The author is grateful to Dr. T. Naito, Subdirector of this Laboratory for his kind and unfailing guidance, and to Dr. A. Okano for valuable discussion and suggestions during the course of this work. The author wishes also to thank Mr. B. Kurihara and Miss K. Hanawa for elemental analyses.

Summary

The rearrangement reaction products of N-acetoacetyl, N-phenylacetyl, and N-cyanoacetyl derivatives of 2- and 4-pyridinesulfonamide 1-oxides with 10% sodium hydroxide at a room temperature were studied and their structures were confirmed.

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86. Renzo Dohmori : Rearrangement of Sulfonamide Derivatives. VIII.*1 Kinetics of the Rearrangement Reaction of Sulfonamide Derivatives with Alkali.

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In the previous paper[1] of this series, certain deductions were made about the reaction mechanism of a rearrangement of N-substituted sulfonamide derivatives in the presence of alkali and this reaction was presumed to be an intramolecular rearrangement.

The present paper deals with the determination of the rate coefficients of ten kinds of sulfonamide derivatives and the discussion of the electronic and steric effects of N-substituents of nitrobenzenesulfonamide and pyridinesulfonamide 1-oxides. The reaction mechanism of this rearrangement is described.

The reactions of their sulfonamides with alkali were consecutive reactions, as described in the preceding paper. However, the reaction rates of the rearrangement could be measured by means of quantitative analysis of sulfur dioxide liberated from that step. In the present series of experiments, large excess aqueous sodium hydroxide solution was used to keep the OH^- concentration constant.

Reactants

N-Acetoacetyl-*p*-nitrobenzenesulfonamide[2]——*p*-Nitrobenzenesulfonamide was reacted with ketene dimer. The product was recrystallized from EtOH to pale yellow needles, m.p. 136°.

N-Acetoacetyl-*o*-nitrobenzenesulfonamide[2]——This compound was obtained from *o*-nitrobenzenesulfonamide as described above and recrystallized from EtOH to pale yellow needles, m.p. 118~119°.

N-Cyanoacetyl-*p*-nitrobenzenesulfonamide[3]——N-Chloroacetyl-*p*-nitrobenzenesulfonamide obtained from *p*-nitrobenzenesulfonamide with chloroacetyl chloride was converted into the corresponding N-cyanoacetyl derivative with NaCN. Recrystallization from EtOH gave pale yellow needles, m.p. 207~209°.

*1 Part Ⅶ. R. Dohmori : This Bulletin, **12**, 595 (1964).

*2 Minamifunabori-cho, Edogawa-ku, Tokyo (堂森廉三).

1) T. Naito, R. Dohmori, M. Shimoda : This Bulletin, **3**, 34 (1955).

2) S. Petersen : Chem. Ber., **83**, 55 (1950).

3) T. Naito, R. Dohmori, M. Sano : Yakugaku Zasshi, **74**, 596 (1954).

N-Cyanoacetyl-*o*-nitrobenzenesulfonamide[3]——This compound was obtained from *o*-nitrobenzenesulfonamide as was the *p*-isomer and recrystallized from EtOH to pale yellow prisms, m.p. 168~170°.

N-Phenylacetyl-*p*-nitrobenzenesulfonamide[3]——*p*-Nitrobenzenesulfonamide was reacted with phenylacetyl chloride. The product was recrystallized from MeOH to pale yellow prisms, m.p. 172~173°.

N-Acetoacetyl-2-pyridinesulfonamide 1-Oxide[4]——2-Pyridinesulfonamide 1-oxide was reacted with ketene dimer. The product was recrystallized from MeOH to colorless plates, m.p. 152~153°(decomp.).

N-Acetoacetyl-4-pyridinesulfonamide 1-Oxide[4]——This compound was obtained from 4-pyridinesulfonamide 1-oxide by the same procedure as described earlier and recrystallized from MeOH to colorless prisms, m.p. 183~184°(decomp.).

N-Phenylacetyl-2-pyridinesulfonamide 1-Oxide[5]——2-Pyridinesulfonamide 1-oxide was reacted with phenylacetyl chloride. The product was recrystallized from MeOH to colorless prisms, m.p. 189~190° (decomp.).

N-Phenylacetyl-4-pyridinesulfonamide 1-Oxide[5]——This compound was obtained from 4-pyridinesulfonamide 1-oxide in a similar method described above. Recrystallization from MeOH gave colorless prisms, m.p. 198~199°(decomp.).

N-Cyanoacetyl-2-pyridinesulfonamide 1-Oxide[*1]——N-Chloroacetyl-2-pyridinesulfonamide 1-oxide obtained from 2-pyridinesulfonamide 1-oxide and chloroacetyl chloride was converted into the corresponding N-cyanoacetyl derivative with NaCN. The product, on recrystallization from MeOH, gave colorless leaflets, m.p. 172°(decomp.).

Typical Rate Measurement by the Gravimetric Analysis of Sulfur Dioxide——Finely powdered N-phenylacetyl-2-pyridinesulfonamide 1-oxide (about 0.5 mmole) was weighed accurately into a 100 ml. Erlenmeyer flask and placed constant temperature bath adjusted to 60.7°±0.05°. After the thermostat had returned to this temperature, *N* NaOH (25 ml., 25 mmoles) adjusted to the same temperature was poured into the flask. To this reaction mixture, which was allowed to stand for definite time intervals was added 30% H_2O_2 (1 ml.). After standing for exactly 10 sec., 5.5 *N* HCl (5 ml.) was added to the mixture to stop the reaction and the mixture was allowed to stand for several hours in an ice bucket. The crystalline materials were filtered off on a glass filter and thoroughly rinsed with dist. H_2O. To the filtrate on the steam bath was added 10% $BaCl_2$ (2 ml.) and the precipitated $BaSO_4$ was treated in the usual manner for gravimetrical analysis.

Rate coefficients were calculated from the expression $kt = \ln a - \ln (a-x)$ (where a is the initial concentration of the sulfonamide derivative and x is the concentration of material changed by this rearrangement for time t, so $(a-x)$ shows the concentration of remaining sulfonamide at time t).[3] Fig. 1 shows that the plot of $\log a/(a-x)$ *vs.* t is linear. The slope of the line was determined by the method

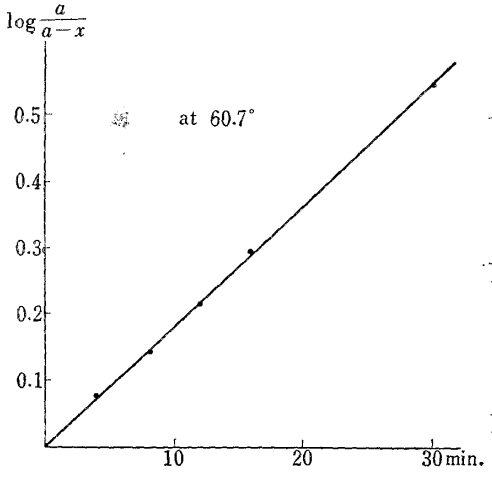


Fig. 1.

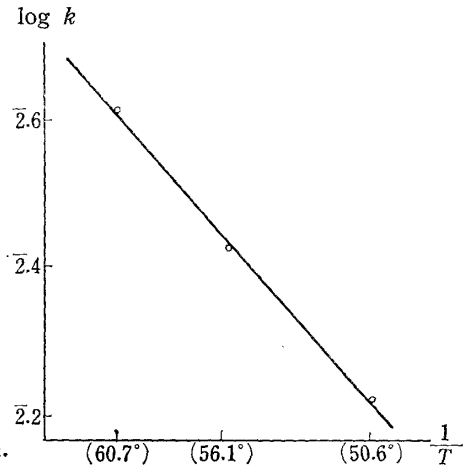


Fig. 2.

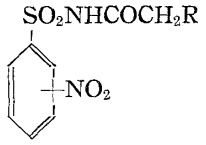
Reaction of N-Phenylacetyl-2-pyridinesulfonamide 1-Oxide

*[3] In practice, $\log a/(a-x)$ were calculated the following formula :

$$\log\frac{a}{(a-x)} = \log\left\{\frac{1}{1-\dfrac{\text{mol. wt. of sulfonamide deriv.} \times \text{BaSO}_4\,(\text{mg.})}{\text{mol. wt. of BaSO}_4 \times \text{sulfonamide deriv. (mg.)}}}\right\}$$

4) T. Naito, R. Dohmori : This Bulletin, 3, 38 (1955).
5) T. Naito, R. Dohmori, T. Kotake : *Ibid.*, 12, 588 (1964).

Table I. Summary of Kinetic Data

Sulfonamide derivs.	R	o- or p-	°C	$k \times 10$
	$COCH_3$	o-	14.9	1.190
			10.0	0.604
			4.9	0.306
		p-	14.9	0.908
			10.0	0.452
			4.9	0.214
	CN	o-	24.8	1.03
			20.1	0.605
			14.9	0.320
		p-	24.8	0.761
			20.1	0.412
			14.9	0.213
	C_6H_5	p-	60.7	0.631
			56.1	0.411
			50.6	0.233

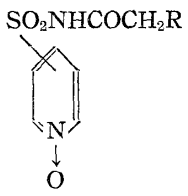
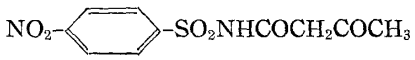
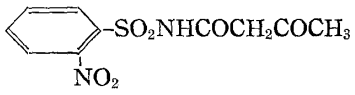
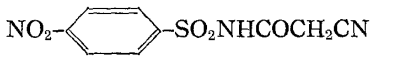
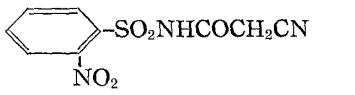
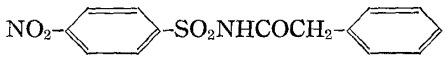
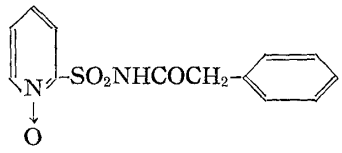
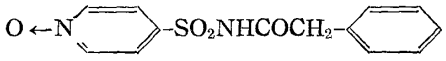
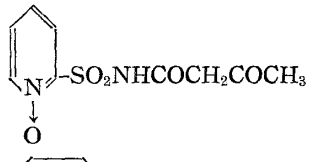
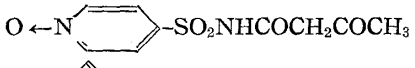
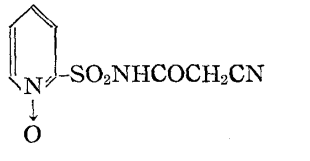
Sulfonamide derivs.	R	α- or γ-	°C	$k \times 10$
	$COCH_3$	α-	4.9	7.12
			0.4	4.30
			− 3.1	2.53
		γ-	4.9	1.24
			0.4	0.689
			− 3.1	0.425
	CN	α-	4.9	6.89
			0.4	4.20
			− 3.1	2.51
	C_6H_5	α-	60.7	0.417
			56.1	0.263
			50.6	0.164
		γ-	60.7	0.484
			56.1	0.310
			50.6	0.200

Table II.

Sulfonamide derivs.	$k^{14.9°}$	ΔH Kcal./mole	ΔS e. u.
	9.08×10^{-2}	22.4	6.58
	1.19×10^{-1}	21.1	2.36
	2.13×10^{-2}	21.3	− 0.27
	3.20×10^{-2}	20.0	− 5.48
	(4.71×10^{-4})	20.0	−13.85
	(3.93×10^{-4})	18.7	−17.24
	(5.84×10^{-4})	17.7	−19.89
	(2.34)	18.6	− 0.21
	(4.28×10^{-1})	19.4	− 1.06
	(2.21)	18.2	− 1.90

of least squares and multiplied by 2.303 to obtain the rate coefficient. The first order rate coefficient $k^{60.7°}$ was 4.17×10^{-2}/min.

Arrhenius activation energy, $\Delta E^{\ddagger}$, was calculated from the expression : $\log k=\log A-\Delta E^{\ddagger}/2.303RT$. In Fig. 2, the plots of $\log k$ *vs.* $1/T$ are shown. The slope of this line ($\Delta E^{\ddagger}/2.303R$) was also calculated by the method of least squares and $\Delta E^{\ddagger}$ was obtained.

The entropy of activation, $\Delta S^{\ddagger}$, was calculated from the standard expression[6] : $k=\kappa T/\mathrm{h}\cdot\exp(\Delta S^{\ddagger}/R)\cdot\exp(-\Delta H^{\ddagger}/RT)$, $\Delta H^{\ddagger}=\Delta E^{\ddagger}-RT$. From the above obtained value of $\Delta E^{\ddagger}$, the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated, $\Delta H^{\ddagger}=18.7$ Kcal./mole, $\Delta S^{\ddagger}=-17$ erg/mole/deg. Rate coefficient at 14.9° was calculated from these values : $k^{14.9°}=3.93\times10^{-4}$/mole.

The reactions of the other compounds were treated by the same technique.

Results and Discussion

Rete measurements are summarized in Table I. From this data, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and rate coefficients at 14.9° were calculated, and the reactions of ten kinds of sulfonamide derivatives with alkali were compared.

Table II shows that pyridinesulfonamide 1-oxide derivatives react ten to one hundred times faster than nitrobenzenesulfonamide derivatives. Okamoto, *et al.*[7] pointed out from the kinetic studies on the substitution reactions of 4-haloquinoline 1-oxides, 4-haloquinolines and 1-nitro-4-halonaphtalenes with piperidine that the order of the accelerating power for nucleophilic substitutions was as follows :

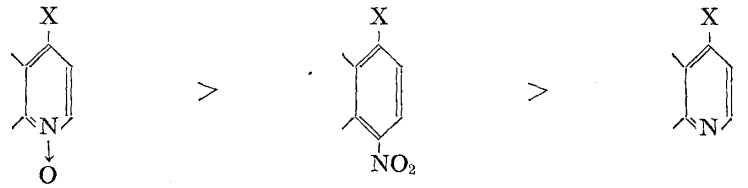


Chart 1.

It is reasonable for the results of these experiments, the rearrangement reaction of pyridinesulfonamide 1-oxide derivatives occurs faster than nitrobenzenesulfonamide derivatives, while for pyridinesulfonamide derivatives it dose not occur.

For the rearrangement reaction of nitrophenylureas with alkali, Backer[8] reported that the rate coefficients of *p*-nitro compounds were somewhat larger than those of *o*-isomers. However, the present results showed that the *o*-nitro compounds (or 2-pyridinesulfonamide 1-oxide derivatives) react slightly faster than *p*-isomers (or 4-isomers), as already observed by Smiles[9] in the rearrangement of *o*- and *p*-nitrobenzene-2'-hydroxysulfones.

The values of the activation energy $\Delta E^{\ddagger}$ were almost same in the reaction of these compounds, but there were great differences in the activation entropy values $\Delta S^{\ddagger}$s. Especially in the case of N-phenylacetyl derivatives, $\Delta S^{\ddagger}$ was much smaller (larger negatively) than that of the corresponding N-substituted derivatives. This fact shows that steric hindrance of these compounds in the transition state is very large. It is also observed that the rate coefficients of these compounds were a hundredth of the other compounds.

In the previous paper,[1] we considered this reaction to be an intramolecular rearrangement. This conclusion depends on the experimental results in which the reaction mixture of

6) S. Glasston, K. J. Laider, H. Eyring : "The Theory of Rate Process," McGraw Hill Book Co., Inc., New York 1941, p. 199.
7) T. Okamoto, H. Hayatu, Y. Baba : This Bulletin, 8, 892 (1960).
8) H. J. Backer, J. Groot : Rec. trav. chim., **68**, 1323 (1949).
9) A. A. Levi, S. Smiles : J. Chem. Soc., **1932**, 1488.

N-acetoacetyl-*p*-nitrobenzenesulfonamide (A) and N-cyanoacetyl-*o*-nitrobenzenesulfonamide (B) in sodium hydroxide solution an exchange reaction between their side chains and aromatic skeletons did not occur, while producing the normal products (C and D). The results of present experiments showed that the rates of reaction velocities of A and B are almost same. These results can be accommodated in our conclusion.

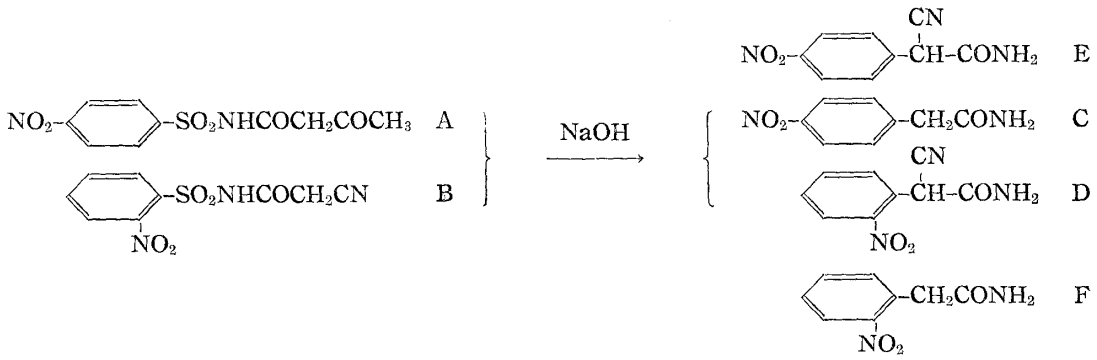


Chart 2.

Smiles and his co-workers[10] pointed out as one of the important factors that the amino group should be converted to an anionic form in the first step of S→N type rearrangement reaction which is the conversion of 2-aminodiphenylthiobenzene into 2-phenylaminobenzenethiol. On the other hand, Roberts and his co-workers[11] showed that in the rearrangement of 2-aminodiphenylether to 2-hydroxydiphenylamine, the O→N type rearrangement is initiated by the direct attack of the amino group on a positive carbon atom. Takahashi and Maki[12] also studied the Smiles S→N type rearrangement of pyridine derivatives and observed that the conversion of 2-aminopyridylsulfonylpyridine into dipyridylamine is effected by hydrochloric acid under certain conditions. This supports the Robert's viewpoint. However, the S→C type rearrangement reaction requires the conversion of the active methylene group into an anionic form in

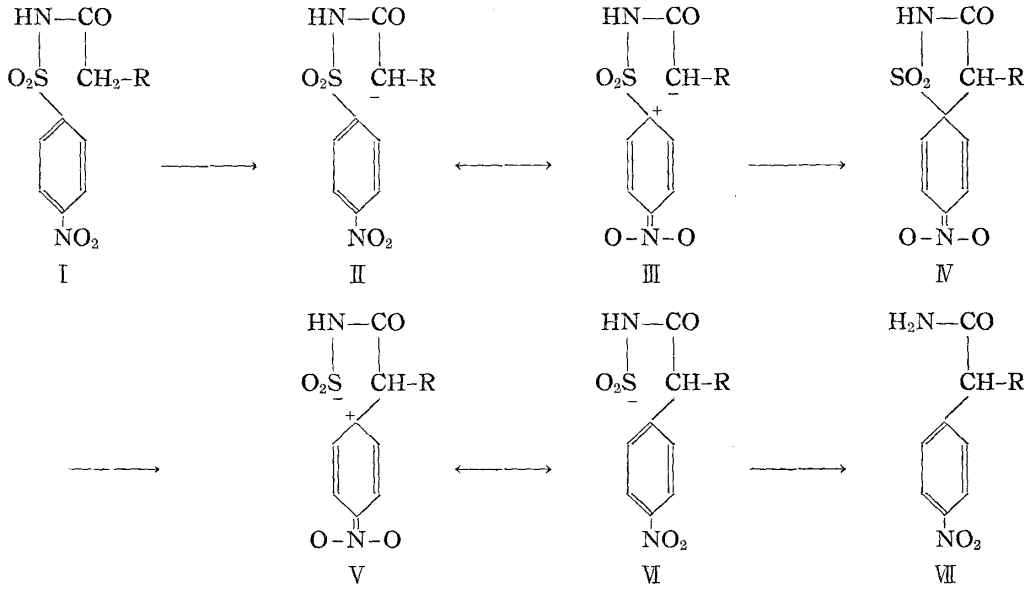


Chart 3.

10) W. J. Evans, S. Smiles : J. Chem. Soc., **1935**, 181.
11) K. C. Roberts, G. M. Woorms : *Ibid.*, **1935**, 1309.
12) T. Takahashi, Y. Maki : This Bulletin, **6**, 369, (1958).

the first step, and then the nucleophilic attack on the positive carbon atom in the benzene ring, since the carbon atom in the side chain differs from N or O atom, is not having a lone pair of electrons.

By summarizing the above data, it is anticipated that this rearrangement reaction will proceed through some intermediate as shown in Chart 3.

In the case of N-substituted *p*-nitrobenzenesulfonamides, the active methylene group is represented as an anion II and III in an alkaline solution. The electron density of C_1-carbon atom in the benzene ring greatly should be increased by the effects of nitro group in the *para*-position and of sulfonyl group. Therefore, the close association between the nucleophilic and electrophilic centers suggests the formation of an isothiazoletype ring compound (IV) as an intermediate. If R is a bulky group, e.s. phenyl, it hinders the formation of such a ring and causes a smaller rate coefficient. In addition, this assumption may be endorsed by the fact which *o*-product has not been isolated as in the experiment of *p*-nitrobenzenesulfonamide derivative. At the same time, the carbon-sulfur bond cleavage must occur to form a new anion V or VI. An anion VI is presumed very unstable and decomposes immediately into VII and sulfur dioxide.

The author wishes to express his deep gratitude to Prof. T. Okamoto, University of Tokyo, for the kind review of this work, to Dr. J. Shinoda, Chairman of Board of Directors, Dr. T. Ishiguro, President of this Company, Dr. M. Shimizu, Director of this Laboratory, for their unfailing encouragement, and to Dr. T. Naito, Subdirector, Dr. A. Okano of this Laboratory, for their informative discussion and suggestions throughout the couse of the present work. He is also indebted to Mr. B. Kurihara and Miss K. Hanawa, for elemental analyses.

Summary

Reaction rates of N-acetoacetyl, N-cyanoacetyl, and N-phenylacetyl derivatives of *o*- and *p*-nitrobenzenesulfonamide and 2- and 4-pyridinesulfonamide 1-oxides with alkali were compared. Rate coefficients, heat constants of activation, and entropies of activation were calculated. Pyridinesulfonamide 1-oxide derivatives reacted faster than nitrobenzene derivatives and reactivities of N-phenylacetyl derivatives were smallest.

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