BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 40 2608—2613 (1967)

Studies of Heteroaromaticity. VIII.[1] Reactivity of Some Nitrile Oxides Conjugated with a Double Bond

Tadashi SASAKI and Toshiyuki YOSHIOKA

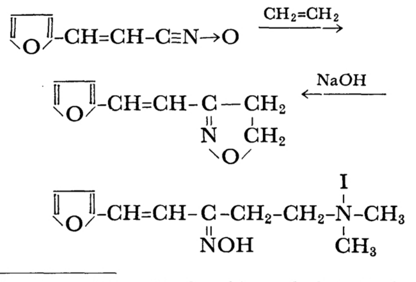
Institute of Applid Organic Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya

(Received May 19, 1967)

Phenyl-, furyl-, and 5-nitro-2-furylacrylonitrile oxides were prepared *in situ* from the corresponding hydroxamoyl chlorides and a base. They reacted with styrene or acrylamide as a dipolarophile to give the corresponding 3, 5-disubstituted isoxazolines in very low yields. These results show that the reactivity of such nitrile oxides was reduced by the presence of a conjugated double bond. Phenyl- and 5-nitro-2-furylacrylonitrile oxides were treated with α-morpholinostyrene to afford 3-styryl-5-morpholino-5-phenyl- and 3-(5-nitro-2-furylvinyl)-5-morpholino-5-phenylisoxazole respectively. The former product was further treated with hydrochloric acid to give 3-styryl-5-phenylisoxazole in a good yield. Phenylacrylonitrile oxide was heated in ethanol with cyanoguanidine, leading to 3-styryl-5-guanidino-1, 2, 4-oxadiazole. 5-Nitro-2-furylacrylhydroxamoyl chloride was treated with sodium azide to give the azido-aldoxime.

In a previous paper of this series,[2] we reported the 1, 3-dipolar cycloaddition reaction of furo- and 5-nitro-2-furonitrile oxide with olefinic and acetylenic compounds, which gave the corresponding isoxazolines and isoxazoles in considerable yields. In this paper, we wish to report on the syntheses of phenyl-, furyl-, and 5-nitro-2-furylacrylonitrile oxides and some reactions there of, because such nitrile oxides are thought to be stabilized by the presence of a conjugated double bond,[3] which might affect the reactivity of such nitrile oxides in the 1, 3-dipolar cycloaddition reaction.

Furylacrylonitrile oxide has previously been prepared by Andrisano and Pappalardo,[4] who have described its 1, 3-dipolar cycloaddition reaction with ethylene to give 3-(2-furylvinyl)isoxazoline, but the yield there was as low as 3%. The structural elucidation of the product was made by comparison with a specimen prepared by another method:



Phenylacrylonitrile oxide was prepared by the routine method from phenylacrylhydroxamoyl chloride[5] and a 5% aqueous NaOH solution. It was stable for as long as about one hour; this fact was demonstrated by the disappearance of the 2330 cm^{-1} absorption band due to $\nu_{\mathrm{C\equiv N}}$ in the IR spectrum. When a nitro group is introduced on a furan ring, the ring stability is believed to increase because of the resonance stabilization.[6] In fact, the stability of 5-nitro-2-furylacrylhydroxamoyl chloride was observed to increase remarkably more than that of furyl- or phenylacrylhydroxamoyl chloride, which caused it to take a long time for complete dehydrochlorination by the preparation of 5-nitro-2-furylacrylonitrile oxide from hydroxamoyl chloride and triethylamine in ether. This might be the main reason why the 1, 3-dipolar cycloaddition products were obtained in lower yields, as is shown in Table 1.

The 1, 3-dipolar cycloaddition reaction of benzonitrile oxide with styrene is known to proceed smoothly when the two components are refluxed in ether for 90 min, though this reaction takes place even at room temperature in a low yield.[7] If the 1, 3-dipolar cycloaddition reaction was carried out by refluxing phenyl-, furyl- and 5-nitro-2-furylacrylonitrile oxide with styrene in ether for 30 min, the yields were only 8, 5 and 7%, while furo- and 5-nitro-2-furonitrile oxide have given yields

---

[1] Part VII: T. Sasaki and M. Ando, *J. Syn. Org. Chem. Japan*, in press.

[2] Part IV: T. Sasaki and T. Yoshioka, This Bulletin, **40**, 2604 (1967).

[3] C. Grandman and H. O. Frommeld, *J. Org. Chem.*, **31**, 4235 (1966).

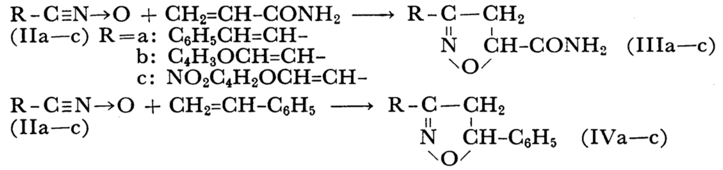
[4] R. Andrisano and G. Fappalardo, *Gazz. chim. ital.*, **88**, 174 (1958).

[5] H. Rheinboldt, *Liebigs Ann.*, **451**, 166 (1927).

[6] T. Sasaki, Doctorate Thesis, unpublished data (1955).

[7] G. Stagno, D'Alcontres and P. Grünanger, *Gazz. chim. ital.*, **80**, 831 (1950).

Table 1. 1,3-Dipolar cycloaddition reaction



$$\begin{array}{l} R\text{-}C{\equiv}N{\rightarrow}O + CH_2{=}CH\text{-}CONH_2 \longrightarrow R\text{-}C{-}CH_2 \text{ , } \overset{\parallel}{N}\ \ \overset{|}{C}H\text{-}CONH_2\ (IIIa{-}c),\ \text{ring closed by } O \\ (IIa{-}c)\ R{=}a{:}\ C_6H_5CH{=}CH\text{-} \\ \qquad b{:}\ C_4H_3OCH{=}CH\text{-} \\ \qquad c{:}\ NO_2C_4H_2OCH{=}CH\text{-} \\ R\text{-}C{\equiv}N{\rightarrow}O + CH_2{=}CH\text{-}C_6H_5 \longrightarrow R\text{-}C{-}CH_2 \text{ , } \overset{\parallel}{N}\ \ \overset{|}{C}H\text{-}C_6H_5\ (IVa{-}c),\ \text{ring closed by } O \\ (IIa{-}c) \end{array}$$

Product	Mp, °C (From solvent)	Yield %	UV λ_{max}^{EtOH} mμ($\varepsilon \times 10^3$)	IR(KBr) cm^{-1}	Microanalyses Found (Calcd) C	H	N
IIIa	205—208 (EtOH)	28	287 (32.6)	3430, 3232 (ν_{NH}) 1665 ($\nu_{C=O}$)	66.73 (66.65	5.56 5.59	12.94 12.96)
IIIb	203—205 (EtOH)	16	312 (29.6)	3400, 3210 (ν_{NH}) 1665 ($\nu_{C=O}$)			13.61 (13.58)
IIIc	209—210 (EtOH)	30	368 (20.6) 275 (15.0)	3500, 3200 (ν_{NH}) 1640 ($\nu_{C=O}$)	47.72 (47.81	3.59 3.61	16.30 16.73)
IVa	117—119 (p. e.*)	8	290 (33.0)	1620 ($\nu_{C=C}$ or $\nu_{C=N}$)	81.55 (81.90	6.13 6.60	5.78 5.62)
IVb	102—104 (p. e.*)	5	318 (30.0)	1625 ($\nu_{C=C}$ or $\nu_{C=N}$)			5.76 (5.85)
IVc	131—132 (p. e.*)	7	370 (17.4) 278 (14.7)	1625 ($\nu_{C=C}$ or $\nu_{C=N}$)	63.90 (63.38	4.22 4.26	8.87 9.86)
Xa♯$_1$	139—141 (p. e.*)	9	288 (32.0)	1620 ($\nu_{C=C}$) 1600 ($\nu_{C=N}$)	72.29 (71.70	4.96 4.96	4.74 4.92)
XIa♯$_2$	258—260 (EtOH)	4	292 (33.6)	3380, 3180 (ν_{NH}) 1680 ($\nu_{C=O}$)	73.65 (73.95	5.54 5.52	9.59 9.58)

* Petroleum ether ♯$_1$ IIa+*p*-Cl-$C_6H_4CH{=}CH_2$ ♯$_2$ IIa+$C_6H_5CH{=}CHCONH_2$

Table 2. Reaction of IIa with acrylamide*

Solvent	Base**	Reaction temp, °C	Reaction time, hr	Product	Yield, %
EtOH	NaOEt	~78	23	IIIa	None
EtOH	NaOEt	10—20	5	IIIa	6
EtOH	Et$_3$N	~78	24	IIIa	None
EtOH	Et$_3$N	10—20	16	IIIa	18
EtOH	Et$_3$N	Reflux	2	IIIa	17
Et$_2$O	5%NaOH	Reflux	1/2	IIIa	28.5

* The yield was 78% when benzonitrile oxide and acrylamide were refluxed in ethanol for 30 min.
** Used for the preparation of IIa from Ia.

of 95 and 68% respectively under the same reaction conditions.[2] The same tendency could be observed when acrylamide was used instead of styrene as a dipolarophile, but in this case the yields were a little higher than when styrene was used. This difference might come from the different thermal stabilities in styrene and acrylamide under the given reaction conditions. Table 1 shows the results of the 1, 3-dipolar cycloaddition reactions of phenyl- (IIa), furyl- (IIb), and 5-nitro-2-furylacrylonitrile oxide (IIc) with several olefins under the same reaction condition of the two components being refluxed in ether for 30 min. Of these reactions, that of IIa with acrylamide was, however, carried out under a variety of conditions; the results are shown in Table 2.

From the results shown in Table 2 it can be said that the most important factor influencing the yield is the base, while Table 1 shows the case in which the highest yield in Table 2 was obtained.

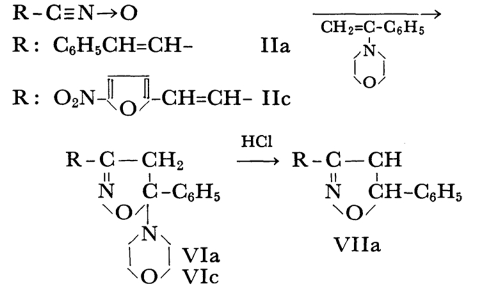
In order to investigate the reactivity of the nitrile oxides conjugated with a double bond other than the 1, 3-dipolar cycloaddition, several nitrile oxides, IIa—c, were treated with enamine and cyanoguanidine, since 5-nitro-2-furonitrile oxide is known to react with enamines to give 3, 5, 5-trisubstituted isoxazolines,[8] and benzonitrile oxide with cyanoguanidine to give 3, 5-disubstituted 1, 2, 4-oxadiazole.[9] IIa and IIc, when treated with α-morpholinostyrene in ether at room temperature for a long time, afforded 3-styryl- (VIa) and 3-(5-nitro-2-furylvinyl)-5-morpholino-5-phenylisoxazoline (VIc) respectively, but in poor yields. The former compound, VIa, was

---

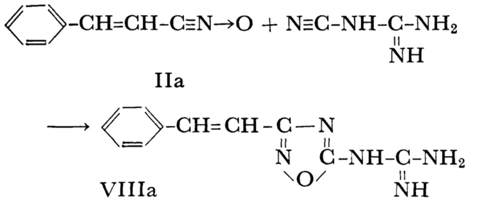
[8] S. Minami and J. Matsumoto, *Chem. Pharm. Bull.*, **15**, 366 (1967).

[9] G. Remberg and H. Brandner, *J. prakt. Chem.*, **31**, 221 (1966).

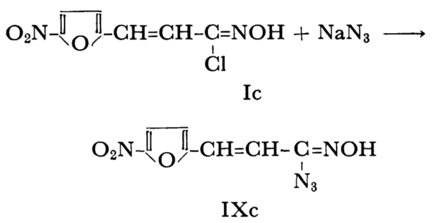
further treated with hydrochloric acid to give 3-styryl-5-phenylisoxazole (VIIa) in a good yield.



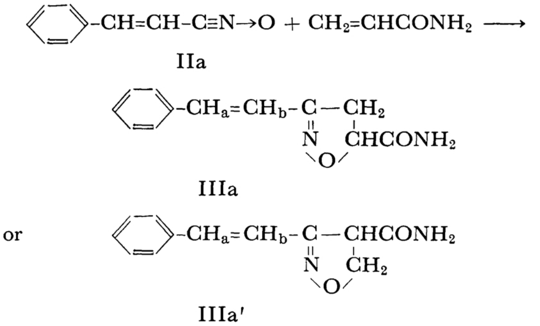
Phenylacrylonitrile oxide (IIa) was heated with cyanoguanidine in ethanol to give 3-styryl-5-guanidino-1, 2, 4-oxadiazole (VIIIa) in a poor yield; this substance was identified as its picrate.



5-Nitro-2-furylacrylhydroxamoyl chloride (Ic) was treated with sodium azide in ethanol at 40—50°C to give the azidoaldoxime (IXc), but in lower yield than when 5-nitro-2-furhydroxamoyl chloride is used.[10]



The Structural Elucidation of the 1, 3-Dipolar Cycloaddition Products. The structure of the reaction product of IIa with acrylamide is either IIIa or IIIa′:



For the sake of comparison, 3-phenyl-5(or -4)-carbamidisoxazoline was prepared by Quilico's method.[11] As is shown in Fig. 1, the NMR spectrum of this compound in DMSO-d_6 shows signals at 4.87 τ (1H, quartet, 5-H of isoxazoline, J,

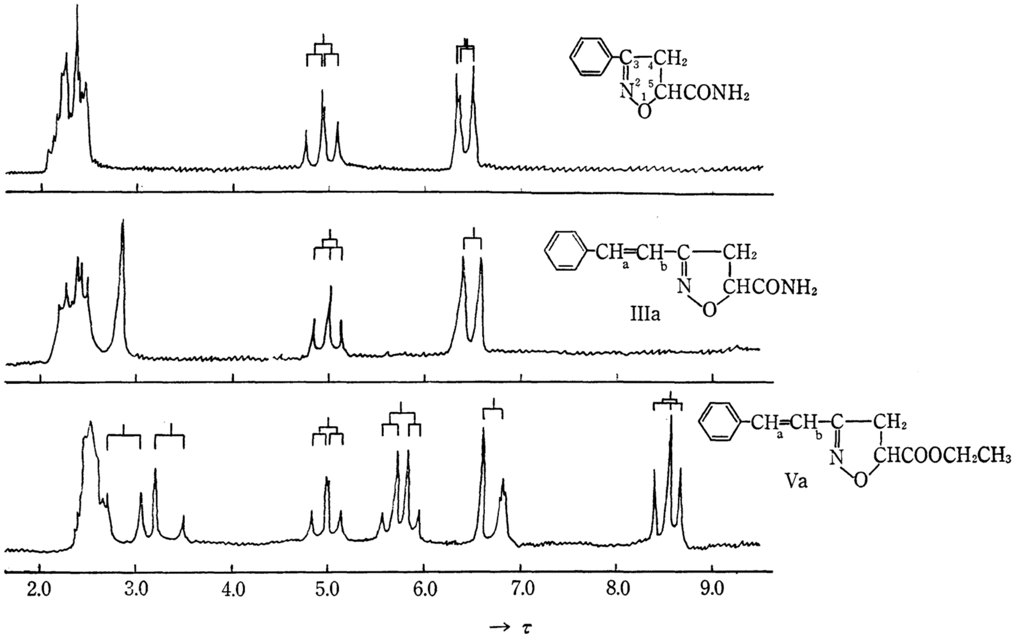


Fig. 1

---

[10] T. Sasaki and T. Yoshioka, *J. Syn. Org. Chem. Japan,* **25**, 658, 665 (1967).

[11] A. Quilico, S. Stagno and P. Grünanger, *Gazz. chim. ital.*, **80**, 741 (1950). They did not elucidate the structure in detail.

9.0 cps)[8] and at 6.42 τ (2H, triplet, 4-H of isoxazoline, *J*, 9.0 cps),[8] as well as around 2.42 τ (7H, multiplet assignable to 5H phenyl protons and 2H amide protons). These results show that the structure of this compound is 3-phenyl-5-carbamidisoxazoline, as is shown in Fig. 1. These assignments can also be applied to IIIa or IIIa′, which also has signals at 4.96 τ (1H, triplet, 5-H of isoxazoline, *J*, 9.0 cps) and at 6.53 τ (2H, doublet, 4-H of isoxazoline, *J*, 9.0 cps), as well as around 2.5 τ (7H, multiplet). Thus, the structure is confirmed to be IIIa. The biggest difference in these two NMR spectra is the presence at a singlet at 2.90 τ in IIIa, it might come from a vinyl linkage, but from this nothing can be said definitely about either cis or trans configuration of the vinyl protons, H_a and H_b, in IIIa.

In order to derive another compound with which the NMR might be measured in $CDCl_3$, IIIa was hydrolyzed to the corresponding acid by refluxing it with hydrochloric acid in ethanol; this acid was then esterified to 5-carbethoxyisoxazoline (Va), the NMR spectrum of which in $CDCl_3$ shows signals at 2.90 τ (1H, doublet, H_a, *J*, 16 cps) and at 3.27 τ (1H, doublet, H_b, *J*, 16 cps), as well as at 5.74 τ (2H, quartet, *J*, 6.4 cps, $-C\underline{H}_2CH_3$) and at 8.67 τ (3H, triplet, *J*, 6.4 cps, $-CH_2-C\underline{H}_3$). Considering that the coupling constant between H_a and H_b is 16 cps, IVa may be concluded to have a trans configuration; consequently IIIa has the same configuration, provided that the abovementioned hydrolysis and esterification have caused no stereoisomerization.

The UV spectral comparison between 3-phenyl-5-carbamidisoxazoline and IIIa in ethanol, shown in Fig. 2, clearly manifests the presence of a conjugated vinyl group in IIIa, in which group bathochromic and hyperchromic effects of IIIa are observed.

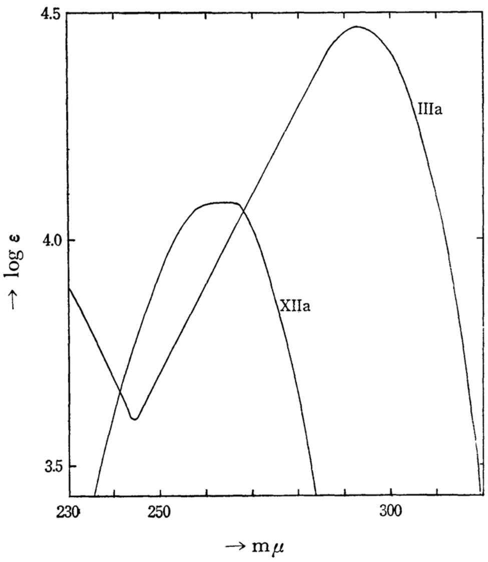


Fig. 2. Comparison of the UV spectra between 3-phenyl-5-carbamidisoxazoline XIIa and 3-styryl-5-carbamidisoxazoline IIIa.

The same structural elucidation by NMR was carried out on the 1, 3-dipolar cycloaddition product of IIa with styrene. As Fig. 3 shows, the NMR of the product in $CDCl_3$ shows signals at 2.53 τ (10H, singlet, phenyl protons), at 2.48 τ (1H, doublet, *J*, 16 cps, H_a), at 3.32 τ (1H, doublet, *J*, 16 cps, H_b), at 4.31 τ (1H, quartet, 5-H of isoxazoline), and at around 6.5 τ (2H, multiplet, 4-H of isoxazoline). The last signal could be divided into 6.37 τ (1H, quartet, H_A)

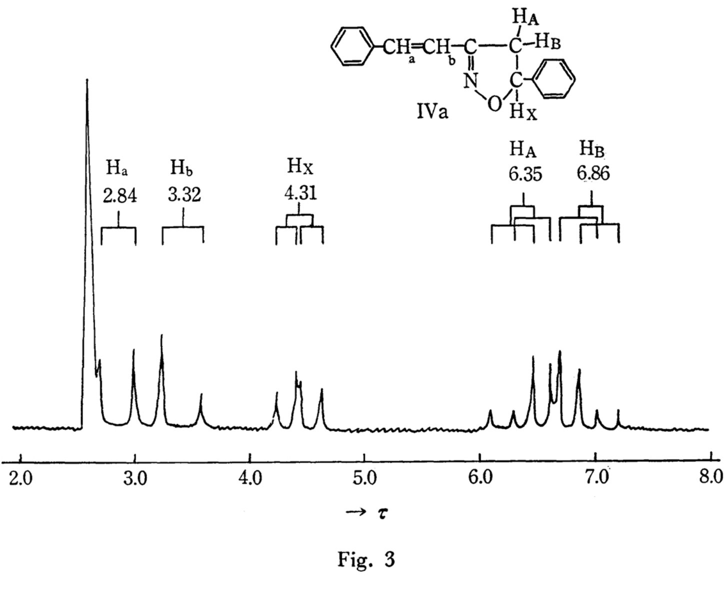


Fig. 3

and 6.86 (1H, quartet, H_B). If an ABX-system[12] is applied to IVa, the values of the coupling constants are given as follows: J_{AB}, 17 cps, J_{AX}, 11 cps and J_{BX}, 9 cps; these values accord well with the results of Minami and Matsumoto.[8] Also, from the fact that the coupling constant between H_a and H_b is 16 cps, IVa may be concluded to have a trans configuration.

It is noteworthy that a vinylog with an electron-withdrawing phenyl group attacks the nitrile oxides, IIa—c, at the same position as that with an electron-attracting carbamide group, both attacks producing 5-substituted isoxazoline derivatives. The same tendency has already been observed by Quilico[13] and by Grünanger[14] when benzonitrile oxide is used. It is quite certain that the reaction proceeds in a sterically-favoring way, as expressed by Huisgen,[15] in which way the steric character of a dipolarophile plays a more important role than the electronic character, as has been shown in a preceding paper.[2]

Experimental

The melting points were determined on a Yanagimoto electric micromelting point apparatus and are not corrected. All the ultraviolet and infrared spectra were recorded on a Hitachi Model EPS-2 recording spectrophotometer and on a JASCO Model IR-S infrared spectrophotometer respectively. The NMR spectra were taken on a Varian A-60 apparatus, with tetramethylsilane as an internal standard, and their chemical shifts are presented in terms of τ values.

Phenylacrylhydroxamoyl Chloride (Ia).[5]

Furylacrylhydroxamoyl Chloride (Ib). This was prepared by previously reported method,[4] but it was too unstable to be isolated and used directly for the preparation of IIb.

5-Nitro-2-furylacrylhydroxamoyl Chloride (Ic). An excess amount of nitrosyl chloride was added to a stirred solution of 0.2 g of 5-nitro-2-furylacrolein oxime[16] in 10 m*l* of anhydrous ether at −30°C, with which the reaction mixture was allowed to stand at −20°C overnight. After the removal of the ether and the surplus of nitrosyl chloride under reduced pressure at room temperature, the residual yellow crystals were recrystallized from benzene - petroleum ether to give a quantitative yield of Ic (mp 139—141°C (dec.)). IR (KBr), 3480 cm^{-1} (ν_{OH}). UV λ_{max}^{EtOH} mμ (ε), 269 (11800), 360 (12700).

Found: C, 38.79; H, 2.30; N, 12.90%. Calcd for $C_7H_5O_4N_2Cl$: C, 38.82; H, 2.33; N, 12.93%.

Phenylacrylonitrile Oxide (IIa). 1.9 g of Ia was dissolved in 50 m*l* of ether, and to this solution there was added 20 m*l* of a 5% NaOH aqueous solution at room temperature, after which the mixture was stirred for 5 min. The ether layer was then separated and dried over anhydrous Na_2SO_4; this ether solution was used directly after filtrating off the Na_2SO_4.

Furylacrylonitrile Oxide (IIb).[4]

5-Nitro-2-furylacrylonitrile Oxide (IIc). 0.9 g of Ic was dissolved in 50 m*l* of ether, and to this solution there was added at room temperature a solution of 0.2 m*l* of triethylamine in 5 m*l* of ether. The precipitated amine salt was filtered off as soon as possible, and the filtrate was used for further reactions.

1, 3-Dipolar Cycloaddition Reactions of Ia—c. The general procedure was that the two components were mixed in ether and the mixture was refluxed for 30 min. After the ether had been removed, the residual crude product was purified by recrystallization from a suitable solvent. The results are shown in Table 1.

3-Phenyl-5-carbethoxyisoxazoline (Va). 0.3 g of IIIa was dissolved in 10 m*l* of ethanol, and to this solution 1 m*l* of concd. HCl was added; the reaction mixture was then refluxed for 10 hr. After the solvent had been removed under reduced pressure, the residue was washed with water and recrystallized from ethanol to give 0.3 g (yield, 91%) of Va as colorless plates (mp 73—75°C). IR (KBr), 1735 cm^{-1} (ν_{CO}). UV λ_{max}^{EtOH} mμ (ε), 287 (29660).

Found: C, 69.00; H, 6.24; N, 5.76%. Calcd for $C_{14}H_{15}O_3N$: C, 68.55; H, 6.16; N, 5.71%.

Reaction of IIa with α-Morpholinostyrene. 3.8 g of Ia (0.03 mol) was dissolved in 50 m*l* of ether, and to this there was added a solution of 3 m*l* of triethylamine in 20 m*l* of ether. After 2 min, the amine salt was filtered off and 3.9 g (0.02 mol) of α-morpholinostyrene was added to the filtrate. The reaction mixture was then kept at room temperature for 2 months; the resulting colorless crystals were filtered off and recrystallized from benzene-ethanol to give 0.7 g of VIa (mp 135—136°C), the yield being 10%. IR (KBr), 1625 ($\nu_{C=C}$), 1610 cm^{-1} ($\nu_{C=N}$). UV λ_{max}^{EtOH} mμ (ε), 292 (32600).

Found: C, 75.16; H, 6.69; N, 8.55%. Calcd for $C_{21}H_{22}O_2N_2$: C, 75.42; H, 6.63; N, 8.38%.

3-Styryl-5-phenylisoxazole (VIIa). To a solution of 0.2 g of VIa in 10 m*l* of ethanol, 0.2 m*l* of concd. HCl was added; the mixture was then refluxed for 1 hr. After the solvent had been removed under reduced pressure, the residue was dissolved in ether. The ether layer was washed with water and dried over anhydrous Na_2SO_4. After the ether had been removed, the residual colorless crystals were recrystallized from ethanol to give 0.2 g of VIIa as colorless needles (mp 149°C). Yield 95%. IR (KBr), 1640 ($\nu_{C=C}$), 1610 cm^{-1} ($\nu_{C=N}$). UV λ_{max}^{EOtH} mμ (ε), 280 (45300).

Found: C, 82.74; H, 5.44; N, 5.75%. Calcd for $C_{17}H_{13}ON$; C, 82.57; H, 5.30; N, 5.66%.

Reaction of IIc with α-Morpholinostyrene. α-Morpholinostyrene (0.75 g) was added to an ethereal solution of IIc, freshly prepared from 0.4 g of Ic, 0.3 m*l* of triethylamine, and 20 m*l* of ether. The reaction mixture was then kept standing at room temperature for one month. The residual oil, after the ether had been removed, was purified by chromatography on a

---

[12] N. S. Becca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco (1964), p. 46.

[13] A. Quilico and G. Speroni, *Gazz. chim. ital.*, **76**, 148 (1946); A. Quilico, G. Gaudiano and A. Ricca, *Tetrahedron*, **7**, 24 (1959).

[14] P. Grünanger and G. Stagno d'Alcontres, *Gazz. chim. ital.*, **80**, 741, 831 (1950); G. Stagno d'Alcontres, *ibid.*, **82**, 627 (1952); P. Grünanger, *ibid.*, **84**, 359 (1954); P. Grünanger and M. R. Langella, *ibid.*, **89**, 1784 (1959).

[15] R. Huisgen, *Angew. Chem.*, **75**, 742 (1963).

[16] M. Ikeda, *Chem. Abstr.*, **50**, 10701 (1956).

silica-gel column (100 mesh, Wako-Junyaku made) using chloroform as an eluent. 20 mg of yellow needles (mp 195—196°C), VIc, were obtained after recrystallization from ethanol. IR (KBr), 1620 cm^{-1} ($\nu_{C=C}$). UV λ_{max}^{EtOH} mμ (ε), 276 (11900), 373 (20300).

Found: C, 61.84; H, 5.25; N, 11.24%. Calcd for $C_{19}H_{19}O_5N_3$: C, 61.78; H, 5.19; N, 11.38%.

Reaction of IIa with Cyanoguanidine. To a boiling solution of 1.8 g (0.01 mol) of Ia and 0.9 g (0.01 mol) of cyanoguanidine in 30 m*l* of ethanol, 20 m*l* of a 5% NaOH aqueous solution were added. The reaction mixture was refluxed for 4 hr and then filtered. After the solvent had been removed under reduced pressure, the residual oil was treated with an alcoholic solution of picric acid. The precipitated crystals were collected and recrystallized from dimethylformamide-ethanol to give VIIIa as colorless crystals (mp 248—249°C (dec.)). Yield, 2.5%.

Found: C, 44.33; H, 2.98; N, 24.17%. Calcd for $C_{17}H_{14}O_8N_8$: C, 44.55; H, 3.09; N, 24.45%.

Reaction of Ic with Sodium Azide. To a stirred solution of 0.53 g (0.0025 mol) in 3 m*l* of methanol, there was added at 40—50°C a solution of 0.36 g (0.005 mol) of sodium azide in 6 m*l* of water; the reaction mixture was then stirred at the same temperature for 30 min. The resulting yellow crystals were collected and recrystallized from methanol to give 0.1 g of IXc (yield, 22%) as yellow needles (mp 162°C (dec.)). IR (KBr), 3280 (ν_{OH}), 2190 cm^{-1} (ν_{N_3}).

Found: C, 37.49; H, 2.19; N, 31.56%. Calcd for $C_7H_5O_4N_2Cl$: C, 37.67; H, 2.26; N, 31.39%.

The authors wish to express their thanks to Mr. Akiho Ishihara for his microanalyses and to the Research Laboratory of the Dainippon Pharmaceutical Co., Ltd., for measuring the NMR spectra.