balance which seems to affect solubility, permeability and diffusibility into the tissues and cells. The steric circumstance of the molecule should also be considered.

The last may possibly explain the fact that the 5-substituted and some of the 4-substituted compounds are inactive or weakly active in spite of their relatively large indices; there would be a severe restriction to the length of the molecule in the transverse direction in order for the 1-naphthoic acid derivatives to reach the site of action or to fill the gap which has been proposed to exist[28] in the plant substrate (receptor protein). This hypothesis seems to explain satisfactorily why the correlation between the growth activity and the theoretical index is close at the 8-position only, though these acids *in vitro* should be attacked by a reagent at the 2- or 4-position far more easily than at the 8-position.

In the benzoic acid derivatives, Veldstra[8] found that all 4-substituents larger than fluorine are incompatible with activity, and Fukui and his associates[20] showed that some of the *p*-chlorobenzoic acids have large theoretical indices at the *ortho* position in spite of their inactivity. Although the molecular geometry of the benzoic acid derivatives is different from that of the 1-naphthoic acid derivatives, the situation *in vivo* may be similar. The same basis may explain the inactivity of 2-naphthoic acid.[29,30]

The above suggestion that an interaction with the plant substrate occurs at the 8-position next to the carboxyl group leads to the suggestion that the role of the molecular complex formation is to facilitate the approach of the molecule to the substrate so that the carboxyl group may easily be subjected to an interaction with another site of the plant substrate.

Acknowledgment.—The authors wish to express their sincere thanks to Prof. Kenichi Fukui and Dr. Chikayoshi Nagata, Department of Fuel Chemistry, Faculty of Engineering, for their constant guidance in the calculation and suggestive discussions, and Prof. Joji Ashida and Mr. Jiro Kato, Department of Botany, Faculty of Science, for their interest in this work.

(28) H. Linser, "The Chemistry and Mode of Action of Plant Growth Substance," Butterworths Scientific Publications, London, 1955, p. 141.

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(30) K. Koshimizu, Diss., Kyoto University, 1959.

[CONTRIBUTION FROM THE PHARMACEUTICAL FACULTY, UNIVERSITY OF TOYAMA]

Studies on Compounds Related to Pyrazine. II. The Reaction of 3-Substituted-2-hydrazinoquinoxalines with Carbonyl Compounds

BY DEN-ITSU SHIHO AND SHOICHIRO TAGAMI

RECEIVED MAY 12, 1959

The reactions of 3-substituted-2-hydrazinoquinoxalines (I) and carbonyl compounds can be summarized as: (1) with carboxylic acids, *s*-triazoloquinoxaline are produced; (2) with ketones or aldehydes, hydrazones are formed which upon pyrolysis give *s*-triazoloquinoxalines; (3) with α-ketonic acids hydrazones are also produced which upon pyrolysis or boiling with organic acids give *s*-triazoloquinoxalines; (4) with β-ketonic esters, either an *s*-triazoloquinoxaline or a pyrazolone derivative is obtained; and (5) the reaction with diketones gives *s*-triazoloquinoxalines, pyrazoles or a pyridazine derivative.

Several purine, alloxazine and pterin derivatives have been shown to be potent agents in cancer chemotherapy; for example, 2,6-diaminopurine which Hitchings[1] prepared as a possible adenine inhibitor and Burchenal[2] tested for activity against leukemia. Roblin[3] and Kidder[4] synthesized a purine inhibitor, 8-azaguanine, which they used with some success in mouse leukemia.[5] Of these compounds 6-mercaptopurine and 8-azaguanine are the most promising anti-cancer agents.

In a previous paper[6] we reported the synthesis of oxazolo[b]quinoxaline which we hoped would inhibit the metabolism of micrö-organisms. With the same aim in mind, we have now prepared some 3-substituted 2-hydrazinoquinoxalines (I) and studied their reactions with carbonyl compounds.

The starting material, 2-hydrazino-3-R-quinoxaline (I) (R = H, CH_3 C_6H_5, $CH(CH_3)C_2H_5$), was prepared as shown in Scheme 1. Condensation of *o*-phenylenediamine with an α-ketonic acid[7] or its ester[8] afforded 2-hydroxy-3-R-quinoxaline which was converted to 2-chloro-3-R-quinoxaline. Treatment of this chloro compound with hydrazine hydrate yielded 2-hydrazino-3-R-quinoxaline.[9]

(1) Reaction of I with Carboxylic Acids and Related Compounds.—According to the literature, a heterocyclic compound such as I, which has a hydrazino group *ortho* to a ring nitrogen, should react with an organic acid, acid chloride or acid anhydride to give the desired *s*-triazoloquinoxaline; in some cases, however, only the acylated intermediate is obtained, depending on the nature of the heterocyclic compound.[10] 2-Hydrazino-3-R-quinoxaline (I) reacted with acid chlorides or

(1) G. H. Hitchings, G. B. Elion, H. V. Werff and A. A. Falco, *J. Biol. Chem.*, **174**, 765 (1948).

(2) J. H. Burchenal, J. R. Burchenal, M. N. Kusihida, S. F. Johnston and B. S. Williams, *Cancer*, **2**, 113 (1949).

(3) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

(4) G. W. Kidder and V. C. Dewey, *J. Biol. Chem.*, **179**, 181 (1949).

(5) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Science*, **109**, 511 (1949).

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(7) O. Hinsberg, *Ann.*, **292**, 245 (1896); H. Burton and C. W. Schopee, *J. Chem. Soc.*, 546 (1937).

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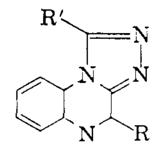
(10) D. Shiho and S. Tagami, *Yakugaku Zasshi*, **76**, 804 (1956).

TABLE I



R	R	Reagent used for ring closure	Yield,[a] %	M.p.,[b] °C.	Formula	Analyses, % Calcd. C	H	N	Found C	H	N	Recrystn. solvent
H	H	$HC(OC_2H_5)_3$	88	234	$C_9H_6N_4$	63.51	3.55	32.94	63.34	3.62	32.79	MeOH
H	H	HCOOH	65	234	$C_9H_6N_4$							MeOH
H	CH_3	CH_3COOH	70	210	$C_{10}H_8N_4$	65.20	4.38	30.42	65.11	4.50	30.52	MeOH
H	CH_3	CH_3COCl	66	210	$C_{10}H_8N_4$							MeOH
		$(CH_3CO)_2O$[c]	55	104	$C_{12}H_{12}O_2N_4$	59.00	4.94	22.94	59.21	5.11	23.06	MeOH
H	C_2H_5	C_2H_5COOH	68	180	$C_{11}H_{10}N_4$	66.72	5.04	28.24	66.53	5.18	28.29	MeOH
H	n-C_3H_7	n-C_3H_7COOH	79	150	$C_{12}H_{12}N_4$	67.91	5.68	26.41	67.75	5.80	26.48	MeOH
H	n-C_4H_9	n-C_4H_9COOH	67	141	$C_{13}H_{14}N_4$	69.00	6.24	24.76	69.21	6.35	24.69	MeOH
H	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2COOH$	45	138	$C_{13}H_{14}N_4$	69.00	6.24	24.76	69.30	6.14	24.61	EtOH
H	C_6H_5	C_6H_5COCl	87	225	$C_{15}H_{10}N_4$	73.15	4.09	22.76	73.33	4.23	22.88	EtOH
H	$C_6H_5CH{=}CH$	$C_6H_5CH{=}CHCOCl$	85	238	$C_{17}H_{12}N_4$	74.98	4.44	20.58	74.78	4.56	20.45	MeOH
H	OH	$ClCOOC_2H_5$	74	300	$C_9H_6ON_4$	58.06	3.25	30.12	58.27	3.42	30.85	AcOH
CH_3	H	$HC(OC_2H_5)_3$	85	247	$C_{10}H_8N_4$	65.27	4.38	30.45	65.39	4.51	30.24	MeOH
CH_3	CH_3	CH_3COOH	75	196	$C_{11}H_{10}N_4$	66.65	5.09	28.26	66.52	5.20	28.34	H_2O
CH_3	CH_3	CH_3COCl	90	196	$C_{11}H_{10}N_4$							H_2O
CH_3	CH_3	$(CH_3CO)_2O$	93	196	$C_{11}H_{10}N_4$							H_2O
CH_3	C_2H_5	C_2H_5COOH	92	152	$C_{12}H_{12}N_4$	67.90	5.69	26.41	67.61	5.83	26.54	i-PrOH
CH_3	n-C_3H_7	n-C_3H_7COOH	80	138	$C_{13}H_{14}N_4$	69.00	6.24	24.76	69.29	6.18	24.82	H_2O
CH_3	n-C_4H_9	n-C_4H_9COOH	85	117	$C_{14}H_{16}N_4$	69.84	6.71	23.45	69.57	6.95	23.52	Me_2CO
CH_3	C_6H_5	C_6H_5COCl	92	203.5	$C_{16}H_{12}N_4$	73.90	4.65	21.45	73.62	4.80	21.27	MeOH
CH_3	$C_6H_5CH{=}CH$	$C_6H_5CH{=}CHCOCl$	77	197.5	$C_{18}H_{14}N_4$	75.50	4.93	19.57	75.43	5.15	19.65	EtOH
CH_3	OH	$ClCOOC_2H_5$	75	283	$C_{10}H_8ON_4$	59.98	4.03	27.98	60.12	4.14	28.09	Pyridine
C_6H_5	H	$HC(OC_2H_5)_3$	94	190	$C_{15}H_{10}N_4$	73.15	4.09	22.76	73.25	4.31	22.82	MeOH–pyr.
C_6H_5	H	HCOOH	93	190	$C_{15}H_{10}N_4$							MeOH–pyr.
C_6H_5	CH_3	CH_3COCl	85	220	$C_{16}H_{12}N_4$	73.83	4.65	21.52	73.57	4.73	21.61	MeOH–pyr.
C_6H_5	CH_3	$(CH_3CO)_2O$	83	220	$C_{16}H_{12}N_4$							MeOH–pyr.
C_6H_5	C_2H_5	C_2H_5COCl	86	160	$C_{17}H_{14}N_4$	74.43	5.14	20.43	74.25	5.31	20.51	MeOH
C_6H_5	n-C_3H_7	n-C_3H_7COCl	91	146	$C_{18}H_{16}N_4$	74.97	5.59	19.43	74.69	5.27	19.65	MeOH
C_6H_5	n-C_4H_9	n-C_4H_9COOH	90	113	$C_{19}H_{18}N_4$	75.55	6.00	18.45	75.32	6.23	18.70	Aq. MeOH
C_6H_5	$(CH_3)_2CHCH_2$	$(CH_3)_2CHCH_2COOH$	91	136	$C_{19}H_{18}N_4$	75.55	6.00	18.45	75.11	6.18	18.83	Aq. MeOH
C_6H_5	C_6H_5	C_6H_5COCl	87	237.5	$C_{21}H_{14}N_4$	78.24	4.37	17.39	78.44	4.26	17.30	MeOH–pyr.
C_6H_5	$C_6H_5CH{=}CH$	$C_6H_5CH{=}CHCOCl$	85	202	$C_{23}H_{16}N_4$	79.29	4.63	16.08	79.17	4.81	16.15	MeOH–pyr.
C_6H_5	OH	$ClCOOC_2H_5$	78	303	$C_{15}H_{10}ON_4$	68.75	3.84	21.41	68.82	3.88	21.60	AcOH

[a] Yields calculated for crude product. [b] All melting points are uncorrected. [c] Ring closure did not occur and the diacetylated derivative was obtained.

organic acids to give 4-R-*s*-[triazolo] [4,3-a]quinoxaline (T), and the acylated intermediate was not obtained. Attempts to prepare this intermediate by the reaction of I with acetic ester under various conditions yielded only the *s*-triazolo compound. Apparently the acylated compound is rather labile and easily undergoes cyclization during recrystallization from methanol to form the triazolo ring.

The reaction of I (R = CH_3, or C_6H_5) with acetic anhydride also gave the triazoloquinoxaline; however, with the unsubstituted 2-hydrazinoquinoxaline (R = H) cyclization did not occur and the diacetylated derivative ($C_{12}H_{12}O_2N_4$) was obtained; see Table I.

Although *s*-triazoloquinoxalines were obtained in good yield by the reaction of I with organic acids, acid chlorides and acetic anhydride (Table I), a red pigment was produced by a side reaction (especially in the case of acid chlorides). No such pigment was formed when the *s*-triazoloquinoxalines were prepared, also in good yield, by the treatment of I with ortho ester. The use of ortho esters, therefore, seems to be the method of choice for the preparation of *s*-triazoloquinoxalines.

The reaction of I with ethyl chloroformate by the method of Druey[11] yielded the 1-hydroxy-*s*-triazolo[4,3-a]quinoxaline which was converted to the 1-chloro derivative. Catalytic reduction of this chloro compound under various conditions did not give the triazoloquinoxaline obtained by the reaction of I and formic acid.

s-Triazoloquinoxaline was also prepared, although in poor yield, by the reaction of 2-chloroquinoxaline with mono- or diacylhydrazine; no acylhydrazinoquinoxaline was obtained in either case as shown in the preceding reaction scheme. Probably in the reaction with the diacylhydrazine, diacylhydrazinoquinoxaline is formed as an intermediate which hydrolyzes to monoacylhydrazinoquinoxaline which in turn undergoes cyclization to give *s*-triazoloquinoxaline.

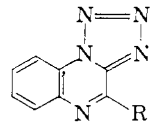
In an attempt to prepare compounds analogous to 8-azaguanine and the 4-substituted tetrazolo-[1,5-a]quinoxalines, the compounds listed in Table II were obtained by the reaction of I with nitrous acid.

(2) **The Reaction of I with Ketones or Aldehydes.**—Elderfield[12] reported that thermal decomposition of imidazoline, obtained as an intermediate in the reaction of *o*-phenylenediamine or its N-monoalkylated compound with a ketone, effected cleavage of the carbon–carbon bond to form the benzimidazole derivative.

(11) J. Druey and B. H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).

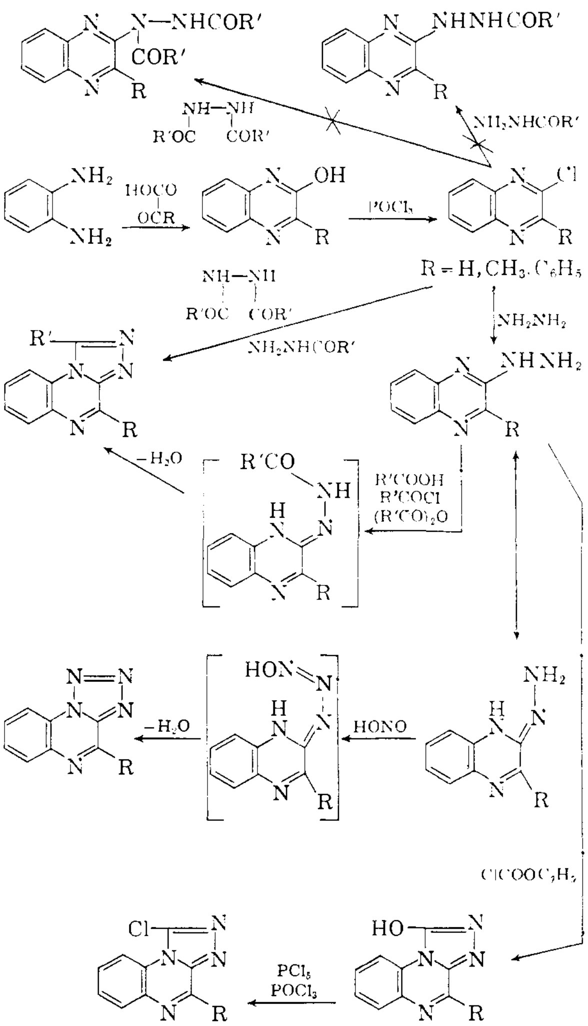
(12) R. C. Elderfield and J. R. McCarthy, THIS JOURNAL, **73**, 974 (1951).

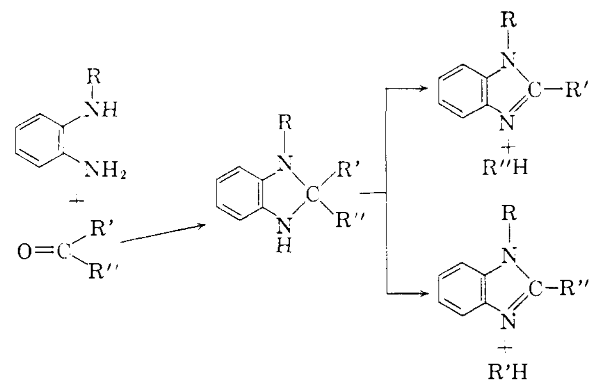
TABLE II



R	M.p.,[a] °C.	Appearance, needles	Yield,[b] %	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
H	198	Pale orange	93	$C_8H_5N_5$	56.18	2.94	40.98	56.12	2.81	40.87
CH_3	151	Colorless	92	$C_9H_7N_5$	58.37	3.81	37.82	58.10	3.93	37.95
C_6H_5	170	Pale yellow	93	$C_{14}H_9N_5$	67.99	3.68	28.33	67.75	3.72	28.39

[a] All melting points are uncorrected. [b] Yields calculated for crude product.





The reaction of I with ketone or aldehyde also resulted in the cleavage of the carbon–carbon or carbon–hydrogen bond to produce the *s*-triazoloquinoxaline. Presumably the first step in this reaction is the formation of the hydrazone II which upon heating gives an intermediate with a five-membered ring (III) from which a hydrocarbon (or hydrogen in the case of the aldehydes) is liberated with the formation of the *s*-triazoloquinoxaline.

The results, listed in Tables III and IV, are in accord with this reaction mechanism. In several cases the hydrazone intermediate was isolated and identified. The ultraviolet absorption spectra of the hydrazones and of the *s*-triazoloquinoxalines formed by their decomposition are shown in Fig. 1.

TABLE III

THE REACTION OF 2-HYDRAZINO-3-R-QUINOXALINES WITH KETONES

Ketone	1-Substituent of triazolo-quinoxaline	Hydrocarbon product	Initial gas evolution temp., °C.
	$R = C_6H_5$		
Methyl ethyl	Methyl	Ethane	215
Methyl *n*-propyl	Methyl	Propane	210
Methyl isopropyl	Methyl	Isopropane	190
Methyl *n*-amyl	Methyl	Pentane	
Methyl isoamyl	Methyl	Dimethylethyl methane	210
Methyl *t*-butyl	Methyl	Isobutane	
Methyl phenyl	Phenyl	Methane	250
Methyl benzyl	Methyl	Toluene	
Benzylacetone	Methyl	Ethylbenzene	
Ethyl phenyl	Phenyl	Ethane	
Phenyl benzyl	Phenyl	Toluene	190
Benzylacetophenone	Phenyl	Ethylbenzene	245
	$R = CH_3$		
Methyl *n*-amyl	Methyl	Pentane	
Methyl *t*-butyl	Methyl	Isobutane	
Methyl benzyl	Methyl[a]	Toluene	

[a] Recrystallized from water.

Further evidence for this reaction course was obtained from the reaction of I ($R = C_6H_5$) (Ip) with methyl benzyl ketone. Thermal decomposition of the hydrazone intermediate should liberate toluene as the hydrocarbon and toluene, determined by gas chromatography, was found to be in the gas produced by the pyrolysis.

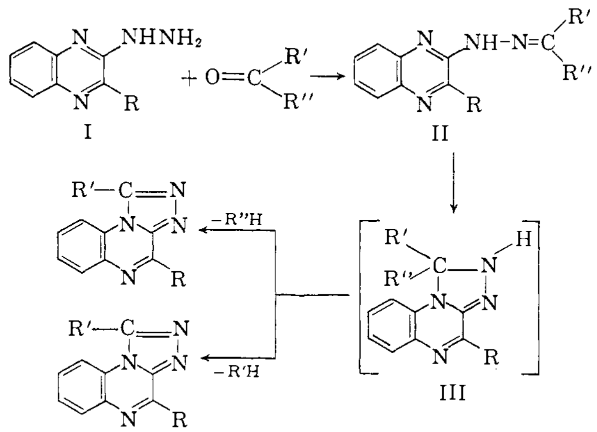
In the reaction of I with unsymmetrical ketones, the results in Table III indicate that the molecule

TABLE IV

REACTION OF 2-HYDRAZINO-3-PHENYLQUINOXALINE (Ip) WITH ALDEHYDES

1-R-4-Phenyl-*s*-triazolo-quinoxaline

Aldehyde	R	M.p., °C.	Formula	Analyses, %: Calcd. C	H	N	Found C	H	N
Acetaldehyde	Methyl	220							
Heptaldehyde	Hexyl	985	$C_{21}H_{22}N_4$	76.33	6.72	16.95	76.34	6.71	17.15
Benzaldehyde	Phenyl	235							
m-Nitrobenzaldehyde	*m*-Nitrophenyl	214	$C_{21}H_{13}O_2N_5$	68.67	3.59	19.07	68.79	3.72	19.21
p-Nitrobenzaldehyde	*p*-Nitrophenyl	252	$C_{21}H_{13}O_2N_5$	68.67	3.59	19.07	68.83	3.79	19.25
Vanillin	3-Methoxy-4-hydroxyphenyl	243	$C_{22}H_{16}O_2N_4$	71.72	4.38	15.21	71.90	4.46	15.12
p-Methoxybenzaldehyde	*p*-Methoxyphenyl	225	$C_{22}H_{16}ON_4$	74.98	4.58	15.90	75.00	4.35	15.72
p-Chlorobenzaldehyde	*p*-Chlorophenyl	258	$C_{21}H_{13}N_4Cl$	70.69	3.67	15.71	70.78	3.79	15.56
2,4-Dichlorobenzaldehyde	2,4-Dichlorophenyl	268	$C_{21}H_{12}N_4Cl_2$	64.47	3.09	14.32	64.55	3.23	14.18



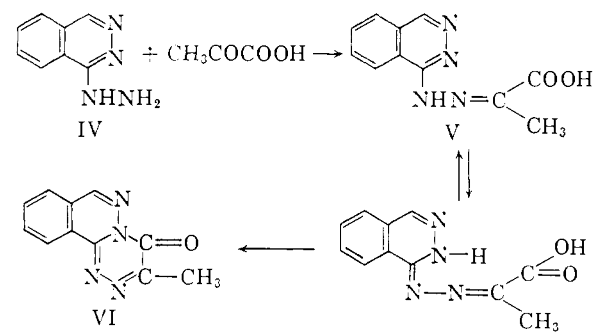
with the larger steric requirement was preferentially liberated as the hydrocarbon. The five-membered ring of III is thought to be subject to a fairly large steric strain, and the splitting off of the larger of the R groups would probably give an *s*-triazolo ring free from strain. Elderfield[12] has defined and determined the initial gas evolution temperature at which the intermediate imidazoline decomposed with the evolution of a gaseous hydrocarbon. He showed the ease of elimination of a branch of an unsymmetrical ketone to decrease in the order: *t*-butyl > isopropyl > benzyl, isobutyl, *n*-propyl, ethyl > methyl, vinyl.

Our results are in accord with those of Elderfield except for the reaction with methyl phenyl ketone, in which the 1-phenyl-*s*-triazoloquinoxaline was formed and methane evolved. Similarly, with the aldehydes (Table IV) the larger group is left behind and hydrogen is liberated. This problem is under investigation.

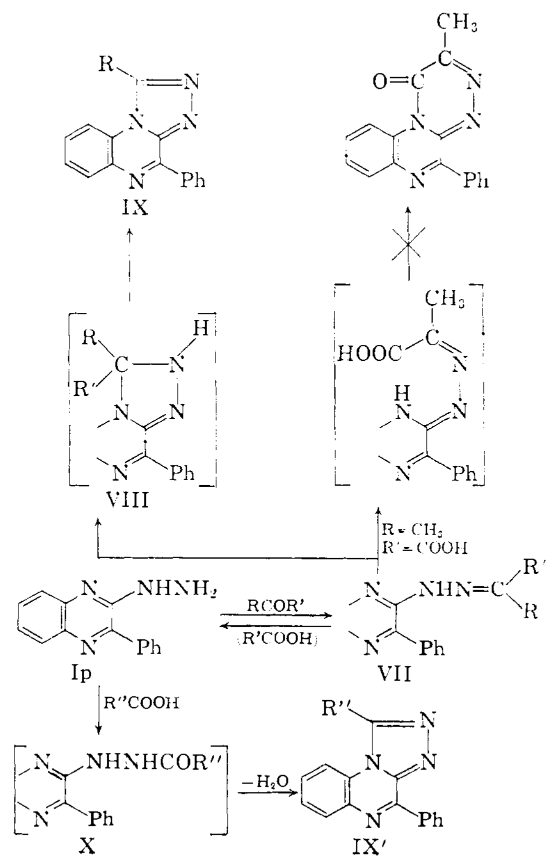
(3) **The Reaction of I with α-Ketonic Acids.**—Druey[11] prepared a compound containing a triazine ring (VI) by pyrolysis of the hydrazone V obtained from the reaction of 1-hydrazinophthalazine (IV) and pyruvic acid.

This procedure, however, gives only a poor yield of VI which was obtained in good yield when V was boiled with glacial acetic acid.

In the present work Ip was treated with pyruvic acid to give the hydrazone VII (R = CH_3, R′ = COOH). This compound upon pyrolysis failed to give a product analogous to VI, but instead yielded 1-methyl-4-phenyl-*s*-triazolo[4,3-a]quinoxaline (IX, R = CH_3) (Tpm) by a reaction similar to that described for Ip and ketones.



The same product, Tpm, was obtained when VII (R = CH_3, R′ = COOH) was boiled with glacial acetic acid for 16–24 hours. With propionic or butyric acid this hydrazone gave 1-ethyl- (IX′, R″ = C_2H_5) (Tpe) and 1-propyl-4-phenyl-*s*-triazolo-



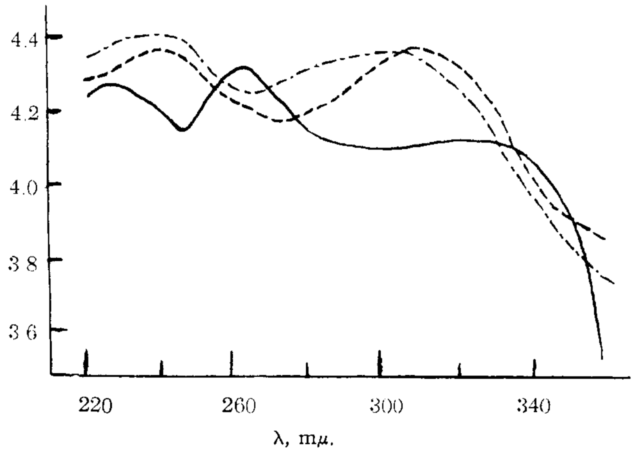
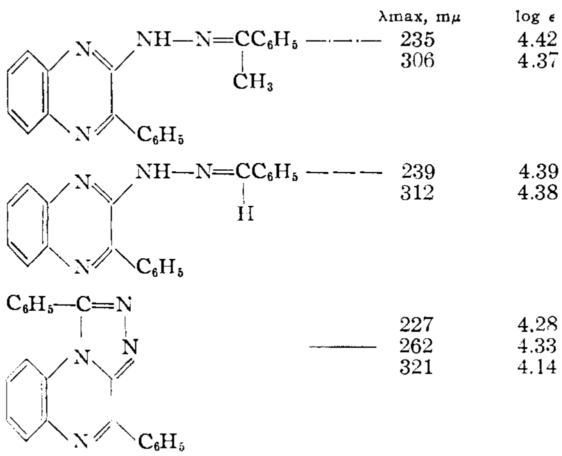


Fig. 1.—Ultraviolet absorption spectra (in 95% EtOH).



[4,3-a]quinoxaline (IX', R = C_3H_7) (Tppr), respectively.

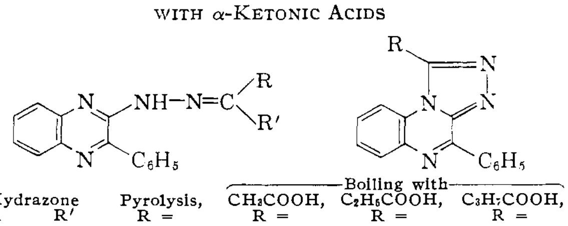
Aqueous solutions of semicarbazide generally react with ketones or aldehydes to form a semicarbazone by the reversible reaction[13]

$$RR'C{=}O + H_2NNHCONH_2 \rightleftarrows RR'C{=}NNHCONH_2$$

Accordingly, the hydrazone formed by the reaction of Ip with pyruvic acid may undergo dissociation when boiled with an organic acid to form

TABLE V

REACTION OF 2-HYDRAZINO-3-PHENYLQUINOXALINE (Ip) WITH α-KETONIC ACIDS



Hydrazone R	R'	Pyrolysis, R =	Boiling with CH₃COOH, R =	C₂H₅COOH, R =	C₃H₇COOH, R =
CH_3	COOH	Tpm, CH_3	Tpm, CH_3	Tpe, C_2H_5	Tppr, C_3H_7
C_2H_5	COOH		Tpm, CH_3[a]	Tpe, C_2H_5[b]	Tppr, C_3H_7[c]
C_6H_5	COOH	Tpp, C_6H_5[d]	Tpm, CH_3[e]	Tpp, C_6H_5[f]	Tpp, C_6H_5[g]
C_6H_5	H	Tpp, C_6H_5	Tpm, CH_3[e]	Tpp, C_6H_5[h]	Tpp, C_6H_5[i]
CH_3	C_6H_5	Tpp, C_6H_5	Tpm, CH_3[e]	Tpp, C_6H_5[j]	

[a] Yields calculated for crude product; yield 95%. [b] Yield 96%. [c] Yield 90%. [d] Heated for 1 hour at 200–220° and recrystallized from methanol–pyridine, yield 60%. [e] Yield 40%, [f] 70%, [g] 71%, [h] 72%, [i] 71%, [j] 44%.

(13) J. B. Conant and P. D. Bartlett, THIS JOURNAL, **54**, 288 (1932).

Ip which would then react with the acid to form the triazole ring *via* the acyl compound X.

When VII (R = C_2H_5, R' = COOH) formed by the reaction of Ip and propionylformic acid was boiled with an organic acid, the product was identical with that obtained from VII (R = CH_3, R' = COOH) under the same conditions. The substance obtained by pyrolysis failed to crystallize (see Table V); VII (R = C_6H_5, R' = COOH), when boiled with glacial acetic acid, gave Tpm (IX', R'' = CH_3). However VII (R = C_6H_5, R' = COOH) produced 1,4-diphenyl-*s*-triazolo[4,3-a]quinoxaline (IX, R = C_6H_5, Tpp) on boiling with propionic or butyric acid, and this substance is identical with the product obtained by pyrolysis of the hydrazone. This means that VII (R = C_6H_5, R' = COOH) does not dissociate to Ip when boiled with propionic or butyric acid but behaves as if it had been subjected to pyrolysis. The hydrazone formed by the reaction of Im and an α-ketonic acid failed to give a crystalline product when subjected to pyrolysis or boiling with an organic acid.

When VII (R = C_6H_5, R' = H) obtained by the reaction of Ip and benzaldehyde was boiled with acetic acid, Tpm (IX', R'' = CH_3) was formed *via* dissociation of the hydrazone to Ip. On the other hand, boiling with propionic or butyric acid produced Tpp (IX, R = C_6H_5) which is also formed on pyrolysis of the hydrazone. Boiling of VII (R = CH_3, R' = C_6H_5), obtained from Ip and methyl phenyl ketone, with acetic or propionic acid produced Tpm (IX', R'' = CH_3) and Tpe (IX', R'' = C_2H_5), respectively, *via* dissociation of the hydrazone to Ip. These results are listed in Table V.

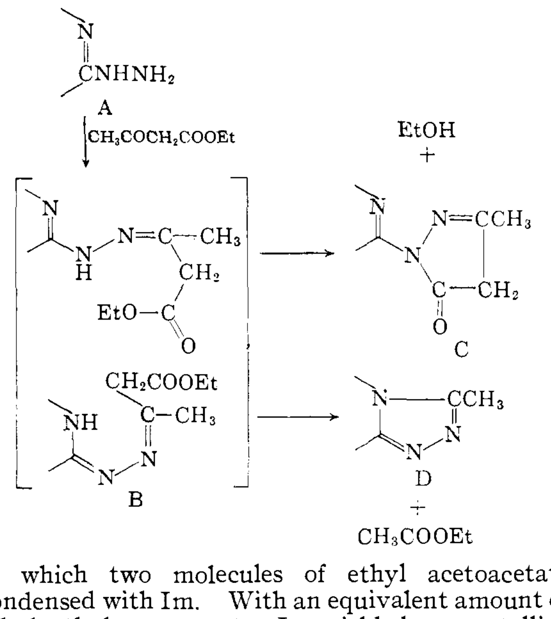
(4) The Reaction between I and β-Ketonic Esters.—According to the literature,[11,14,15] the reaction of hydrazino derivatives of nitrogen-containing heterocyclic compounds (A), in which the hydrazino group is *ortho* to a ring nitrogen, with ethyl acetoacetate under various conditions gives 3-methyl-5-pyrazolone (C) or 3-methyl-*s*-triazolo derivatives (D) *via* ethyl acetoacetate hydrazone (B).

In the present work, when 2-hydrazino-3-R-quinoxalines (I, R = H, CH_3, $CH(CH_3)C_2H_5$, C_6H_5) were allowed to react with β-ketonic esters, pyrazolones (XIII) corresponding to (C), or *s*-triazolo compounds (XV) corresponding to (D) were obtained; see Table VI. The product formed was dependent upon the 3-substituent of the quinoxaline and the β-ketonic ester used.

Direct heating of Ip with an equivalent amount or excess ethyl acetoacetate at 180° resulted in the formation of Tpm through degradation of the intermediate hydrazone with elimination of ethyl acetate. The reaction of Im with equivalent ethyl acetoacetate at both low and high temperatures gave an oil which did not crystallize; with excess ethyl acetoacetate at 180°, the reaction gave crystals of a lactone-type pyrazolone (XIV)

(14) H. Beyer and D. Stehwien, *Arch. Pharm.*, **286**, 13 (1953).

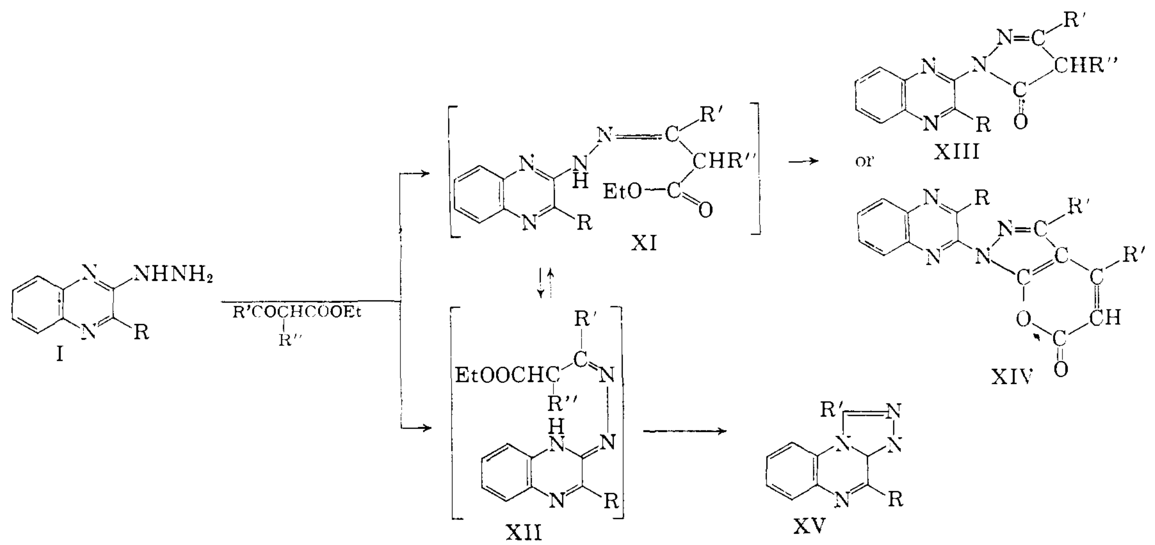
(15) L. S. Efros and L. R. Davidenkov, *Zhur. Obshchei Khim.*, **21**, 2046 (1951); *C.A.*, **46**, 8100 (1952).



in which two molecules of ethyl acetoacetate condensed with Im. With an equivalent amount of ethyl ethylacetoacetate, Im yielded a crystalline pyrazolone derivative.

C_6H_5) with acetylacetone[16] at 100 or 200° gives a pyrazole derivative *via* dehydration of the intermediate hydrazone XVI. The pyrazole is also obtained when I (R = $CH(CH_3)C_2H_5$) is heated with acetylacetone at 100–160°; when the mixture is heated in a sealed tube at 220°, a trace of the triazole compound is obtained. These results suggest that dehydration of the intermediate hydrazone to give the pyrazole ring occurs more readily than formation of a triazole ring by pyrolysis of the hydrazone. However, when there is a large group, such as $CH(CH_3)C_2H_5$, in the *o*-position of I, its steric hindrance seems to affect the reaction and a triazole ring is formed *via* the intermediate XVIII.

The products obtained with various diketones and quinoxalines are listed in Table VII. The 2-hydrazinoquinoxalines (I) irrespective of the group in 3-position reacted with $C_2H_5COCH_2COC_2H_5$, $C_6H_5COCH_2COC_6H_5$ and $CH_3COCH_2COCH_2C_6H_5$ to give the pyrazole derivative XVII, and no triazole was obtained. With $CH_3COCH_2COC_6H_5$, compound I(R = H) yielded the pyrazole (reaction temperature 130–140°), while compound I (R = CH_3) gave a triazole (reactions temperature



In the reaction of ethyl acetoacetate with 2-hydrazinoquinoxaline (I, R = H), only an oil was obtained; however with ethyl ethylacetoacetate or ethyl butylacetoacetate, the products were pyrazolone derivatives (XIII, R = H, R′ = CH_3, R″ = C_2H_5, and R = H, R′ = CH_3, R″ = *n*-C_4H_9, respectively), and no *s*-triazolo compound was obtained. The reaction of ethyl acetoacetate with I (R = $CH(CH_3)C_2H_5$) gave an *s*-triazolo compound XV (R = $CH(CH_3)C_2H_5$, R′ = CH_3) and no pyrazolone. However, in the case of the reaction of ethyl benzoylacetate, propyl *p*-methylbenzoylacetate or ethyl *p*-chlorobenzoylacetate with I(R = C_6H_5, $CH(CH_3)C_2H_5$), only pyrazolones were obtained. These results cannot be explained entirely by steric hindrance due to R; the nature of the β-ketonic ester also seems to be a determining factor.

(5) The Reaction between I and β- or γ-Diketones.—The reaction of I (R = H, CH_3 or

130–160°) which was identical with 1,4-dimethyl-*s*-triazoloquinoxaline obtained by the reaction of I (R = CH_3) and methyl benzyl ketone. Both I (R = C_6H_5 and $CH(CH_3)C_2H_5$) reacted within a few minutes with $CH_3COCH_2COC_6H_5$ to give triazole derivatives.

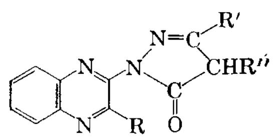
Pyrazoles were obtained from $C_2H_5COCH_2COC_6H_5$ and I (R = H, CH_3), and no triazole was formed even when compound I (R = CH_3) was heated with the diketone at 190° for 1 hour; compound I (R = C_6H_5 and $CH(CH_3)C_2H_5$) gave triazoles. Similar results were obtained with $C_3H_7COCH_2COC_6H_5$.

In the reaction of I with diketones containing a phenyl group adjacent to a carbonyl, either a pyrazole or a triazole derivative is formed depending on the substituent in the 3-position of I; the triazole is formed more readily in such a case than

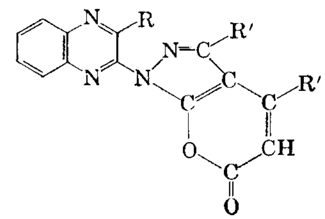
(16) L. Knorr, *Ber.*, **20**, 1104 (1887).

TABLE VI

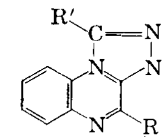
REACTION OF 2-HYDRAZINO-3-R-QUINOXALINE WITH β-KETONIC ESTERS



Pyrazolone (A)



Lactone-type Pyrazolone (B)



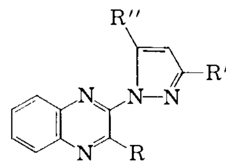
Triazole (C)

No.[d]	R	β-Ketonic ethyl ester	M.p.,[a] °C.	Product	R′	R″	Appearance, needles	Formula	Analysis, % Calcd. C	H	N	Found C	H	N	Yield,[b] %	Recrystn. solvent
1	H	Ethylacetoacetate	144	A	CH_3	C_2H_5	Colorless	$C_{14}H_{14}ON_4$	66.12	5.55	22.04	66.23	5.41	22.15	78	MeCOOEt
2	H	*n*-Butylacetoacetate	118	A	CH_3	$(CH_2)_3CH_3$	Colorless	$C_{16}H_{18}ON_4$	68.06	6.43	19.84	68.25	6.40	19.59	91	MeCOOEt
3	H	Benzoylacetate	217	A	C_6H_5	H	Pale yellow	$C_{17}H_{12}ON_4$	70.82	4.20	19.44	70.53	4.15	19.33	61	MeOH–pyr.
4	H	*p*-Methylbenzoylacetate[c]	218	A	$C_6H_4CH_3(p)$	H	Pale yellow	$C_{18}H_{14}ON_4$	71.51	4.67	18.54	71.58	4.51	18.33	66	MeOH–pyr.
5	H	*p*-Chlorobenzoylacetate	228	A	$C_4H_6Cl(p)$	H	Pale yellow	$C_{17}H_{11}ON_4Cl$	63.26	3.44	17.36	63.16	3.54	17.21	72	Pyridine
6	CH_3	Acetoacetate	235	B	CH_3		Colorless	$C_{17}H_{14}O_2N_4$	66.65	4.61	18.29	66.75	4.48	18.21	47	MeOH–pyr.
7	CH_3	Ethylacetoacetate	145	A	CH_3	C_2H_5	Colorless	$C_{15}H_{16}ON_4$	67.14	6.01	20.88	67.30	6.24	20.80	60	MeCOOEt
8	CH_3	Benzoylacetate	212	A	C_6H_5	H	Yellow	$C_{18}H_{14}ON_4$	71.51	4.67	18.53	71.77	4.50	18.25	16	MeOH–pyr.
9	CH_3	*p*-Methylbenzoylacetate[c]	210	A	$C_6H_4CH_3(p)$	H	Yellow	$C_{19}H_{16}ON_4$	72.13	5.10	17.71	72.33	5.26	17.57	98	MeOH–pyr.
10	CH_3	*p*-Chlorobenzoylacetate	231.5	A	$C_6H_4Cl(p)$	H	Yellow	$C_{18}H_{13}ON_4Cl$	64.20	3.89	16.64	64.41	3.73	16.41	90	Pyridine
11	C_6H_5	Acetoacetate	220	C	CH_3		Colorless	$C_{16}H_{12}N_4$	73.83	4.65	21.52	73.56	4.54	21.69	86.5	MeOH–pyr.
12	C_6H_5	Ethylacetoacetate	220	C	CH_3		Colorless	$C_{16}H_{12}N_4$							79	MeOH–pyr.
13	C_6H_5	*n*-Butylacetoacetate	220	C	CH_3		Colorless	$C_{16}H_{12}N_4$							72	MeOH–pyr.
14	C_6H_5	Diethylacetoacetate	220	C	CH_3		Colorless	$C_6H_{12}N_4$							35	MeOH–pyr.
15	C_6H_5	Butyrylacetoacetate	220	C	CH_3		Colorless	$C_6H_{12}N_4$							23	MeOH–pyr.
16	C_6H_5	Benzoylacetate	257	A	C_6H_5	H	Colorless	$C_{23}H_{16}ON_4$	75.81	4.43	15.38	75.73	4.58	15.20	20	Pyridine
17	$CH(CH_3)(C_2H_5)$	Acetoacetate	145.5	C	CH_3		Colorless	$C_{14}H_{16}N_4$	69.97	6.71	23.32	69.56	6.57	23.55	50	MeOH
18	Same	Ethylacetoacetate	145.5	C	CH_3		Colorless	$C_{14}H_{16}N_4$							40	MeOH
19	Same	*n*-Butylacetoacetate	145.5	C	CH_3		Colorless	$C_{14}H_{16}N_4$							59	MeOH
20	Same	Diethylacetoacetate	145.5	C	CH_3		Colorless	$C_{14}H_{16}N_4$							21	MeOH
21	Same	Butyrylacetoacetate	145.5	C	CH_3		Colorless	$C_{14}H_{16}N_4$							15	MeOH
22	Same	Benzoylacetate	180	A	C_6H_5	H	Colorless	$C_{21}H_{20}ON_4$	73.24	5.85	16.27	73.10	5.71	16.20	21	Aq. EtOH
23	Same	*p*-Methylbenzoylacetate[c]	159	A	$C_6H_4CH_3(p)$	H	Yellow	$C_{22}H_{22}ON_4$	73.71	6.19	15.63	73.54	6.30	15.41	43	MeOH

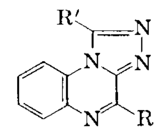
[a] All melting points are uncorrected. [b] Yields calculated for crude product. [c] Propyl ester. [d] Conditions: no. 3, heat for 30 min. at 150° and triturate with methanol; 4, heat for 30 min. at 120° and triturate with methanol; 5, heat for 10 min. at 130° and triturate with methanol; 8, heat for 3 hr. at 160–170° and triturate with ether; 9, heat for 20 min. at 140–150° and triturate with ether; 10, heat for 30 min. at 130–140° and triturate with methanol; 11, heat for 5 hr. at 150–180° and triturate with methanol; 12–14, heat for 80 min. at 100–150° and triturate with methanol; 15, heat for 80 min. at 100–200° and triturate with methanol; 18–21, heat for 2 hr. at 100–180° and triturate with petroleum ether; 22, heat for 5 hr. at 170° and triturate with ether; 23, heat for 1 hr. at 120–190° and triturate with ether.

TABLE VII

REACTION OF 3-R-2-HYDRAZINOQUINOXALINES WITH β-DIKETONES



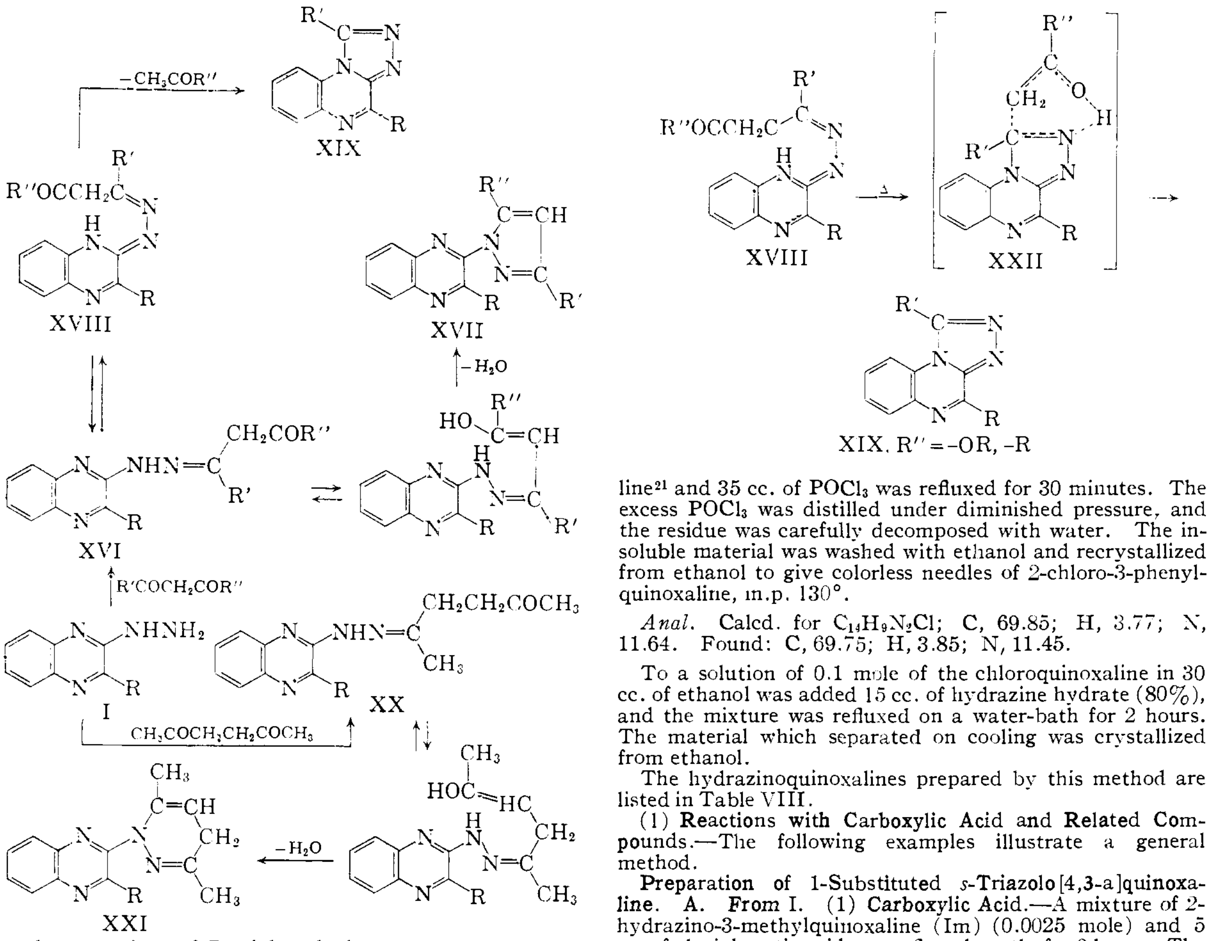
Pyrazole (P)



Triazole (T)

No.[d]	R	$R'COCH_2COR''$	M.p.,[a] °C.	Product	R'	R''	Appearance	Formula	Analyses, % Calcd. C	H	N	Found C	H	N	Yield,[b] %	Recrystn. solvent
1	H	$CH_3COCH_2COCH_3$	110	P	CH_3	CH_3	Colorless needles	$C_{13}H_{12}N_4$	69.62	5.39	24.99	69.35	5.30	25.21	71.4	MeOH
2	H	$C_2H_5COCH_2COC_2H_5$	64	P	C_2H_5	C_2H_5	Colorless needles	$C_{14}H_{16}N_4$	71.40	6.39	22.21	71.29	6.34	22.35	80	Aq. MeOH
3	H	$CH_3COCH_2COCH_2C_6H_5$	127	P	CH_3	$CH_2C_6H_5$	Colorless needles	$C_{19}H_{16}N_4$	75.98	5.39	18.65	76.26	5.40	18.54	76	MeOH
4	H	$CH_3COCH_2COC_6H_5$	129	P	CH_3	C_6H_5	Colorless needles	$C_{18}H_{14}N_4$	75.50	4.93	19.57	75.76	4.96	19.42	95	EtOH
5	H	$C_2H_5COCH_2COC_6H_5$	96	P	C_2H_5	C_6H_5	Colorless plates	$C_{19}H_{16}N_4$	75.98	5.37	18.65	75.96	5.46	18.43	66	MeOH
6	H	$C_3H_7COCH_2COC_6H_5$	72	P	C_3H_7	C_6H_5	Colorless leaflets	$C_{20}H_{18}N_4$	76.41	5.77	17.82	76.29	5.63	17.82	70	Aq. MeOH
7	H	$C_6H_5COCH_2COC_6H_5$	142	P	C_6H_5	C_6H_5	Pale pink needles	$C_{23}H_{16}N_4$	79.29	4.63	16.08	79.29	4.57	16.28	90	MeOH
8	CH_3	$CH_3COCH_2COCH_3$	117	P	CH_3	CH_3	Colorless needles	$C_{14}H_{14}N_4$	70.56	5.92	23.52	70.36	5.82	23.33	74	MeOH
9	CH_3	$C_2H_5COCH_2COC_2H_5$	[c]	P	C_2H_5	C_2H_5	Colorless oil	$C_{16}H_{18}N_4$	72.15	6.81	21.04	72.35	6.73	21.32	65	
10	CH_3	$CH_3COCH_2COC_6H_5$	196	T	CH_3		Colorless needles	$C_{11}H_{10}N_4$							73	MeCOOEt
11	CH_3	$C_2H_5COCH_2COC_6H_5$	94	P	C_2H_5	C_6H_5	Pale yellow needles	$C_{20}H_{18}N_4$	76.41	5.77	17.82	76.24	5.80	17.53	40	Aq. MeOH
12	CH_3	$C_3H_7COCH_2COC_6H_5$	82	P	C_3H_7	C_6H_5	Colorless needles	$C_{21}H_{20}N_4$	76.80	6.14	17.06	76.57	6.20	17.35	63	Aq. MeOH
13	CH_3	$C_6H_5COCH_2COC_6H_5$	135	P	C_6H_5	C_6H_5	Pale pink needles	$C_{24}H_{18}N_4$	79.44	5.01	15.55	79.58	5.13	15.37	85	EtOH
14	C_6H_5	$CH_3COCH_2COCH_3$	115	P	CH_3	CH_3	Colorless needles	$C_{19}H_{16}N_4$	75.98	5.37	18.65	75.67	5.25	18.36	70	MeOH
15	C_6H_5	$C_2H_5COCH_2COC_2H_5$	98	P	C_2H_5	C_2H_5	Colorless needles	$C_{21}H_{20}N_4$	76.80	6.14	17.06	76.66	6.08	17.26	57	Aq. MeOH
16	C_6H_5	$CH_3COCH_2COCH_2C_6H_5$	116	P	CH_3	$CH_2C_6H_5$	Colorless needles	$C_{25}H_{20}N_4$	79.76	5.36	14.88	79.53	5.32	14.67	62	Aq. MeOH
17	C_6H_5	$CH_3COCH_2COC_6H_5$	220	T	CH_3		Colorless needles	$C_{16}H_{12}N_4$							77	MeOH–pyr.
18	C_6H_5	$C_2H_5COCH_2COC_6H_5$	160	T	C_2H_5		Colorless needles	$C_{17}H_{14}N_4$							31	MeOH
19	C_6H_5	$C_3H_7COCH_2COC_6H_5$	146	T	C_3H_7		Colorless needles	$C_{18}H_{16}N_4$							52	MeOH
20	C_6H_5	$C_6H_5COCH_2COC_6H_5$	134	P	C_6H_5	C_6H_5	Pale yellow plates	$C_{29}H_{20}N_4$	82.05	4.75	13.20	81.69	4.80	13.50	76.4	EtOH
21	$-CH(CH_3)(C_2H_5)$	$CH_3COCH_2COCH_3$	64	P(C)	CH_3	CH_3	Colorless plates	$C_{17}H_{20}N_4$	72.82	7.19	19.99	72.51	7.20	19.67	71	Aq. MeOH
			145	T	CH_3		Colorless needles	$C_{14}H_{16}N_4$								MeOH
22	Same	$CH_3COCH_2COC_6H_5$	145	T	CH_3		Colorless needles	$C_{14}H_{16}N_4$							38	MeOH
23	Same	$C_2H_5COCH_2COC_6H_5$	123	T	C_2H_5		Colorless needles	$C_{15}H_{18}N_4$	70.83	7.13	22.04	70.49	6.93	22.34	26	*n*-Hexane

[a] All melting points are uncorrected. [b] Yields calculated for crude product. [c] B.p. 165-167° (3 mm.). [d] Conditions: no. 3, heat at 100–140° and triturate with petroleum ether; 7, heat at 140–180°; 10, heat for 20 min. at 130–160°; 11, heat for 1 hr. at 190°; 16, heat at 130–180°; 17, heat for 5 min. at 140–150°; 18, heat for 1 hr. at 180°; 19, heat for 1 hr. at 110–160°; 20, heat for 30 min. at 150–220° and triturate with butanol–petroleum ether; 21C, heat for 4 hr. at 150–160°; 22, heat for 3 min. at 130–140°; 23, heat for 1 hr. at 170°.



in the reaction of I with ethyl acetoacetate. Our results indicate that the factor determining this competitive reaction is the steric effect of the 3-substituent of I.

The formation of olefins by the pyrolysis of carboxylic esters appears to be analogous to the Chugaev reaction.[17-19] In this transformation, intermolecular hydrogen bonding of an oxygen atom is the first step which is followed by *cis* elimination as shown by Curtin.[20] We have, therefore, assumed that in the formation of a five-membered ring from XVIII the reaction proceeds through a cyclic transition state (XXII) which undergoes *cis* elimination with the formation of XIX.

The reaction of I (R = H) with the γ-diketone, $CH_3COCH_2CH_2COCH_3$, failed to give a crystalline product, but with I (R = CH_3, C_6H_5 or $CH(CH_3)$-C_2H_5) a pyridazine ring (XXI) was formed immediately; there was no evidence for the formation of a triazole ring by cleavage of a carbon–carbon bond of the intermediate hydrazone.

Experimental

2-Hydrazino-3-R-quinoxaline (I); 2-Chloro-3-phenylquinoxaline.—A mixture of 4 g. of 2-hydroxy-3-phenylquinoxaline[21] and 35 cc. of $POCl_3$ was refluxed for 30 minutes. The excess $POCl_3$ was distilled under diminished pressure, and the residue was carefully decomposed with water. The insoluble material was washed with ethanol and recrystallized from ethanol to give colorless needles of 2-chloro-3-phenylquinoxaline, m.p. 130°.

Anal. Calcd. for $C_{14}H_9N_2Cl$: C, 69.85; H, 3.77; N, 11.64. Found: C, 69.75; H, 3.85; N, 11.45.

To a solution of 0.1 mole of the chloroquinoxaline in 30 cc. of ethanol was added 15 cc. of hydrazine hydrate (80%), and the mixture was refluxed on a water-bath for 2 hours. The material which separated on cooling was crystallized from ethanol.

The hydrazinoquinoxalines prepared by this method are listed in Table VIII.

(1) **Reactions with Carboxylic Acid and Related Compounds.**—The following examples illustrate a general method.

Preparation of 1-Substituted *s*-Triazolo[4,3-a]quinoxaline. A. From I. (1) Carboxylic Acid.—A mixture of 2-hydrazino-3-methylquinoxaline (Im) (0.0025 mole) and 5 cc. of glacial acetic acid was refluxed gently for 2 hours. The excess acetic acid was distilled under reduced pressure, and the solid residue recrystallized from water. If an oil or a red pigment was obtained, the distillation residue was extracted with boiling ethyl acetate; the extract was heated with Norit, filtered and concentrated to dryness prior to recrystallization.

(2) **Acyl Chloride.**—Acetyl chloride (0.0023 mole) was added to cold pyridine (6 cc.). Then Ip (0.002 mole) was added with stirring and the mixture slowly heated on a steam-bath until most of the solid dissolved. The reaction mixture was heated at 100° for 1 hour and the solvent removed under reduced pressure. After the oily residue had been poured into water and allowed to stand at room temperature, the product separated. It was recrystallized from ethanol–pyridine with Norit as the decolorizing agent.

(3) **Acid Anhydride.**—A mixture of Im (0.0025 mole) and acetic anhydride (3 cc.) was refluxed for 1 hour, and then the excess acetic anhydride distilled under diminished pressure. The oily residue which separated soon solidified and was recrystallized from water.

(4) **Ortho Ester.**—Compound Ip (0.002 mole) was refluxed with ethyl orthoformate (5 cc.) for 1 hour. Upon cooling, almost pure triazoloquinoxaline separated, which was washed with methanol, dried and crystallized from methanol–pyridine.

B. From 2-Chloroquinoxaline. (1) Monoacylhydrazine.—2-Chloroquinoxaline (0.8 g.) was heated with monoacetylhydrazine (1.4 g.) in a mixture of ethanol (1.5 cc.) and pyridine (0.5 cc.) for 3 hours at 120° in a sealed tube. The mixture was then poured into water, and the solid which separated was extracted with boiling ethyl acetate to remove a red pigment. The extract was heated with Norit, filtered and concentrated to dryness. The crude product was recrystallized from methanol as colorless needles, m.p. 210°, yield 0.13 g. A mixed melting point determination with 1-methyl-*s*-triazolo[4,3-a]quinoxaline, obtained by the reac-

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(19) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 2459 (1949).

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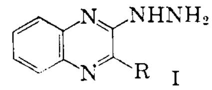
(21) H. Burton and C. W. Shoppee, *J. Chem. Soc.*, 548 (1937).

TABLE VIII


I

R	M.p.,[a] °C.	Appearance, needles	Yield,[b] %	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
H	167	Pale orange	87	$C_8H_8N_4$	59.97	5.04	34.99	60.03	5.21	34.85
CH_3	172	Pale orange	94	$C_9H_{10}N_4$	62.05	5.78	32.17	62.25	5.92	32.01
C_6H_5	140	Pale orange	93	$C_{14}H_{12}N_4$	71.16	5.12	23.72	70.96	5.25	23.56
$CH(CH_3)(C_2H_5)$[c]	112	Orange	80	$C_{12}H_{16}N_4$	66.64	7.46	25.90	66.84	7.31	26.26

[a] All melting points are uncorrected. [b] Yields calculated for crude product. [c] Recrystallized from methanol.

tion of 2-hydrazinoquinoxaline with acetic acid, showed no depression.

(2) **Diacylhydrazine.**—2-Chloroquinoxaline (0.4 g.) was heated with diacetylhydrazine (1.1 g.) in 3 cc. of ethanol for 4 hours at 120° in a sealed tube. The reaction mixture, treated as described above, yielded 0.1 g. of colorless needles, m.p. 210°; the mixed melting point with 1-methyl-*s*-triazolo[4,3-a]quinoxaline showed no depression.

1-Chloro-4-phenyl-*s*-triazolo[4,3-a]quinoxaline.—2-Hydrazino-3-phenylquinoxaline (0.002 mole) was added with stirring to 0.004 mole of ethyl chloroformate in 6 cc. of pyridine. The mixture was first heated slowly on a steam-bath until most of the solid dissolved, and then at 100° for 2 hours. The solvent was removed under reduced pressure. The oily residue was poured into water and the solid which separated was boiled for 15 minutes with a 4% sodium hydroxide solution, filtered, and the filtrate was neutralized with acetic acid. The 1-hydroxy-4-phenyl-*s*-triazolo[4,3-a]quinoxaline so obtained was recrystallized from acetic acid or pyridine.

This hydroxy compound (0.52 g.) was heated with a mixture of $POCl_3$ (4 cc.) and PCl_5 (1.2 g.) in a sealed tube for 6 hours at 200°. The reaction mixture was poured into water, and the resulting solid recrystallized from ethanol–pyridine to give 0.25 g. (5.5%) of the 1-chloro derivative, m.p. 135°.

Anal. Calcd. for $C_{15}H_9N_4Cl$: C, 64.17; H, 3.23; N, 19.96. Found: C, 63.94; H, 3.32; N, 19.84.

4-Substituted Tetrazolo[1,5-a]quinoxaline.—To an ice-cooled solution of 2-hydrazinoquinoxaline (0.0025 mole) in acetic acid (12%, 14 cc.) was added dropwise a solution of $NaNO_2$ (0.0026 mole) in water (2 cc.), and the mixture was kept at room temperature for 1 hour. The precipitate was recrystallized from methanol.

(1) **Reactions of I with Ketones and Aldehydes.**—The following procedures are typical of the reaction of I with ketones; the temperature and duration of heating varied.

With Methyl Ethyl Ketone; 1-Methyl-4-phenyl-*s*-triazoloquinoxaline(Tpm).—A mixture of methyl ethyl ketone (2 cc.) and 0.4 g. of Ip was refluxed for 30 minutes on a steam-bath, then the excess ketone was distilled and the residue was heated for 2 hours at 230°. The pyrolysis residue in the reaction flask was chilled and triturated with cold methanol. The crude product (0.19 g., m.p. 212°) was dissolved in methanol–pyridine, treated with charcoal and recrystallized to give colorless needles, m.p. 220°, which was undepressed on admixture with Tpm obtained by the reaction of Ip with acetic acid.

With Methyl Phenyl Ketone. (a) **1,4-Diphenyl-*s*-triazoloquinoxaline(Tpp).**—A mixture of acetophenone (0.24 g.) and Ip (0.4 g.) was heated for 4 hours at 180–200° (at this temperature, only the hydrazone was obtained) and then for 70 minutes at 260–270°. The pyrolysis residue, treated as above, yielded colorless needles melting at 235°; no depression of melting point occurred on admixture with Ipp prepared by the reaction of Ip with benzoyl chloride.

(b) **Hydrazone.**—Acetophenone (0.24 g.) was added to a solution of Ip (0.4 g.) in methanol; the mixture was refluxed for 2 hours and then chilled. The crude hydrazone (0.49 g.) was recrystallized from methanol, m.p. 125°.

Anal. Calcd. for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; N, 16.56. Found: C, 78.01; H, 5.45; N, 16.62.

With Methyl Benzyl Ketone; Detection of Toluene.—A mixture of methyl benzyl ketone (3 cc.) and Ip (4.7 g.) was heated for 6 hours at 150–230°. During the reaction the distillate was collected, taken up in ether and redistilled. The fraction boiling at 105–115° was identified as toluene by oxidation to benzoic acid with potassium permanganate. The pyrolysis residue, treated in the usual way, yielded Tpm.

With Methyl Amyl Ketone. 1,4-Dimethyl-*s*-triazoloquinoxaline(Tmm).—A mixture of methyl amyl ketone (1.5 cc.) and Im (0.6 g.) was heated for 3 hours at 150° and then for 4 hours at 240°. The pyrolysis residue was chilled and triturated with cold ethyl acetate. The crude product (0.27 g.) was dried on a porcelain plate and recrystallized from ethyl acetate as colorless needles, m.p. 196°; the melting point was not depressed on admixture with Tmm obtained by the reaction of Im and acetic acid.

With Methyl Benzyl Ketone. Hydrazone.—Methyl benzyl ketone (0.4 cc.) was added to a solution of Im (0.43 g.) in methanol; the mixture was kept at room temperature for 24 hours, after which the methanol was allowed to evaporate at room temperature. The hydrazone, m.p. 127°, was recrystallized from methanol at a low temperature.

Anal. Calcd. for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25; N, 19.30. Found: C, 74.44; H, 6.27; N, 19.01.

The following procedures are typical for the reaction of I with aldehydes; the temperature and duration of the pyrolysis varied somewhat.

With Benzaldehyde.—Benzaldehyde (0.21 g.) was added to a solution of Ip (0.4 g.) in methanol, the mixture was heated for 5 minutes on a steam-bath, and the hydrazone separated. The hydrazone was recrystallized from methanol and dried at 100° (2 mm.); m.p. 118°.

Anal. Calcd. for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.81; H, 5.05; N, 17.10.

The hydrazone was heated for 1 hour at 230–250°; then the pyrolysis residue was chilled and triturated with methanol. The crude product (0.36 g.) was recrystallized from methanol–pyridine as colorless needles which melted at 235° alone and on admixture with Ipp.

(3) **Reaction of I with α-Ketonic Acid.**—The following examples illustrate a general method.

Reaction of 2-Hydrazino-3-phenylquinoxaline (Ip) with Pyruvic Acid. (a) **Formation of The Hydrazone VII** ($R = CH_3$, $R' = COOH$).—To a solution of Ip (0.7 g.) in methanol (30 cc.) was added 0.34 g. of pyruvic acid; the mixture was heated for a few minutes on a steam-bath and cooled. The solid was collected, washed with cold methanol and dried.

(b) **Pyrolysis.**—The hydrazone (0.47 g.) was heated at 200° until foaming ceased, about 40 minutes. The pyrolysis residue, treated as described under the reaction of Ip with methyl ethyl ketone, yielded Tpm, m.p. 220°.

(c) **Boiling with Carboxylic Acid.** (i).—A mixture of the hydrazone (0.6 g.) and glacial acetic acid (15 cc.) was refluxed for 20 hours. The excess acetic acid was distilled under diminished pressure, and the residue was triturated with cold methanol. The crude product (0.25 g.) was recrystallized from methanol–pyridine to give Tpm, m.p. 220°.

(ii). A mixture of the hydrazone (0.6 g.) and propionic acid (15 cc.) was refluxed for 24 hours and treated as above. The crude product (0.26 g.) was recrystallized from ethyl acetate to give colorless needles, m.p. 160°, which were identified by a mixed melting point determination with 1-ethyl-4-phenyl-*s*-triazolo[4,3-a]quinoxaline (Tpe) obtained by the reaction of Ip and propionyl chloride.

(iii).—A mixture of the hydrazone (0.6 g.) and butyric acid (18 cc.), treated as in the preceding experiment, yielded 1-propyl-4-phenyl-*s*-triazolo[4,3-a]quinoxaline (Tppr), m.p. 146°, which was identified by a mixed melting point determination with an authentic sample prepared from Ip and butyryl chloride.

(4) **The Reaction between I and β-Ketonic Esters.**—The following procedures exemplify general methods; experimental details are included in Table VI.

Preparation of 1-(3-R-Quinoxalin-2-yl)-3-R′-4-R″-2-pyrazolin-5-ones. (a).—A mixture of ethyl ethylacetoacetate (0.0031 mole) and Im (0.0025 mole) was heated in an oil-bath for 2 hours at 140–150°. The mixture was chilled and triturated with cold ethyl acetate. The crude product was recrystallized from ethyl acetate (Table VI, 1, 2 and 7).

(b).—A mixture of ethyl benzoylacetate (0.0039 mole) and Ip (0.0026 mole) was heated in an oil-bath for 3 hours at 160–180°. The mixture was chilled and triturated with methanol. The crude product was recrystallized from pyridine.

Preparation of Lactone-type Pyrazolone.—A mixture of Im (0.43 g.) and ethyl acetoacetate (1.5 cc.) was heated in an oil-bath under reflux for 5 hours. The yellow needles which separated were washed with cold methanol and recrystallized from methanol–pyridine.

Preparation of 1-R′-4-R-*s*-Triazolo[4,3-a]quinoxaline.—A mixture of ethyl acetoacetate (0.003 mole) and 2-hydrazino-3-*sec*-butylquinoxaline (0.002 mole) was heated for 1 hour at 90–100° and then for 4 hours at 150–180°. The pyrolysis residue in the reaction flask was chilled and triturated with petroleum ether to remove decomposition tars. The residue was dissolved in methanol, treated with Norit, and recrystallized to give 1-methyl-4-*sec*-butyl-*s*-triazolo-[4,3-a]quinoxaline as colorless needles, m.p. 145.5°.

(5) **The Reaction between I and Diketones. Reaction of I with β-Diketones.**—The following examples illustrate a general method; experimental details are given in Table VII.

(a).—A mixture of 2-hydrazinoquinoxaline (0.0025 mole) and $CH_3COCH_2COCH_3$ (0.003 mole) was heated in an oil-bath at 120–160° until foaming ceased. The reaction mixture was chilled and triturated with cold methanol. The crude product was recrystallized from methanol to give 1-(quinoxalin-2-yl)-3,5-dimethylpyrazole as colorless needles (no. 3, 4, 5, 6, 7, 11, 12, 16, 20 and 21; Table VII).

(b).—To a solution of 2-hydrazinoquinoxaline (0.0025 mole) in ethanol (5 cc.) was added 0.003 mole of $C_2H_5COCH_2COC_2H_5$, and the mixture was refluxed for 30 minutes. The reaction mixture was distilled under a diminished pressure and the residue was triturated with aqueous methanol. The crude product was recrystallized from aqueous methanol to give 1-(quinoxalin-2-yl)-3,5-diethylpyrazole as colorless needles (no. 8, 9, 13, 14 and 15).

(c).—A mixture of Ip (0.0025 mole) and $CH_3COCH_2COC_6H_5$ (0.003) mole was heated for 5 minutes at 140–150°. The crude product was recrystallized from methanol–pyridine as colorless needles, m.p. 220°, which were identified by a mixed melting point determination with Tpm (no. 10, 18, 19, 22 and 23).

(d).—A mixture of 2-hydrazino-3-*sec*-butylquinoxaline (0.0025 mole)and $CH_3COCH_2COCH_3$ (0.005 mole) in methanol was heated for 3 hours at 200–220° in a sealed tube, the reaction mixture was triturated with petroleum ether, and the residue was recrystallized from methanol. The product separated as colorless needles; the melting point (145°) was not depressed on admixture with 1-methyl-4-*sec*-butyl-*s*-triazolo[4,3-a]quinoxaline.

Reaction of I with the γ-Diketone.—$CH_3COCH_2CH_2COCH_3$. (a).—A mixture of Im (0.38 g.) and $CH_3COCH_2CH_2COCH_3$ (0.38 g.) was heated for 1 hour at 150–250°. The reaction mixture was chilled and triturated with petroleum ether. The crude product (0.48 g.) was recrystallized from aqueous ethanol to give yellow needles of 1-(3-methylquinoxalin-2-yl)-3,6-dimethyl-4-hydropyridazine, m.p. 203°.

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 71.40; H, 6.47; N, 22.08.

(b).—A mixture of Ip (0.4 g.) and the γ-diketone (0.23 g.) was heated for 20 minutes at 140–150°. The crude product (0.4 g.) was recrystallized from ethanol to give colorless needles of 1-(3-phenylquinoxalin-2-yl)-3,6-dimethyl-4-hydropyridazine, m.p, 184°.

Anal. Calcd. for $C_{20}H_{18}N_4$: C, 76.41; H, 5.77; N, 17.82. Found: C, 76.85; H, 5.77; N, 17.57.

(c).—Colorless needles of 1-(3-*sec*-butylquinoxalin-2-yl)-3,6-dimethyl-4-hydropyridazine were prepared by procedure b; m.p. 142°.

Anal. Calcd. for $C_{18}H_{22}N_4$: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.23; H, 7.61; N, 19.31.

OKUDA, TOYAMA, JAPAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TEXAS TECHNOLOGICAL COLLEGE]

The "Thermal" Rearrangement of Hydrazo Compounds. III.[1] The Kinetics and Mechanism of the Rearrangement of 2,2′-Hydrazonaphthalene in Polar Solvents

BY H. J. SHINE AND J. C. TRISLER[2]

RECEIVED JANUARY 11, 1960

The products of rearrangement of 2,2′-hydrazonaphthalene (I) in ethanol, aqueous ethanol, acetone and tetrahydrofuran have been quantitatively isolated. The two products, 2,2′-diamino-1,1′-binaphthyl (II) and 3,4:5,6-dibenzocarbazole (III) are formed in approximately the same proportions in these solvents; that is 80–85% of II and 15–20% of III. The rates of rearrangement of I have been measured in these solvents and in others at several temperatures. At 80° the rates in anhydrous ethanol are faster than those in acetone, dioxane, tetrahydrofuran and pyridine, the rates in the last four solvents being close to each other. The rate of rearrangement in aqueous ethanol increases with water concentration and a plot of log rate constant against Grunwald–Winstein "Y" values is linear. From rates of rearrangement at 80°, 90°, 98° and 105° in ethanol, dioxane and pyridine, the activation energies and entropies of activation were found to be 23.2, 29.5 and 30.9 kcal./mole and −13.4, −4.6 and −1.6 cal./deg./mole. Attempts to obtain similar data for acetone and tetrahydrofuran solutions were not successful. It is believed that these experiments show that the rearrangement of I in hydroxylic solvents involves a transition state that is polar. It is believed that the rate is enhanced in solutions of alcohols by hydrogen-bonding from hydroxyl hydrogen to the hydrazo nitrogens. The transformation of I to II and III *via* the polar transition state thus formed is enhanced as the solvent becomes more ionizing; that is, more aqueous. The rates of rearrangement in the non-ethanolic solutions are believed to suffer some retardation by hydrogen-bonding from hydrazo hydrogen to solvent, but for the most part to be independent of the solvent.

In recent years, the mechanism of an unusual type of benzidine rearrangement, a so-called "thermal" rearrangement, has been the subject of research in several laboratories. Several interpretations have been given. The base-catalysis idea of the original discoverers, Meisenheimer and Witte,[3] was shown to be incorrect by Krolik and Lukashev-

(1) From the Ph.D. thesis of J. C. Trisler, Texas Technological College, 1959. For Part II see ref. 5. Part of this work was presented at the Meeting of the American Chemical Society, Fall, 1958.

(2) Robert A. Welch Foundation Fellow, 1956–1959.

(3) J. Meisenheimer and K. Witte, *Ber.*, **36**, 4153 (1903).