proton:



$$\mathrm{H_2N{-}C({=}NR){-}} + \mathrm{EtOH_2^+} \rightleftharpoons \mathrm{H_2N{-}\overset{+}{C}({=}NHR){-}} + \mathrm{EtOH}$$

A similar effect has recently been reported by Bell and Spiro (*J.*, 1953, 429) for the base-catalysed bromination of ethyl malonate in which the velocity varies with the bromine concentration at low values, and is determined by the rates of reaction of the enol and of the anion with bromine. A comparison of the equilibrium concentrations of the labile intermediates involved is instructuve. For our autocatalytic runs (Fig. 1) at low [H$^+$] we have:

$$\mathrm{T} \rightleftharpoons \mathrm{I} + \mathrm{H}^+ \xrightarrow{k} \text{etc.}$$

$$\text{Rate of reaction} = k_{\text{obs.}}[\mathrm{T}] = k[\mathrm{I}][\mathrm{H}^+]$$

Consider [I] when [T] = 1:

$$k_{\text{obs.}} = k[\mathrm{I}][\mathrm{H}^+] = k[\mathrm{I}]\sqrt{nK_a/20}\,.\,\sqrt{(x_1 + x_2)} \text{ (see p. 3822)}$$

Hence the slope of the lines in Fig. 1 is equal to $k[\mathrm{I}]\sqrt{nK_a/20}$. K_a in alcohol can be estimated to be about 10^{-15} since the corresponding values for pyrrole and phenol in water are $10^{-16 \cdot 5}$ and 10^{-10}. Hence k[I] can be calculated. The neutralisation of an amidine being assumed to require negligible activation energy, $k \approx 3 \times 10^{11}$ l. mole^{-1} sec.$^{-1}$, the gas collision number; whence the following values are calculated for [I] from Fig. 1: 10^{-7} mole/l. at 70° and 2×10^{-8} mole/l. at 60°. From values quoted by Bell and Spiro (*loc. cit.*) concentrations of the same order, *viz.*, 10^{-5} and 2×10^{-7} mole/l., are calculated for the enol and the anion of ethyl malonate in equilibrium with 1 mole/l. under their experimental conditions.

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