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Studies on the Reaction Mechanisms in Heterocyclic Compounds. III.[1] Chemical and Kinetic Studies on the Reaction of 2-Hydrazino-3-phenylquinoxaline with Carbonyl Compounds. (3)

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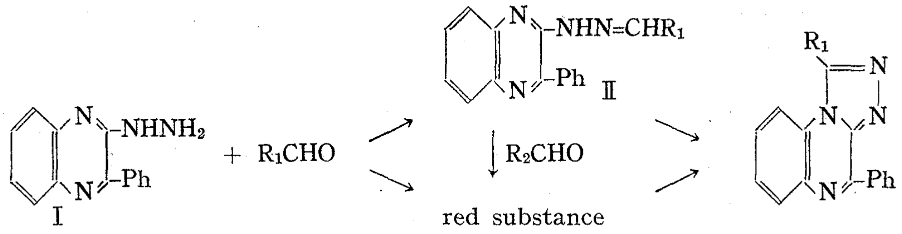
A red substance was obtained by the reaction of 2-hydrazino-3-phenylquinoxaline with excess aliphatic aldehyde. The structure of this substance was studied and the reaction rate was found to follow second-order kinetics. From these results, a mechanism was proposed and possible explanations for the red color were discussed.

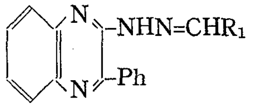
Addition of an aliphatic aldehyde to 2-hydrazino-3-phenylquinoxaline (I) gives a hydrazone compound (II) whose pyrolysis results in dehydrogenative cyclization to *s*-triazoloquinoxaline. In this reaction, addition of an equimolar amount of the aldehyde to I gives a yellow hydrazone (II) while a slight excess of the aldehyde gives a labile red substance.

In the present series of work, structure and formation mechanism of this red substance were examined.



This red substance is also obtained on the addition of the aldehyde to II and, when allowed to stand for a long time in a solvent, it undergoes decomposition to the *s*-triazolo compound.

Table I. Reaction of 2-Hydrazino-3-phenylquinoxaline with Aldehydes

									Red substance			
			Analysis (%)							Analysis (%)		
R_1	mp (°C)	Formula	Calcd.			Found			mp (°C)	Found		
			C	H	N	C	H	N		C	H	N
C_2H_5	124	$C_{17}H_{16}N_4$	73.89	5.84	20.84	73.28	5.81	20.41	127	75.33	5.99	18.64
C_3H_7	93	$C_{18}H_{18}N_4$	74.45	6.25	19.30	74.62	6.41	19.50	125	76.14	6.86	16.96
C_4H_9	86	$C_{19}H_{20}N_4$	74.97	6.62	18.41	74.51	6.52	18.72				
$(CH_3)_2$>$CHCH_2$	98	$C_{19}H_{20}N_4$	74.97	6.62	18.41	74.85	6.32	18.82				
$(CH_3)_2$>CH	145	$C_{18}H_{18}N_4$	74.45	6.25	19.30	74.35	6.35	19.40				

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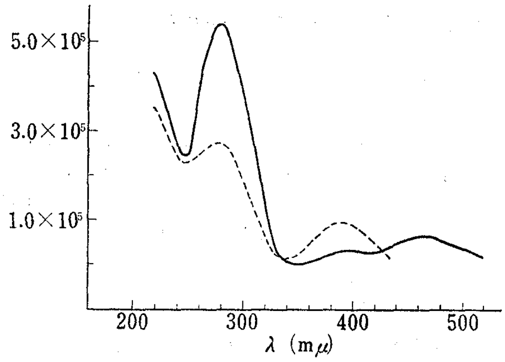
[1] Part II: S. Tagami, K. Sasayama, and D. Shiho, *Yakugaku Zasshi*, **86**, 622 (1966).

[2] Location: *Gofuku, Toyama.*

These facts suggest that addition of an excess aldehyde to I results in the formation of II which further reacts with excess aldehyde to form the red substance. The infrared spectrum of I in carbon tetrachloride exhibits two absorptions for –NH at 3450 and 3350 cm^{-1}, which disappear in the spectrum of the red substance. Consequently, the red substance is considered to have been formed by the reaction of –NH in II and –CHO in the aldehyde. Elemental analyses of II and of the red substance are given in Table I. Molecular weight of the red substance ($R_1=C_2H_5$), measured by the vapor pressure osmometer, gave the value of 597.27 close to a twofold value of the molecular weight of II ($R_1=C_2H_5$), 276.33.



Compound	λ_{max} (mμ)	ε_{max}
Hydrazone		
($R_1=C_2H_5$)	278	27750
- - - (in 95% EtOH)	386	10900
Red substance		
($R_1=R_2=C_2H_5$)	284	54000
——(in 95% EtOH)	465	6070

Fig. 1. Ultraviolet Absorption Spectra of Hydrazone and Red Substance

The ultraviolet spectra shown in Fig. 1 indicate that the absorptions in the region of 240—320 mμ are very similar in the hydrazone and the red substance. Maximum absorbance of II shows ε_{max} 27750(278 mμ) and that of the red substance is ε_{max} 54000(284 mμ), the absorption intensity of the latter being about twice that of II.

These data suggest that the structure of the red substance is possibly represented by IV. If $R_1=R_2=C_2H_5$, the theoretical values of the elemental analysis of IV would be C, 74.97; H, 6.12 N, 18.97%, mol. wt., 592.72, which agree well with the experimental values of C, 75.33: H, 5.99; N, 18.64%; mol. wt., 597. 27. In the ultraviolet spectrum of the red substance, the absorption at 240—320 mμ shows a twofold intensity and this can be understood from the IV structure. A problem still remains as to the origin of the difference in the absorptions in the visible region.

In order to confirm the structure of this red substance, further examinations were made on the reaction mechanism of its formation. If the red substance forms by the reaction between –NH and R_2CHO, there should be many examples of this reaction mechanism. If the same mechanism is followed, their activation energy and entropy should be similar. In order to

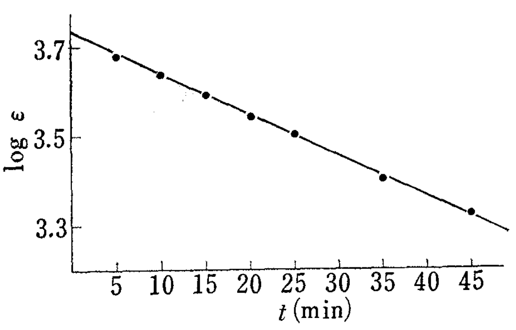


Fig. 2. Red Substance Formation

1×10^{-4} M butyraldehyde(3-phenyl-2-quinoxalinyl)hydrazone
6.0×10^{-3} M propionaldehyde
temp. 40°

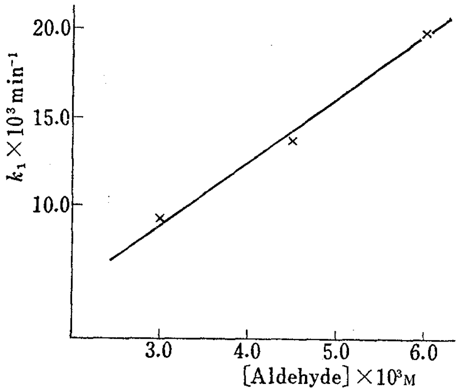


Fig. 3. Plots of the Rate Constants of Butyraldehyde(3-phenyl-2-quinoxalinyl)hydrazone *vs.* Propionaldehyde Concentrations

prove this point, the reaction rate was measured from the rate of the disappearance of the hydrazone by the use of the absorption at 386 mμ in the visible region of the ultraviolet spectrum shown in Fig. 1. If the amount of R_2CHO used is about 30 times that of the hydrazone, the reaction is measured as the pseudo-first-order kinetics. This result is given in Table II and in Fig. 2. By variation in the concentration of the aldehyde, as shown in Table III and Fig. 3, $k_2=k_{obs}/(A)$ is established, and this reaction is indicated as the second-order reaction.

Table II. Kinetic Results for the Reaction of R_1CHO-(3-Phenyl-2-quinoxalinyl)hydrazones with R_2CHO

R_1	R_2	Temp. (°C±0.1)	$k_1\times 10^3$ (min^{-1})	$E_{exp.}$ (kcal)	ΔS (e.u.)
C_2H_5	C_2H_5	30	6.25	4.48	−61.01
		40	7.76		
		50	9.74		
	C_3H_7	30	3.43	6.49	−58.01
		40	6.00		
		50	7.00		
	$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CHCH_2$	30	2.25	8.84	−51.72
		40	3.25		
		50	5.59		
C_3H_7	C_2H_5	30	16.16	8.72	−48.39
		40	22.11		
		50	39.76		
	C_3H_7	30	8.06	8.64	−51.27
		40	13.05		
		50	19.04		
	$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CHCH_2$	30	6.27	7.74	−53.80
		40	10.18		
		50	12.63		
	$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CH$	30	0.67	3.73	−70.94
		40	0.94		
		50	1.13		

Table III. Reaction of 1.0×10^{-4}M Butyraldehyde (3-Phenyl-2-quinoxalinyl)hydrazone with R_2CHO at 40°±0.1°

R_2	Aldehyde ($\times 10^3$M)	$k_1\times 10^3$ min^{-1}	k_2 liter/mole·min
C_2H_5	3.0	9.33	3.43
	4.5	13.53	
	6.0	19.81	
C_3H_7	3.0	1.21	2.27
	4.5	9.71	
	6.0	13.05	
$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CHCH_2$	3.0	0.99	0.89
	4.5	2.12	
	6.0	3.64	

Examination of relationship between log k_1 from Table II and Taft's σ^* value[3] showed that a linear relation is established, as shown in Fig. 4. Further, an isokinetic relationship[4] was found to be established between ΔE and ΔS, as shown in Fig. 5. Assumption of the reaction mechanism from these values indicates that the k_1 values decrease gradually with increase in electron donating nature from the alkyl group to the carbonyl–carbon in the aldehyde. Therefore, this reaction is a nucleophilic attack of the lone–pair electrons of the NH group in II on the carbonyl–carbon of the aldehyde, as seen in the reaction between amines and a carbonyl, to form an addition compound of the structure III. This fact was proved by the disapperance of the NH band in the infrared spectrum and from the k_1 values. Further, the dimeric structure of the red substance suggests that one more mole of II makes the nucleophilic attack on the addition compound (III) to form the red substance (IV). This fact may be understood from the example[5] that the formation of a hydrobenzamide from ammonia and aromatic aldehyde is considered to obey the following mechanism.

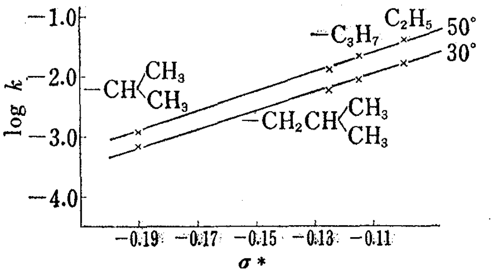


Fig. 4. Taft's σ^* Constants and Rate Plots for the Reaction of Butyraldehyde (3-Phenyl-2-quinoxalinyl)-hydrazone with R_2CHO

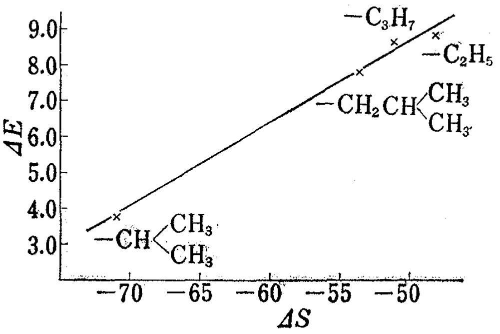


Fig. 5. Energy-Entropy Plots for the Reaction of Butyraldehyde (3-Phenyl-2-quinoxalinyl)hydrazone with R_2CHO

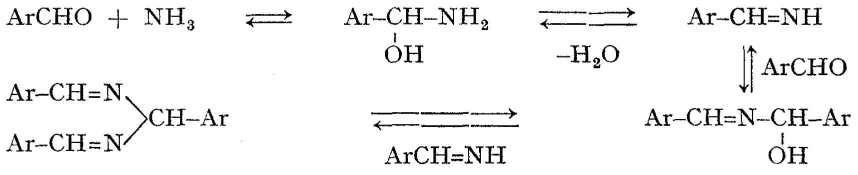


Table IV. Energy and Entropy of Activation for the Reaction of Aldehyde with Amine

Aldehyde	Amine	E (kcal)	ΔS (e.u.)
Benzaldehyde	ammonia	9.75	−40.3
	t-butylamine	7.7	−46.3
p-Dimethylaminobenzaldehyde	ammonia	10.9	−43.7
p-Chlorobenzaldehyde	butylamine	7.0	−41.3
p-Nitrobenzaldehyde	butylamine	8.0	−33.7

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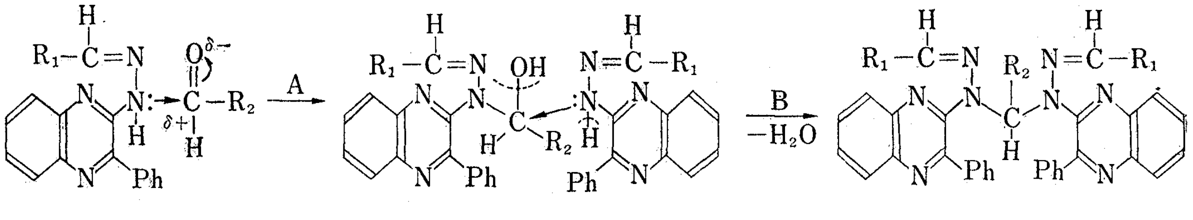
3) R.W. Taft, Jr., in "Steric Effects in Organic Chemistry," ed, M.W. Newman, Chap. 6, John wiley and Sons, New York, 1956.

4) J.E. Leffler and E. Grundwald, "Rate and Equilibria of Organic Reactions," John Wiley and Sons, New York, 1963.

5) *a*) Y. Ogata, A. Kawasaki, and N. Okumura, *J, Org. Chem.*, **29**, 1985 (1964); *b*) G.M. Santerre, C. J. Hanarote, and T.I. Crowell, *J. Am. Chem. Soc.*, **80**, 1254 (1958).

6) B.M. Anderson and W.P. Jenks, *J. Am. Chem. Soc.*, **82**, 1773 (1960); E.H. Cordes and W.P. Jenks, *ibid.*, **84**, 830 (1962); W.P. Jenks, *ibid.*, **81**, 475 (1959).

The values of ΔE and ΔS in Table II are in good agreement with the values given in the literature$^{5a-6)}$ for the reaction between carbonyl compounds and amines, as shown in Table IV. This fact also suggests that the mechanism for the formation of the red substance is similar to that of the above reaction, and a similar transition state is considered to be formed. It is seen from the literature$^{7)}$ that, in a reaction where a total number of molecules decreases or where a neutral molecule forms a transition state of a strong polarity, ΔS shows a negative value. If the rate-determining step is the addition of =NH to R-CHO, the large negative value of ΔS can be understood. If this reaction were considered from the substituent effect, establishment of the Taft's law (Fig. 4) indicates that this reaction is dependent only on the polar effect. Further, establishment of the isokinetic relationship indicates that, irrespective of the kind of aldehydes used, the reaction follows the same mechanism or takes the same transition state. These kinetic results endorse the structure (IV) of the red substance and the following mechanism is proposed for its formation.



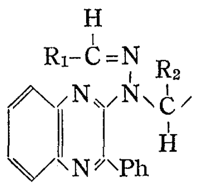
II III IV

Since this is a second-order reaction, the rate-determining step may be the addition of hydrazone to aldehyde. Considering the large negative value of ΔS, the rate-determining step in this reaction is Step A.

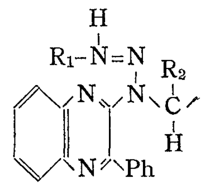
Finally, reason for the red color of this substance is considered to be as follows. The yellow color of the hydrazone (II) is probably due to the resonance of the side-chain -NH-N=CH group with the quinoxaline skeleton. When the hydrazone reacts with the aldehyde and takes the dimeric structure (IV), the phenyl group in the 2-position of the quinoxaline ring exerts a steric interference on R_2 and it takes a distant position from the phenyl group. Consequently, -NH-N=CH-R group becomes bent due to the steric bulk of the R_2 group and cannot undergo resonance with the quinoxaline skeleton, resulting in the red shift. Such a red shift due to the twisting of the conjugate system is seen in the case of cyanine dyes,$^{8)}$ and the red shift is thought to be caused by the increased energy in the ground state than in the excited state due to steric hindrance.

Another explanation is illustrated by the following example where the compound cannot take the *trans* form due to the steric interference of R_2 and less sterically hindered *cis* form takes preference.

In such a case, the lone-pair electrons of the ring nitrogen in the quinoxaline skeleton and the p_π orbital of the π-electron of the $^{R_1}_{H}{>}C{=}N-$ bond overlap, and a new intramolecular bond is formed through the space.



cis



trans

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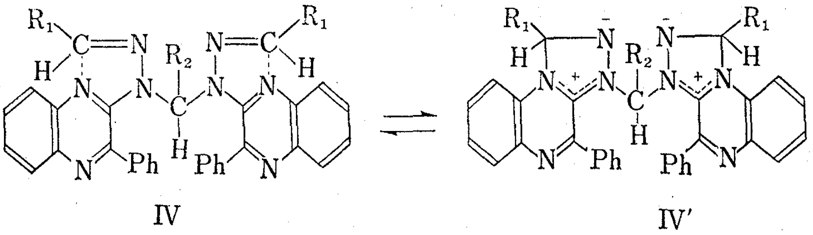
7) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, 1960, p. 181.

8) K.J. Brunings and A.H. Corwin, *J. Am. Chem. Soc.*, **64**, 593 (1942); M.J.S. Dewar, "Steric Effects in Conjugated Systems," Chap. 5, Butterworth Scientific Publications, Ltd., London, 1958.



Consequently, resonances like IV′ occur in the excited state, the energy decreases, and the energy difference between the excited and ground states decreases, resulting in a red shift. However, reason for the red color must await further study.

Experimental

Hydrazone——The following procedures are typical of the reaction of 2-hydrazino-3-phenylquinoxaline (I) with aldehydes.

To a solution of 0.01 mole of I in isopropanol was added 0.01 mole of an aldehyde, with external cooling in ice water. The resulting hydrazone was recrystallized from petroleum benzin as pale yellow needles.

Red Substance——To a warm solution of 0.01 mole of I in MeOH was added 0.015 mole of an aldehyde. The resulting red substance was recrystallized from MeOH.

Rate Measurements of the Red Substance——The rates were measured by following the decrease of the hydrazone peak at 386 mμ with Hitachi spectrophotometer model Eρ S–2. All kinetic determinations were made with the concentration of hydrazone greatly in excess of that of the aldehyde so that pseudo–first–order kinetics were obtained. Solvent used was a mixture of 500 ml of 95% EtOH and 500 ml of phosphate buffer ($\mu = 0.2$) which maintained pH 7.5–8.5. A typical experiment for the rate measurements was as follows: 2×10^{-4}M hydrazone (25 ml) and 6.0×10^{-3}M aldehyde (25 ml) which had previously attained thermal epuilibrium were mixed in a 100 ml thermostated flask kept at 30.0°±0.1°. Aliquots were periodically withdrawn and their absorbances at 386 mμ were determined by a spectrophotometer.

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