Supplementary Material Available. The mass spectral characterization of column fractions 3–6 and authentic 2′-Am and 3′-Am as their trimethylsilyl derivatives will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3674.

References and Notes

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(2) The abbreviations used in this paper are as follows: gc, gas chromatography; 2′-Am, 2′-*O*-methyladenosine; 3′-Am, 3′-*O*-methyladenosine; 2′-Ae, 2′-*O*-ethyladenosine; 3′-Ae, 3′-*O*-ethyladenosine.

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Kinetics of the Formation of *N*-Arylsydnones from *N*-Nitroso-*N*-Arylglycines

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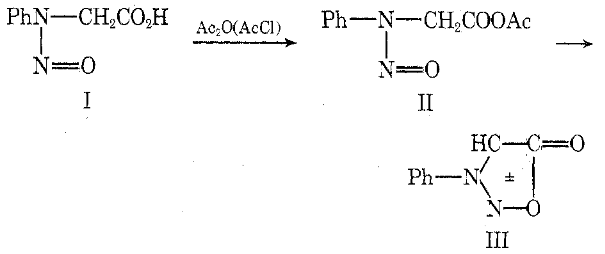
The formation of *N*-arylsydnones by the reaction of *N*-nitroso-*N*-arylglycines with acid anhydrides (mainly dichloroacetic anhydride) has been kinetically studied by means of uv spectrophotometry of the produced sydnones in dioxane or other solvents. The rate is expressed as $v = k_2[R^1C_6H_4N(NO)CHR^2COOH][(RCO)_2O]$, and virtually no effect was observed on addition of RCO_2H or pyridine. An electron-withdrawing group on *N*-phenyl (R^1) retards the reaction, while the same group on the α carbon (R^2) accelerates it. An electron-withdrawing group on acid anhydride accelerates the reaction in general. These findings suggest a mechanism involving rate-determining cyclization of the hydrogen-bonded acid anhydride of the substrate by a nucleophilic attack of the nitroso oxygen on the carbonyl carbon.

Since the discovery of sydnone,[1] which was prepared by the condensation of *N*-nitroso-*N*-phenylglycine with acetic anhydride, some analogous mesoionic compounds have been prepared, but no kinetic study on the formation has appeared.[2,3]

A mechanism involving acetyl glycinoyl anhydride (II) (eq 1) has been postulated on the basis of the formation of II by the reaction of I with acetyl chloride, the formation of sydnone (III) from II on heating, and some other facts.[3b]



(1)

However, since no kinetic study was done, the mechanism is still obscure. That is, is the main path truly that *via* anhydride II? Which step is rate determining? Does an attack of nitroso oxygen on carbonyl carbon or an attack of carbonyl oxygen on nitroso nitrogen occur? To clarify these uncertainties, we carried out kinetic studies of the reaction by means of uv spectrophotometry of the product with some *N*-nitroso-*N*-arylglycines and with some substituted acetic anhydrides. The following is a summary of our results which suggest a probable and more accurate mechanism for the reaction.

Table I
Second-Order Rate Constant for the Reaction of *N*-Nitroso-*N*-phenylglycine with Dichloroacetic Anhydride in Dioxane at 23°

Initial concn ($10^{-4}M$)		
Substrate	Acid anhydride	k_2, M^{-1} sec^{-1}
2.74	6.00	9.5
2.74	9.01	11.5
2.74	12.01	8.6
2.74	30.03	11.7
3.28	6.00	9.4
3.83	6.00	11.7
4.38	6.00	10.1
4.93	6.00	11.6
5.47	6.00	10.0

Results

Kinetics. The rates of the reactions of all the glycines and acid anhydrides studied can be expressed as $v = k[ArN(NO)CH_2CO_2H][(RCO)_2O]$. A typical kinetic run for the reaction of *N*-nitroso-*N*-phenylglycine with dichloroacetic anhydride in dioxane is shown in Table I, where the second-order rate constants hold a satisfactory constancy. No reaction occurs with *N*-nitrosophenylglycine ester in the presence of dichloroacetic anhydride, in agreement with the observation in acetic anhydride by Baker, *et al.*[3b]

Effect of Acid and Base. The reaction gives rise to acetic acid, but, as shown in Table II, virtually no effect of ace-

Table II
Effect of Acid and Base on the Second-Order Rate Constant k_2 for the *N*-Nitroso-*N*-phenylglycine with Acid Anhydride in Dioxane at 50°

[PhN(NO)-CH_2CO_2H], *M*	[$(RCO)_2O$], *M*	[Acid], *M*	[Base], *M*	k_2, M^{-1} sec^{-1}	
0.952	Ac_2O (10.58)			1.47×10^{-5}	Av 1.62 × 10^{-5}
0.824	Ac_2O (9.86)	AcOH (1.19)		1.67×10^{-5}	
1.87	Ac_2O (10.28)			1.71×10^{-5}	
5.46×10^{-3}	$(ClCH_2CO)_2O$ (6.01×10^{-2})			2.59×10^{-2}	
5.46×10^{-3}	$(ClCH_2CO_2)O$ (6.00×10^{-2})		Pyridine (6.18×10^{-2})	2.71×10^{-2}	

Table III
Effect of Structure of Acid Anhydride on the Second-Order Rate Constant for the Reaction of *N*-Nitroso-*N*-phenylglycine with Acid Anhydride

Acid anhydride	Registry no.	pK_a of parent acid at 25°	Solvent	Temp, °C	k_2, M^{-1} sec^{-1}
Ac_2O	108-24-7	4.76	Dioxane	50	~0
			Ac_2O	50	1.62×10^{-5}
$(ClCH_2CO)_2O$	541-88-8	2.86	Dioxane	50	2.65×10^{-2}
$(Cl_2CHCO)_2O$	4124-30-5	1.29	Dioxane	23	10.3
$(Cl_3CCO)_2O$	4124-31-6	0.63	Dioxane	23	3.26×10^{-2}
			Dioxane	40	0.205
$(F_3CCO)_2O$	407-25-0	0.23	Dioxane	23	

Table IV
Second-Order Rate Constants for the Reactions of *N*-Nitroso-*N*-arylglycines with Dichloroacetic Anhydride in Dioxane at 23°

Substituent in Ph	Initial concn, *M*: Substrate	Initial concn, *M*: Acid anhydride	k_2 (av),[b] M^{-1} sec^{-1}
p-CH_3O	3.41–6.02	6.03–12.05	24.0 ± 1.0
p-CH_3	6.03	6.00–18.01	18.7 ± 0.9
H[a]			10.3 ± 0.3
p-Cl	4.00–6.00	6.01–18.07	5.21 ± 0.37
m-Cl	4.01–6.02	6.02–18.07	3.32 ± 0.22

[a] See Table I. [b] ± denotes standard deviation of several runs.

tic acid was observed on the rate even in the presence of added acetic acid. Also there is no effect of added base, pyridine, on the rate, although the addition of pyridine raises the yield by 10–20%.

Effect of Substituent in Anhydride. The introduction of halogen into acetic anhydride exerts such a remarkable acceleration influence on the reaction that the reaction temperature must be lowered as shown in Table III. The table shows apparently that an increase of acidity of the parent acid results in the acceleration of the reaction, except for trichloroacetic anhydride for which the formed trichloroacetic acid should decompose the produced sydnone rapidly. Trifluoroacetic anhydride was easily vaporized (bp 39°) and induced the decomposition of sydnone; hence the rate measurement with this anhydride was inaccurate.

Table V
Second-Order Rate Constants for the Reaction of α-Substituted *N*-Nitroso-*N*-phenylglycine with Dichloroacetic Anhydride in Dioxane at 23°

α substituent	Initial concn, *M*: Substrate	Initial concn, *M*: Acid anhydride	k_2 (av),[b] M^{-1} sec^{-1}
CH_3	2.00–6.01	5.97–17.92	8.62 ± 0.46
C_6H_5	1.00–2.00	2.01–6.02	16.3 ± 0.3
p-ClC_6H_4	1.02	1.00–3.99	59.6 ± 9.8
H[a]			10.3 ± 0.3

[a] See Table I. [b] ± denotes standard deviation of several runs.

Table VI
Effect of Solvent on the Second-Order Rate Constants for the Reaction of *N*-Nitroso-*N*-phenylglycine with Dichloroacetic Anhydride

Solvent	Temp, °C	k_2, M^{-1} sec^{-1}	ε[a]	E_T[b]
Dioxane	23	10.3	2.21 (25°)	36.0
Acetonitrile	23	3.18	37.5 (20°)	46.0
Acetone	24	0.338	20.7 (25°)	42.2
Chloroform	24	0.0255	4.81 (20°)	39.1
Tetrahydrofuran	23	0.00305	7.58 (25°)	37.4
Acetic anhydride	22	0	20.7 (19°)	

[a] Dielectric constant: J. A. Riddick and W. B. Bunger, "Techniques of Chemistry," Vol. II, 3rd ed, Wiley-Interscience, New York, N. Y., 1970. [b] Transition energy estimated from the absorption of a reference compound: K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, *Justus Liebigs Ann. Chem.*, **661**, 1 (1963); **669**, 95 (1963).

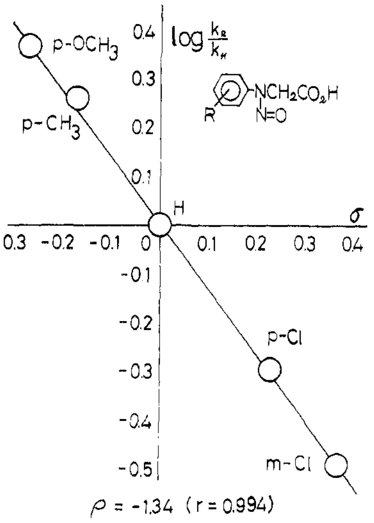


Figure 1. *Hammett plots for the reaction of N-nitroso-N-arylglycines with dichloroacetic anhydride in dioxane at 23°.*

Effect of Substituent in Phenylnitrosoglycine. The rate data for some ring-substituted *N*-nitroso-*N*-phenylglycines with dichloroacetic anhydride at 23° are compiled in Table IV. The data fit Hammett's equation (Figure 1) giving a ρ value of −1.34 (*r* = 0.994) with σ.

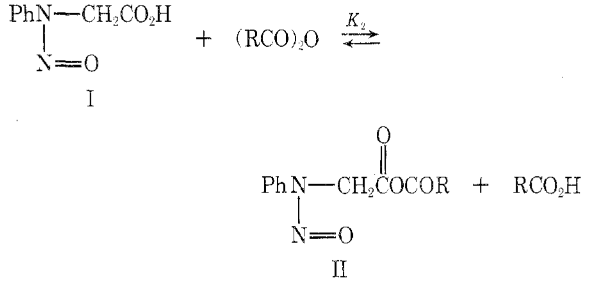
Table V shows the effect of the α substituent in the glycine under the same conditions as above, in which it is apparent that an electron-withdrawing α substituent increases the rate.

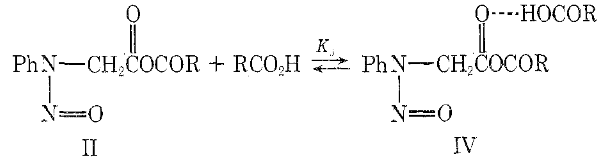
Solvent Effect. The effect of solvent on the rate of reaction of *N*-nitroso-*N*-phenylglycine with dichloroacetic anhydride at 22–24° is listed in Table VI, which indicates that dioxane is the most suitable solvent among them for the reaction.

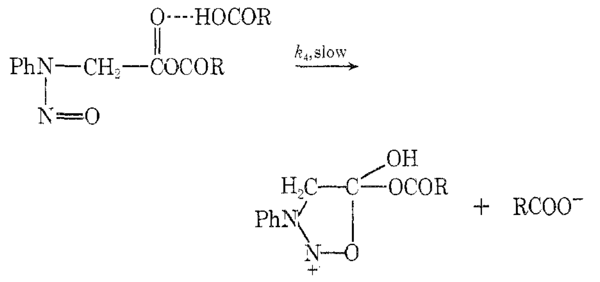
Discussion

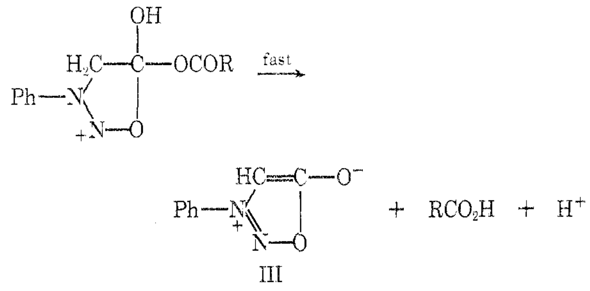
Our observed results are summarized as follows. (i) The rate is $v = k[\text{substrate}][(RCO)_2O]$. (ii) Ethyl *N*-nitroso-*N*-phenylglycinate which does not react with acid anhydride cannot give sydnone. (iii) Added acetic acid or pyridine only slightly influences the rate. (iv) The reaction with dichloroacetic anhydride is very slow in an excess amount of acetic anhydride. (v) Electron-withdrawing groups in acetic anhydride accelerate the reaction except for Cl_3 or F_3 groups. (vi) An electron-withdrawing group in the *N*-phenyl group of the substrate retards the reaction ($\rho = -1.34$), while an electron-withdrawing group in α carbon accelerates the reaction.

These observations suggest a mechanism which involves a rate-determining attack of nitroso oxygen on the carbonyl carbon (activated by hydrogen-bonded acetic acid) of *mixed anhydride (IV), giving a cyclized product which rapidly eliminates acetic acid and proton to form sydnone.*


$$\mathrm{PhN(N{=}O)CH_2CO_2H\ (I) + (RCO)_2O \overset{K_2}{\rightleftharpoons} PhN(N{=}O)CH_2C(=O)OCOR\ (II) + RCO_2H}$$
(2)


$$\mathrm{PhN(N{=}O)CH_2C(=O)OCOR\ (II) + RCO_2H \overset{K_3}{\rightleftharpoons} PhN(N{=}O)CH_2C(=O{\cdots}HOCOR)OCOR\ (IV)}$$
(3)

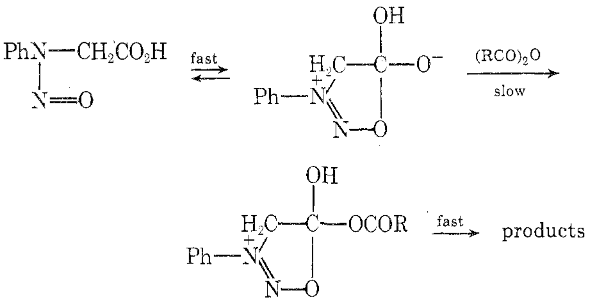

(4)


(5)

This mechanism, with the rate-determining step of eq 4, leads *to the following rate equation, which is unaffected by* added acetic acid or pyridine: $v = K_2K_3k_4[\mathrm{I}][(RCO)_2O]$. If unassociated anhydride $PhN(NO)CH_2COOCOR$ (II) were cyclized, the rate law would be $v = K_2K_3k_4[\mathrm{I}][(RCO)_2O]/[RCO_2H]$, which disagrees with our observation.

Very strong acid can accelerate the decomposition of sydnone and hence lowers the apparent rate constant, while pyridine suppresses the decomposition of product and increases the yield. The retardation of reaction with dichloroacetic anhydride in excess acetic anhydride is ascribed to the very low equilibrium concentration of $PhN(NO)CH_2COOCOCHCl_2$ because of the shift of equilibrium to $PhN(NO)CH_2COOCOCH_3$ which is much more slowly cyclized than the former.

Another mechanism, shown in eq 6, is consistent with kinetics and the other observations (i–iii, v, and vi), but this is inconsistent with observation iv, since the rate with dichloroacetic anhydride according to eq 6 should be higher or comparable in acetic anhydride compared with that in dioxane. Also, the isolation of acid anhydride intermediate II by Baker, *et al.*,[3b] and the lower electrophilicity of COOH than that of COOCOR disfavor the mechanism of eq 6.


(6)

A mechanism involving an irreversible slow attack of the *glycine on the anhydride (eq 2 in the forward direction* only) fits the rate law, but it is inadequate in view of (i) the observation that an electron-withdrawing α substituent in nitrosophenylglycine increases the rate and (ii) the isolation of mixed anhydride II in the other case.[3b]

The observed *ca.* 10^3-fold faster rate for dichloroacetic anhydride than that for acetic anhydride seems to be too large, since Cl atoms are three atoms away and the inductive effect decreases *ca.* $(2.8)^3$-fold. However, this observation is conceivable because (i) dichloroacetic acid has an acidity constant 3.5 pK units (8×10^3-fold) higher than acetic acid, although the chloro substituent of $CHCl_2CO_2H$ is two atoms away from the oxygen atom, and (ii) $k_{\text{obsd}} = K_2K_3k_4$, and all the constants would increase by introduction of the Cl atom; that is, the effect is triplicated in k_{obsd}.

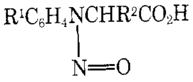
Substituent Effect. As stated above, electron-withdrawing groups in acetic anhydride accelerate the cyclization because they increase the electrophilicity of carbonyl carbon of the substrate. On the contrary, an electron-withdrawing group in the phenyl ring retards the reaction, since it lowers the nucleophilicity of nitroso oxygen which attacks the carbonyl carbon, although the group can more weakly raise the electrophilicity of carbonyl carbon. Reasonable trends were observed with substituents on α carbon, *i.e.*, an electron-withdrawing group on α carbon accelerates the cyclization because of an increase of electrophilicity of the carbonyl carbon. It is of interest to note that the steric hindrance effect is rather small in view of the comparison of α-CH_3 and α-C_6H_5.

The failure of reaction with ethyl *N*-nitroso-*N*-phenylglycinate supports the above mechanism, since the more electron-attracting acyl group in anhydride II is favorable for a nucleophilic attack of NO compared with the ethoxy group in ester.

An alternative mechanism involving a rate-determining nucleophilic attack of COO^- on N of N=O is inconsistent with these substituent effects, *i.e.*, the reverse polar effect would be observed in this mechanism.

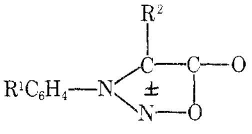
Solvent Effect. Table VI shows that the dielectric constants of solvent are related little to the rate constant, while the E_T value, which is a measure of solvent polarity,[7] parallels fairly well with rate except for dioxane having a large k value. This is convincing, since the rate-determining step is the separation of opposite charges. The abnor-

Table VII
Ultraviolet Absorption Peaks and Extinctions of *N*-Nitroso-*N*-arylglycines and Sydnones[a] and Melting Points of Sydnones



$R^1C_6H_4N(N{=}O)CHR^2CO_2H$

I

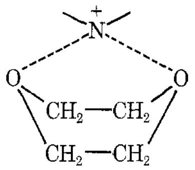


III

Substituent		I			III				
R^1	R^2	λ_{max}, nm	Registry no.	ϵ_{max}	λ_{max}, nm	Registry no.	ϵ_{max}	Mp, °C	Lit. mp, °C
H	H	270	6415-68-5	5520[b]	310	120-06-9	4,490[b]	138.0	137[5]
p-CH_3O	H	284	52827-01-7	7580	323[c]	3815-80-3	5,050	123.5	126 dec[3c]
					279		8,600		
p-CH_3	H	276	52827-02-8	6560	320	3483-19-0	5,070	145.5	145[3a]
p-Cl	H	276	13728-11-5	7720	322	829-31-2	3,770	112	113[3a]
m-Cl	H	273	52827-03-9	6530	323	52827-07-3	3,770	141	145.5
H	CH_3	266	52827-04-0	5800	315	3483-16-7	5,050	99	99[1]
H	C_6H_5	257	52827-05-1	4950	340	3815-83-6	9,640	189	185[3a]
H	*p*-ClC_6H_4	256	52827-06-2	5510	343	52827-08-4	12,120	129.5	129 dec[3b]

[a] In dioxane. [b] In methanol. [c] Shoulder.

mal acceleration in dioxane may be ascribed to its ability for the facile solvation of cation in the form of VI as reported in some other cases.[4]



VI

Experimental Section

Materials. *N*-Arylglycines were prepared by the reaction of the corresponding anilines with chloroacetic acid or its ester in ethanol.[3a] The obtained *N*-arylglycines were nitrosated[5] with aqueous HNO_2 at 0°, giving *N*-nitroso-*N*-arylglycines. Identification of obtained *N*-arylglycines and *N*-nitroso-*N*-arylglycines was done by their ir and nmr spectra and also by the comparison of melting points with those of literature. The substituents and melting points of obtained *N*-nitroso-*N*-arylglycines were: none, 105–105.3° (lit.[5] mp 103–104°); *p*-OMe, 114–115° dec (lit.[3c] 121° dec); *p*-Me, 107–109° dec; *p*-Cl, 119–119.5° dec (lit.[3a] mp 114°); *m*-Cl, 109–111° dec (lit.[6] mp 106.5–107.5°).

α-Substituted *N*-nitroso-*N*-phenylglycines were similarly prepared by the nitrosation of the corresponding substituted phenylglycines.[3b] The α substituents, melting points of *N*-phenylglycine, and melting points of *N*-nitroso-*N*-phenylglycine were: CH_3, 167°, 88.6–89.0° (lit.[1] mp 80–81°); Ph, 183.7° (lit.[3a] mp 185°), 98–99°; *p*-ClC_6H_4, 185–186° (lit.[3b] mp 178°), 83.5–84.5°.

Acetic anhydride was purified by distillation over P_2O_5, bp 137° (lit.[7] 139°). Other carboxylic anhydrides were prepared by refluxing the corresponding carboxylic acid with P_2O_5 for *ca.* 10 hr[8] by checking the absence of carboxylic acid by ir spectra. Their boiling points were: $(ClCH_2CO)_2O$, 203–215°; $(Cl_2CHCO)_2O$, 120–122° (29–30 mm); $(Cl_3CO)_2O$ 114–116° (23 mm); $(CF_3CO)_2O$, 41.6°. Their identification was done by ir spectra.

Authentic samples of sydnones were prepared by refluxing the corresponding *N*-nitroso-*N*-arylglycine with acetic anhydride.[5] Their melting points and uv absorptions together with the uv absorption of parent nitrosoarylglycines are listed in Table VII.

Kinetics. For the substrates of the slower reaction, which was completed within 1 hr, the kinetic experiments were conducted in a flask dipped in an ordinary thermostat. Aliquots (1–0.5 ml) were pipetted out from the reaction solution at appropriate time intervals, diluted with methanol to 6×10^{-4} *M* sydnone to measure its concentration by means of uv spectrophotometry at a wavelength of 340 nm.

For the rapid reactions, dilute solutions (each 5 ml) of nitrosoarylglycine and acid anhydride were mixed and transferred immediately to a thermostated photocell. The rate was directly measured similarly by uv spectrophotometry (340 nm or otherwise 343 nm for phenyl-*N*-nitroso-α-chlorophenylglycine alone). Second-order rate constants were calculated from the slopes of plots of log $(b - x)/(a - x)$] *vs.* time, where a and b $(a \neq b)$ denote the initial concentrations of nitrosoglycines and acid anhydrides, respectively, and x is the concentration of formed sydnones. With a large excess of acid anhydride, pseudo-first-order rate constants can be calculated from plots of logarithmic extinction *vs.* time. It should be noted that the humidity of the air, especially over 60%, tends to decompose the used acid anhydride and lowers the reproducibility of data.

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