worked up as described above. wt. 60 mg (37%); mp 145—146°; $[\alpha]_D^{22}$ +89° (c=0.2, H_2O) {*cyclo*(–DPro–Phe–)[8a]: mp 148—150°; $[\alpha]_D^{20}$ +92° (c=0.2, H_2O)}.

Acknowledgement We are grateful to Misses C. Chida for her assistance and to the staff of the Central Analysis Laboratory, Department of Chemistry, Tohoku University for elemental analysis.

References and Notes

1) Amino acids, peptides and their derivatives are of the L-configuration unless otherwise stated. Abbreviations used are those recommended by the IUPAC-IUB Commission on Biochemical Nomenclature: *Biochemistry*, **11**, 1726 (1972). Other abbreviations: Boc=*tert*-butoxycarbonyl, Z=benzyloxycarbonyl, Me=methyl, Et=ethyl, Bzl=benzyl, Bzl(NO_2)=*p*-nitrobenzyl, NMM=N-methylmorpholine, TLC=thin-layer chromatography.
2) Location: *Komatsushima, Sendai 983, Japan.*
3) E. Fischer, *Chem. Ber.*, **39**, 2893 (1906).
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Synthesis of Furan Derivatives. LXXXVII. Kinetic Studies of the Thermal Curtius Rearrangement of 2-Benzofuroyl Azide and Related Compounds[1]

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(Received May 30, 1980)

The kinetics of the thermal Curtius rearrangement of benzoheteroaroyl azides, *i.e.*, 2-benzofuroyl azide (**2**), 2-benzothenoyl azide (**4**), 2-indolecarbonyl azide (**6**), 2-, 3-, 4-, 5-, 6-, and 7-quinolinecarbonyl azides (**8**, **10**, **12**, **13**, **14**, and **15**), and 1- and 2-naphthoyl azides (**17** and **18**), in toluene were studied by infrared spectrophotometry to determine how the annelation of the benzene ring to side *b* of 2-furoyl, 2-thenoyl, and 2-pyrrolecarbonyl azides (**1**, **3**, and **5**) and 2-, 3-, and 4-pyridinecarbonyl azides (**7**, **9**, and **11**) affects the rearrangement and its rate.

The annelation effect slightly promotes the rearrangement; the effect on the thiophene ring and pyrrole ring is greater than that on the furan ring, and the effect on the pyridine ring of 4-pyridinecarbonyl azide (**11**) is greater than that on the pyridine ring of 2- and 3-pyridinecarbonyl azides (**7** and **9**).

Keywords——acyl azide; thermal Curtius rearrangement; annelation effect; infrared spectrophotometric method; activated three-membered intermediate; compensation effect; structure-activity relationship; PMO method; intramolecular electrophilic reagent; electron-deficient nitrogen

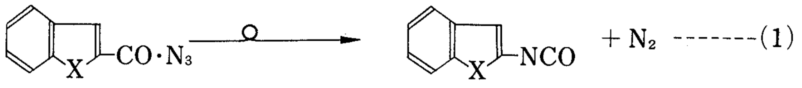
The kinetics of the thermal Curtius rearrangement of acyl azides to the corresponding isocyanates in inert solvents have been widely investigated,2) and questions pertaining to several mechanistic aspects of this reaction have been amply discussed.3) It has been reported2b,d) that electron-releasing groups in the *meta* position of benzoyl azide increase the rate of the rearrangement and that electron-attracting groups decrease it, whereas all substituents in the *para* position decrease the rate. Furthermore, in the cases of the acyl azides of furan, thiophene, and pyridine, structural variation of the heteroaromatic ring does not exert a powerful influence on the rate as compared with the case of benzoyl azide. Previously4) we reported a comparative kinetic study of the substitution effect in the rearrangement of five-membered heteroaromatic acyl azides, *i. e.*, 5-substituted 2-furoyl and 5-substituted 2-thenoyl azides, and six-membered aromatic or heteroaromatic acyl azides, *i. e.*, *p*-substituted benzoyl and 2-, 3-, and 4-pyridinecarbonyl azides, by an infrared (IR) spectrophotometric method. Our data indicated that the substituents of furoyl and thenoyl azides had little influence on the rate of the rearrangement as compared with the unsubstituted acyl azides. Subsequently, our attention has been focused on the effect of fusion of a benzene ring to side *b* of five- or six-membered heteroaromatic acyl azides such as 2-furoyl azide (**1**), 2-thenoyl azide (**3**), 2-pyrrolecarbonyl azide (**5**), and 2-, 3-, and 4-pyridinecarbonyl azides (**7**, **9**, and **11**).

We now report a kinetic study of the thermal Curtius rearrangement of 2-benzofuroyl azide (**2**), 2-benzothenoyl azide (**4**), 2-indolecarbonyl azide (**6**), and 2-, 3-, and 4-quinolinecarbonyl azides (**8**, **10**, and **12**), which was undertaken to determine the annelation effect5) on the rearrangement rate. For reference, comparative experiments on 5-, 6-, and 7-quinolinecarbonyl azides (**13**, **14**, and **15**) and 1- and 2-naphthoyl azides (**17** and **18**) were carried out.6)

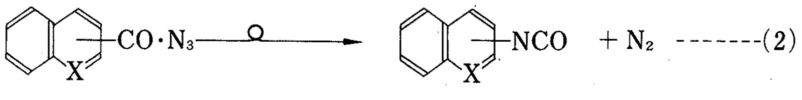
All authentic acyl azides (**1**—**18**) used in the present experiments were readily prepared by the diphenyl phosphorazidate (DPPA) method7) (see "Experimental").

Results and Discussion

The rearrangement of the above bicyclic acyl azides to the corresponding isocyanates in toluene takes place quantitatively according to the stoichiometric equations 1 and 2 (Chart 1). The rearrangement was followed kinetically, as described previously;4) the acyl azides



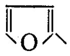
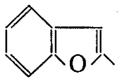
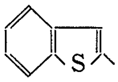
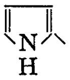
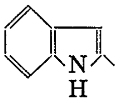
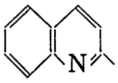
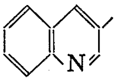
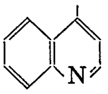
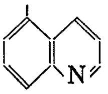
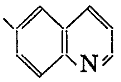
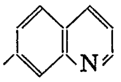
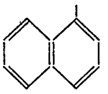
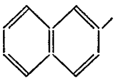
No.	X
2	O
4	S
6	NH



No.	X	Position of $-CO\cdot N_3$
8	N	2
10	N	3
12	N	4
13	N	5
14	N	6
15	N	7
17	C	1
18	C	2

Chart 1

Table I. Kinetic Results for the Curtius Rearrangement of Aroyl or Heteroaroyl Azides ($Ar \cdot CO \cdot N_3$)

No.	Ar	Rate constant, $k \times 10^5$ (sec^{-1})								$\Delta E^{\neq}$ kcal/mol	log PZ (sec^{-1})	$\Delta S^{\neq}$ at 80° (e.u.)
		30°	40°	50°	60°	70°	80°	90°	100°			
1						5.00	11.5	32.5	88.8	$24._5$	$11._3$	$-8._9$
2						4.60	15.7	44.8	135	$28._4$	$13._8$	$2._3$
3						3.20	8.02	28.8	90.7	$28._7$	$13._7$	$2._1$
4					1.39	4.22	14.3	40.3		$26._4$	$12._4$	$-3._5$
5						1.47	3.32	9.65	27.7	$24._5$	$10._7$	-11
6						3.17	10.0	29.5	76.7	$27._0$	$12._7$	$-2._3$
7						32.2	79.5	258	670	$26._1$	$13._1$	-0.6_7
8				2.03	8.77	31.8	123			$29._3$	$15._2$	$8._7$
9						6.65	17.8	58.5	170	$27._7$	$13._4$	0.8_7
10					2.08	7.35	20.7	61.8		$25._8$	$12._3$	$-4._4$
11						6.58	17.2	58.5	183	$28._4$	$13._9$	$2._7$
12			6.02	22.5	74.8	237	(652)[a]			$25._1$	$13._4$	0.4_8
13			5.97	20.7	69.2	208	(622)[a]			$24._4$	$12._8$	$-1._9$
14						6.72	21.7	69.0	213	$29._3$	$14._5$	$5._5$
15				0.657	2.45	8.30	24.7	79.7		$27._3$	$13._3$	0.2_7
16						6.50	17.7	58.8	167	$27._8$	$13._5$	$1._0$
17		2.18	8.63	35.0	118		(122_5)[a]			$26._3$	$14._3$	$4._8$
18					1.90	6.85	25.0	75.7		$28._8$	$14._2$	$4._4$

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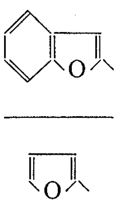
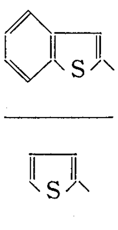
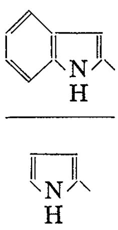
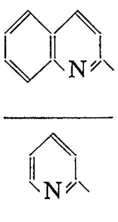
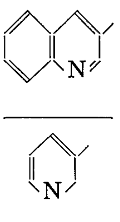
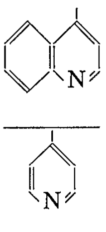
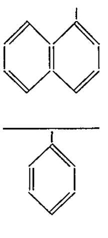
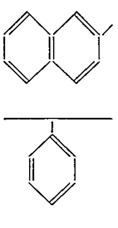
a) Calculated from the Arrhenius equation.

Table II. Effect of Annelation on the Partial Relative Rates of the Curtius Rearrangement in Benzofuroyl Azide and Related Compounds

								
$\frac{k_B{}^{a)}}{k_M{}^{b)}}$	1.3	1.7	3.0	1.5	1.1	37	69	1.4

a) k_B: rate constant of the bicyclic acyl azide at 80°.
b) k_M: rate constant of the monocyclic acyl azide at 80°.

gave good pseudo-first-order kinetics up to about 75% completion of each reaction. First-order rate constants (k) for the bicyclic and the corresponding monocyclc acyl azides are listed in Table I. The activation energies ($\Delta E^{\neq}$) and the frequency factors (log PZ) were calculated from the Arrhenius equation by the least-squares method (Table I). The partial relative rates between the bicyclic and the corresponding monocyclic acyl azides at 80° are presented in Table II.

The data shown in Tables I and II indicate that the rate of rearrangement of the bicyclic acyl azides is faster than that of the corresponding monocyclic acyl azides. Interestingly, the reaction velocities of 4- and 5-quinolinecarbonyl azides (**12** and **13**) and 1-naphthoyl azide (**17**) are faster than those of 2- and 3-quinolinecarbonyl azides (**8** and **10**) and 2-naphthoyl azide (**18**). According to the perturbational molecular orbital (PMO) method,[8] the position of attack in an electrophilic or nucleophilic substitution reaction is determined by the magnitude of the delocalization energy (ΔE_{deloc}) or reactivity number ($N_{r'}$,) of each atomic center. The smaller the value of $N_{r'}$, the easier the reaction.[9] For example, the calculated $N_{r'}$,[8,9] values (Chart.2) for benzene and the 1- and 2-positions in naphthalene predict that naphthalene is more reactive to electro- or nucleophiles than benzene (1.81 or 2.12 for naphthalene$<$2.31 for benzene). Similarly, naphthalene preferentially undergoes substitution at the 1-position rather than the 2-position (1.81 for the 1-position $<$2.12 for the 2-position). Qualitatively, the trends of reactivity observed in our experiments with benzoyl azide (**16**) and 1- and 2-naphthoyl azides (**17** and **18**) agree well with those predicted by the PMO method.

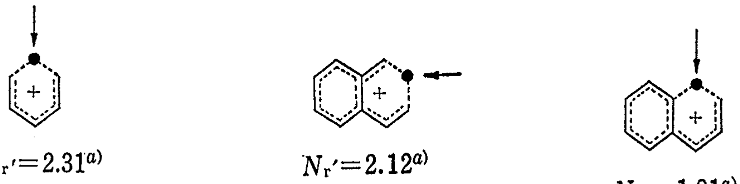

$N_{r'}=2.31^{a)}$
$N_{r'}=2.12^{a)}$
$N_{r'}=1.81^{a)}$
a) Lit. 10)

Chart 2

As shown in Fig. 1, the plot of log k at 80° in the reaction of monocyclic acyl azides against that of the corresponding bicyclic acyl azides is linear with a slope of 1.88 (r=0.961), except for 2-pyridine- and 2-quinolinecarbonyl azides (**7** and **8**), benzoyl and 1-naphthoyl azides (**16** and **17**), 4-pyridine- and 4-quinolinecarbonyl azides (**11** and **12**), and benzoyl and 5-quinolinecarbonyl azides (**16** and **13**). A higher value than unity indicates that each fused ring of the bicyclic acyl azides is more efficient than the single ring of the corresponding

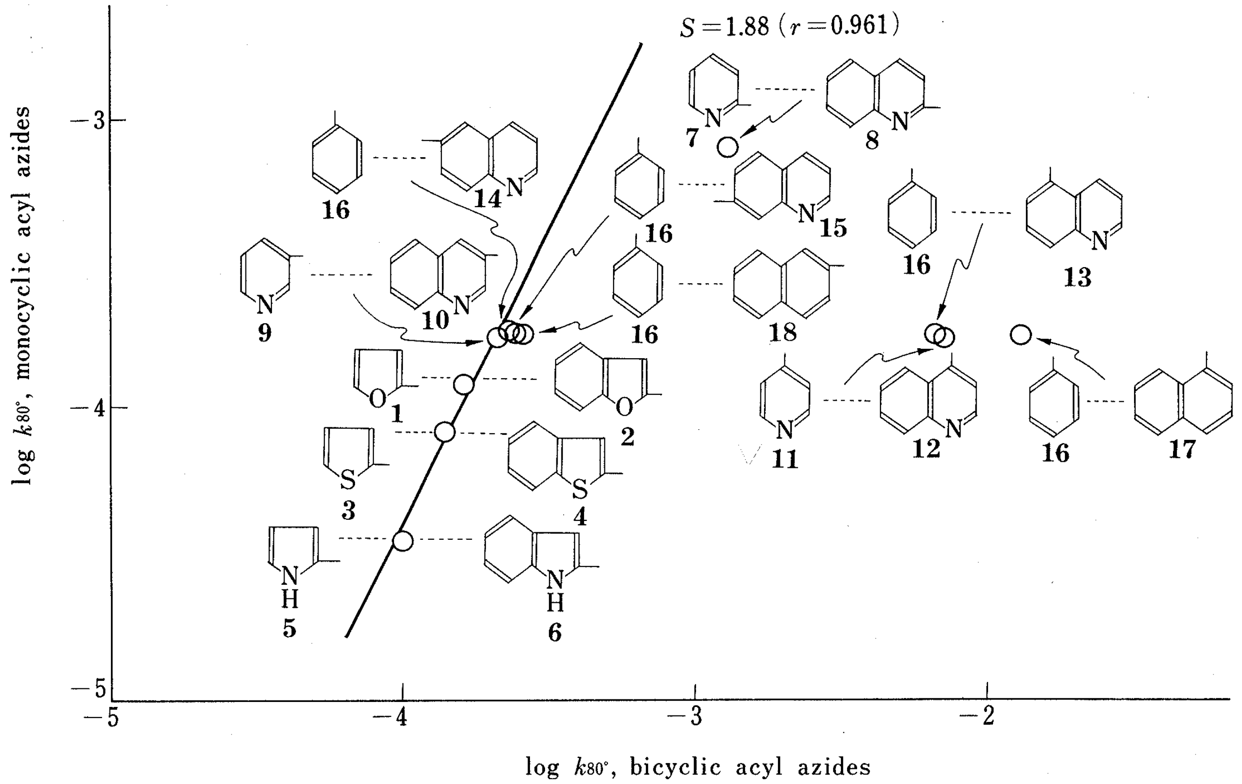
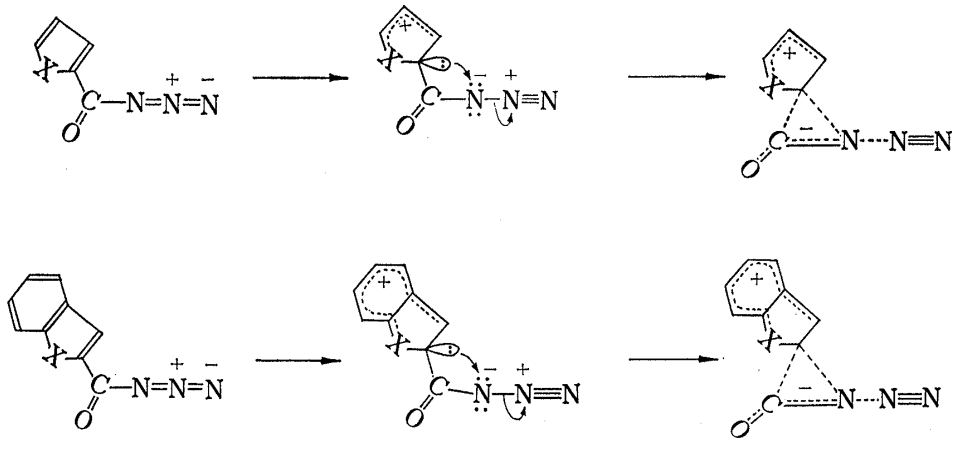


Fig. 1



X : O, S, and NH

Chart 3

monocyclic acyl azides in transmitting an electronic effect from the aromatic ring to the electron-deficient nitrogen which acts as an intramolecular electrophilic reagent. Accordingly, the higher velocity of rearrangement of the bicyclic acyl azides than the corresponding monocyclic acyl azides may be ascribable to readier formation of an activated three-membered intermediate as a transition state (Chart 3).

Regarding the activation parameters (Table I), qualitative considerations indicate that $\Delta E^{\ddagger}$ and $\log PZ$ tend to compensate for each other. As shown in Fig. 2, the plot of $\Delta E^{\ddagger}$ against $\log PZ$ for the rearrangement of the bicyclic acyl azides is linear with a slope of 0.654 ($r=0.991$), except for 1-naphthoyl azide (**17**), 2-, 4-, and 5-quinolinecarbonyl azides (**8**, **12**, and **13**), and 2-indolecarbonyl azide (**5**). This value is close to that of 0.619 for six-membered aromatic or heteroaromatic acyl azides, as reported previously.[4] The linear relationship between $\Delta E^{\ddagger}$

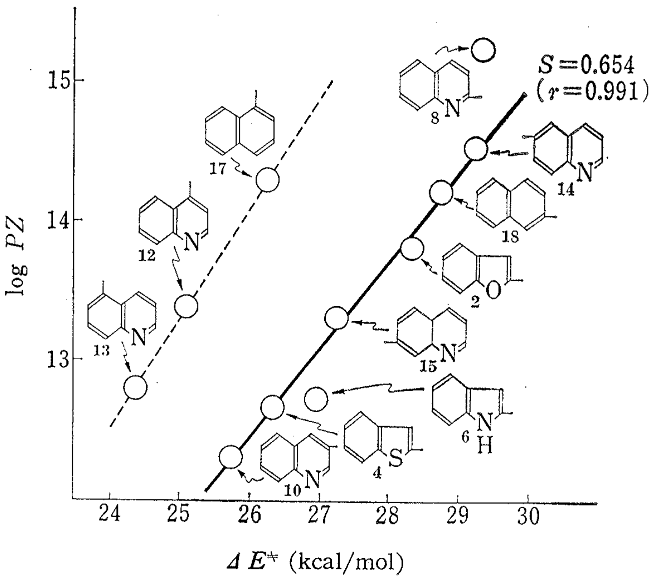


Fig. 2. The Compensation Effect in the Curtius Rearrangement of Benzoheterocycles and Related Compounds

and log PZ suggests that the rearrangements of the compounds (**2**, **4**, **9**, **14**, and **18**) proceed along the same reaction pathway.

In conclusion, the annelation effect of the benzene ring fused to side *b* of 2-furoyl, 2-thenoyl, and 2-pyrrolecarbonyl azides (**1**, **3**, and **5**) and 2-, 3-, and 4-pyridinecarbonyl azides (**7**, **9**, and **11**) slightly promotes the thermal Curtius rearrangement, as compared with the corresponding parent acyl azides. The effect on the rate constants of compounds **1**, **3**, and **5** is to increase them by factors of 1.0, 1.3, and 2.3, respectively, and in the case of compounds **7**, **9**, and **11**, by factors of 1.3, 1.0, and 33, respectively (Table II). Thus, the annelation effect on thiophene and pyrrole rings is greater than that on the furan ring, and the effect on the pyridine ring of 4-pyridinecarbonyl azide (**11**) is greater than that on the pyridine ring of 2- and 3-pyridinecarbonyl azides (**7** and **9**). In addition, the rearrangement of 4- and 5-quinolinecarbonyl azides (**12** and **13**) and 1-naphthoyl azide (**17**) takes place faster than that of the other quinolinecarbonyl azides (**8**, **10**, **14**, and **15**) and 2-naphthoyl azide (**18**).

Experimental[10]

Materials[11]——The acyl azides (**1**—**18**) used for the rearrangement experiments were directly prepared by the reaction of the corresponding carboxylic acid with DPPA[7] in the presence of an equal amount of triethylamine, as described previously;[12] 2-furoyl azide (**1**),[13] mp 62—63°; 2-benzofuroyl azide (**2**),[14] mp 108—109°; 2-thenoyl azide (**3**),[2d,4] mp 32—33°; 2-benzothenoyl azide (**4**),[15] mp 110—111°; 2-pyrrolecarbonyl azide (**5**),[4] mp 101—103°; 2-indolecarbonyl azide (**6**),[16] mp 141—142°; 2-pyridinecarbonyl azide (**7**),[2d] mp 49—50°; 2-quinolinecarbonyl azide (**8**),[17] mp 105—107°; 3-pyridinecarbonyl azide (**9**),[2d] mp 47—48°; 3-quinolinecarbonyl azide (**10**),[18] mp 92—93°; 4-pyridinecarbonyl azide (**11**),[2d] mp 50—51°; benzoyl azide (**16**),[2b] mp 27—28°; 2-naphthoyl azide (**18**),[2d] mp 76—77°.

4-Quinolinecarbonyl Azide (**12**)——A solution of DPPA (2.7 g, 0.01 mol) in dimethylformamide (DMF) was added dropwise to a DMF solution (10 ml) of 4-quinolinecarboxylic acid[19] (1.7 g, 0.01 mol) and triethylamine (1 g, 0.01 mol) with stirring in an ice-water bath. The resulting mixture was stirred for 1.5 hr in an ice-water bath, and immediately poured into a mixture of ether and ice. The organic layer was washed with 10% sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. The ether layer was concentrated *in vacuo* to give 1.7 g (85%) of **12**, which was recrystallized from cyclohexane–ether (1: 1) to yield colorless needles, mp 67—68°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2150 (N_3).

5-Quinolinecarbonyl Azide (**13**)——Compound (**13**) was prepared by the reaction of 5-quinolinecarboxylic acid[19] (1.7 g, 0.01 mol) with DPPA (2.7 g, 0.01 mol) and triethylamine (1 g, 0.01 mol) by the same procedure as used for **12**, and was recrystallized from cyclohexane-ether (1: 1) to yield colorless needles, 1.6 g (80%), mp 56—57°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2160 (N_3).

6-Quinolinecarbonyl Azide (**14**)——A DMF solution (3 ml) containing DPPA (2.7 g, 0.01 mol) was added dropwise to DMF (10 ml) containing 6-quinolinecarboxylic acid[19] (1.7 g, 0.01 mol) and triethylamine (1 g, 0.01 mol) with stirring in an ice-water bath. The resulting mixture was stirred for 3 hr at room temperature, and poured into a mixture of ether and ice. The organic layer was washed with 10% sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. The ether layer was concentrated *in vacuo* to give 1.7 g (85%) of **14**, which was recrystallized from cyclohexane–benzene (1: 1) as pale yellow needles, mp 94—95°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2160 (N_3).

7-Quinolinecarbonyl Azide (**15**)——Compound (**15**) was prepared by the reaction of 7-quinolinecarboxylic acid[19] (1.7 g, 0.01 mol) with DPPA (2.7 g, 0.01 mol) and triethylamine (1 g, 0.01 mol) by the same procedure as used for **14**, and was recrystallized from cyclohexane–benzene (1 : 1) to yield pale yellow needles, 1.5 g (75%), mp 112—114°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2150 (N_3).

1-Naphthoyl Azide (17)——Compound (**17**) was prepared by the reaction of 1-naphthalenecarboxylic acid (1.7 g, 0.01 mol) with DPPA (2.7 g, 0.01 mol) and triethylamine (1 g, 0.01 mol) by the same procedure as used for **12** to yield a colorless oily material, 1.4 g (71%). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2150 (N_3).

All acyl azides (**1**—**18**) were used without further purification. Before measurement, they were dried over phosphorus pentoxide.

Kinetic Procedure——The kinetics of the thermal Curtius rearrangement of acyl azides (**1**—**18**) were studied by means of the IR spectrophotometric method described previously.[4] Toluene[20] (50 ml) was heated with stirring in a thermostat-controlled oil-bath[21] at the temperatures shown in Table I. Each acyl azide (about 0.1 g) was added and about 0.3 ml portions of the reaction mixture were quickly withdrawn at regular intervals. The IR spectra of chilled samples were checked from 2400 cm^{-1} to 2000 cm^{-1} *vs* toluene. The amount of unchanged acyl azide was obtained from the intensity of the characteristic -N_3 asymmetric stretching at 2140—2160 cm^{-1}. There was no interference of this band with that of the corresponding rearrangement product, isocyanate.

The pseudo-first-order rate constants (k) were calculated from the customary first order rate expression as follows;

$$k = 2.303/t \cdot \log a/x$$

where a is the initial concentration (mol/l) of each acyl azide, and x is the residual concentration (mol/l) of the unchanged acyl azide at time t (sec.). All reactions were repeated twice to at least 75—80% completion with less than 3% deviation of the two rate constants. Activation parameters ($\Delta E^{\neq}$ and log PZ) were calculated from the Arrhenius equation by least-squares treatment of a plot of log k against $1/T$.

Acknowledgement The authors are indebted to Dr. S. Kumada, Director of Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., and Dr. U. Kashihara, Ueno Chemical Applied Research Laboratories, for providing many intermediates.

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[Chem. Pharm. Bull. 29(1) 244—249 (1981)]

Reaction of N-Hydroxyacetoacetanilide with Carbonyl Reagents[1,2]

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(Received July 24, 1980)

The reaction of N-hydroxyacetoacetanilide derivatives (**1a**—**g**) with hydroxylamine in aqueous ethanol gave 3-methyl-4-arylhydrazono-5-isoxazolones (**3a**—**g**). When ethanol or chloroform was used as the reaction medium, the reaction of N-hydroxyacetoacetanilide (**1a**) with carbonyl reagents gave N-phenylhydroxylamine derivatives and five-membered heterocycles such as 3-methyl-5-isoxazolone or 3-methyl-5-pyrazolone derivatives.

The mechanism of the formation of these products is discussed.

Keywords——N-hydroxyacetoacetanilide; carbonyl reagents; cyclization; elimination; 3-methyl-4-arylhydrazono-5-isoxazolone; 3-methyl-5-pyrazolone; 1-phenyl-3-methyl-5-pyrazolone

Reactions of 1,3-dicarbonyl compounds such as β-ketoesters or β-diketones with carbonyl reagents are widely used for the preparation of heterocyclic compounds such as pyrazolone and isoxazolone derivatives.[3] In connection with our continuing studies on acetoacetyl compounds, we have been interested in the synthetic utility of N-hydroxyacetoacetanilide as a 1,3-dicarbonyl substrate in the reaction with carbonyl reagents. The reason for this is that N-hydroxyacetoacetanilide has not only an acetoacetyl moiety but also an N-hydroxy group in its structure. The reaction of N-hydroxyacetoacetanilide derivatives with carbonyl reagents gave isoxazolone or pyrazolone derivatives through the oxime, hydrazone, or semicarbazone intermediates followed by cyclization and elimination of the N-phenylhydroxylamine moiety. The present paper describes these results in detail.

Following the procedure described in the literature,[4] N-hydroxyacetoacetanilide (**1a**, R=H) was allowed to react with a 3-fold molar excess of hydroxylamine in aqueous ethanol to give a yellow crystalline product (**3a**), $C_{10}H_9N_3O_2$, mp 189°, and azoxybenzene (**4a**) in 23.8 and 41.7% yields, respectively.

Compound **3a** was identified as 3-methyl-4-phenylhydrazono-5-isoxazolone by comparison of its spectral data with those of an authentic sample reported in the literature[5]: the infrared (IR) spectrum of **3a** showed characteristic bands at 3200 cm^{-1} (NH) and 1710 cm^{-1} (C=O). The nuclear magnetic resonance (NMR) spectrum of **3a** showed signals at 2.36 ppm (3H, singlet, 3-CH_3), 12.6 ppm (1H, broad, disappeared on addition of D_2O, NH) as well as aromatic proton signals at about 7.4 ppm (5H). The mass spectrum of **3a** showed its molecular ion peak at *m*/*e* 203.

Similarly, other N-hydroxyacetoacetanilide derivatives (**1b**—**g**) were allowed to react