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Studies of Heteroaromaticity. XXIV. 1,3-Dipolar Cycloaddition of *C*-(5-Nitro-2-furyl)-*N*-phenylnitrone(1)

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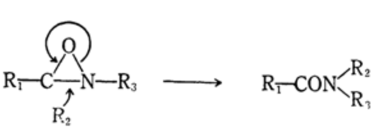
C-(5-Nitro-2-furyl)-*N*-phenylnitrone (I) was prepared from 5-nitro-2-furfural and phenylhydroxylamine in an 80% yield. The 1,3-dipolar cycloaddition reactions of I with various olefins were carried out, and the corresponding 5-substituted isoxazolidine derivatives were obtained. The structual elucidation of these products was made on the basis of the nmr spectral data. Several observations support the theory that these reactions proceed *via* a concerted one-step process.

In a previous paper(2) we reported the 1,3-dipolar cycloaddition reactions of a nitrone derived from orotaldehyde. This paper will deal with its preparation and with its 1,3-dipolar cycloaddition reactions with several olefins of a nitrone containing a nitrofuran ring as a heaterocyclic side chain. Furthermore, the structural elucidation of the products will be discussed, mainly on the basis of the nmr spectral data.

Results and Discussion

C-(5-Nitro-2-furyl)-*N*-phenylnitrone (I) was prepared from 5-nitro-2-furfural and phenylhydroxylamine in an 80% yield by the usual procedure.(3) All attempts to synthesize I by the thermal isomerization of the corresponding oxaziridine derivative (III), which might be produced as an intermediate in the direct peracetic acid-oxidation of *N*-(5-nitro-2-furfurylidene)aniline (II), were unsuccessful, though this is regarded as a general procedure for preparing nitrones,(4) and from the tar-like products, 5-nitro-2-furanilide (IV) was isolated as a crystalline product in a 20% yield. Various alkyloxaziranes are known to be converted to amides under pyrolytic conditions through such a concerted rearrangement mechanism as:(5)



This amide (IV) is, therefore, assumed to be produced *via* the oxazirane (III) by a mechanism similar to that are described above; in fact, IV could not be isolated from the reaction of I with acetic anhydride when heated as low as 80°C.

The nitrone structure of I was confirmed by the elemental analysis and by the presence in the infrared spectrum of a 1096 cm^{-1} absorption due to $\nu_{N\rightarrow O}$. A bathochromic shift of the ultraviolet absorption maximum of I compared with that of II (*cf.* Fig. 1) indicates some contribution to a conjugation of an azomethine linkage with a nitrofuran ring by the formation of N→O bonding.

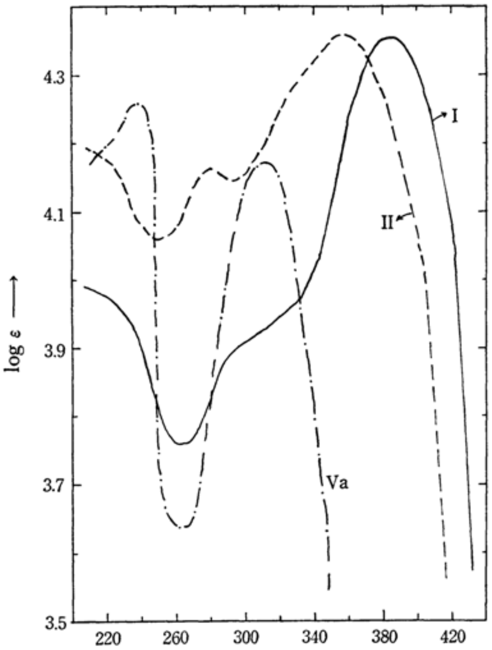


Fig. 1. UV comparison of I, II and Va (in EtOH).

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(1) Part XXIII of this series: T. Sasaki and T. Yoshioka, This Bulletin, submitted.

(2) Part XXI of this series: T. Sasaki and A. Ando, This Bulletin, **41**, 2960 (1968).

(3) L. I. Smith, *Chem. Revs.*, **23**, 193 (1938).

(4) M. F. Hawthorne and R. D. Strahm, *J. Org. Chem.*, **22**, 1263 (1957).

(5) W. D. Emmons, "Oxaziranes" in 'Heterocyclic Compounds,' A. Weissberger, ed., InterseiencePu blishers, New York, N. Y. (1964), p. 635.

I was sensitive to the light and gradually decomposed to a black tar; therefore, it must be stored in a dark and cool place.

The 1,3-dipolar cycloaddition of I was carried out both in ethanol and in toluene at each refluxing temperature by using several olefins. The results are summarized in Table 1.

As is obvious from this table, the yields of Va, for instance, were 41% after 5 hrs' refluxing in ethanol and 98% after 2 hrs' refluxing in toluene,

TABLE 1. 1,3-CYCLOADDITION WITH OLEFINS

Olefin	Reaction temp.,* °C	Reaction time, hr	Yield %	Product (mp, °C)	UV λ_{max}^{EtOH} mμ ($\varepsilon \times 10^{-4}$)	Microanalyses Found (Calcd)		
						C	H	N
Styrene	E T	5 2	41** 98	Va (118)	314(1.2) 236(1.5)	68.31 (68.85	4.39 4.80	8.52 8.33)
4-Vinylpyridine	E T	30 6	26** 88	Vb (107)	311(1.0) 232(1.3)	64.05 (64.09	4.10 4.48	11.85 12.46)
Isoprene***	90	24	31	Vc (80)	313(1.6) 233(1.9)			9.07 (9.33)
Allyl alcohol	E T	72 3.5	16** 95	Vd (100)	311(1.5) 231(1.6)	57.70 (57.93	4.57 4.86	9.30 9.65)
Allyl bromide	T	2	66	Ve (126)	313(2.0) 233(2.1)	47.82 (47.61	2.96 3.71	7.74 7.93)
Acryl amide	T	4	77	Vf (124)	311(1.8) 230(1.9)	55.40 (55.44	4.09 4.32	13.28 13.86)
trans-Stilbene	T	12 48	7 10	Vg (125)	311(2.3) 237(3.1)	73.37 (72.80)	4.57 4.89	6.88 6.79)
Dicyclopentadiene	E	48	16**	Vh+Vh′				
	T	4	47	Vh (184)	313(1.7) 231(2.2)	69.37	5.37	7.54
			19	Vh′ (133)	312(1.8) 241(1.2)	69.41 (69.21	5.41 5.53	7.46 7.69)
Cyclooctadiene	T	9.5	61	Vi (115)	312(1.4) 229(2.5)	67.22 (67.04	5.53 5.92	8.06 8.23)
Methallyl chloride	T	12	44	Vj (109)	313(1.9) 238(2.0)	55.80 (55.82	4.44 4.67	8.71 8.67)

* E: refluxing in ethanol T: refluxing in toluene.

** accompanied with the recovered I.

*** in a sealed tube.

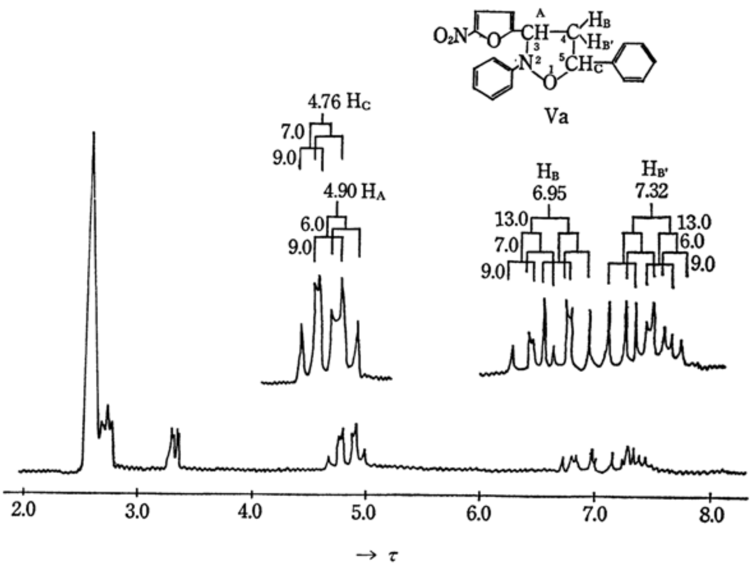
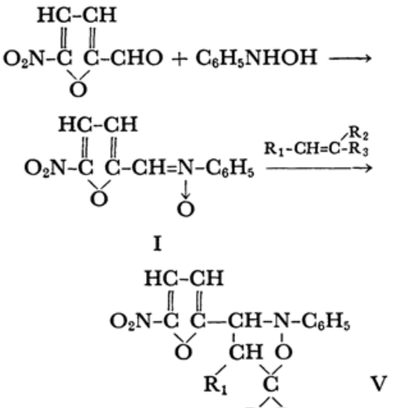


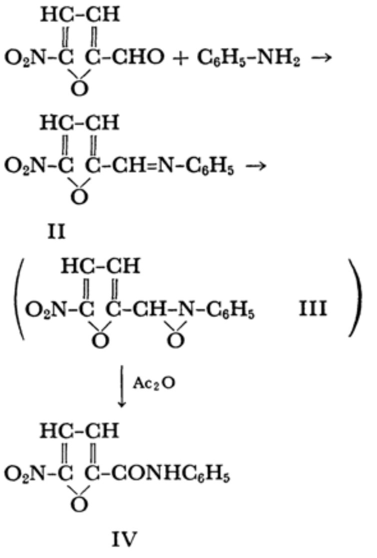
Fig. 2. NMR spectrum of Va (in $CDCl_3$ by τ-values).

indicating these reactions proceeded by the general principle of the larger temperature dependence rather than the polarity dependence of the solvent used.⁶⁾ This trend can be observed in other cases in Table 1. It can be concluded that the yields of the 1,3-dipolar cycloaddition products are much more influenced by the reaction temperature and by the steric factor of the dipolarophilic olefins than by the polarity of the solvent and by the electronic character of the olefins. All these features seem to support the theory that the 1,3-dipolar cycloaddition of I proceeds *via* the concerted one-step mechanism suggested by Huisgen.⁸⁾



I

V

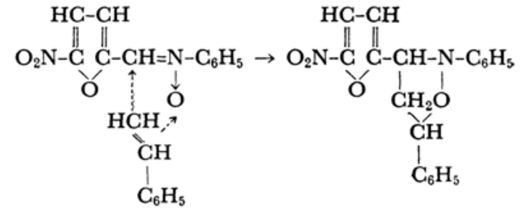


II

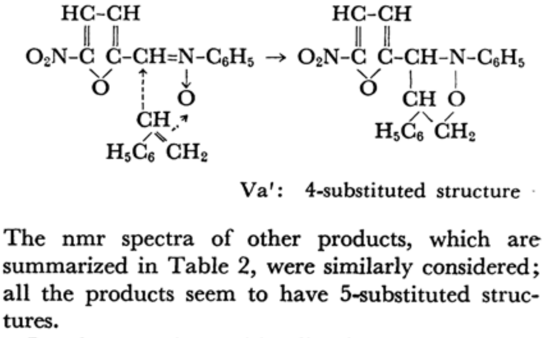
III

IV

The occurrence of the cycloaddition of I at the N→O linkage is established by the disappearance of an N→O absorption in the infrared spectrum of Va; it is further supported by a hypsochromic shift of Va compared with that of I in their ultraviolet spectra, as is indicated in Fig. 1. For Va, there are two possible structures, Va and Va′, depending on which of two different directions of addition holds. Figure 2 shows the nmr spectrum of Va, in which the signals at 2.5—3.5 τ (12 H) are readily assignable to benzene and nitrofuran ring protons, while those at 4.90 τ (1 H, quartet) and at 4.76 τ (1 H, quartet) should be assigned to two methine protons at the C-3 and C-5 respectively of an isoxazolidine ring.⁷⁾ These results support a 5-substituted structure for Va rather than the corresponding 4-substituted structure Va′.



Va: 5-substituted structure



Va′: 4-substituted structure

The nmr spectra of other products, which are summarized in Table 2, were similarly considered; all the products seem to have 5-substituted structures.

In the reaction with dicyclopentadiene, two products, Vh and Vh′, with the same elemental analyses and only slightly different ultraviolet spectra, but with different nmr spectra could be isolated. (*Cf.* Tables 1 and 2). Alder and Stein⁹⁾ have distinguished *endo*- and *exo*-dicyclopentadiene by their chemical conversion to their adducts with phenyl azide and Bruson and others¹⁰⁾ have repotred that *endo*-dicyclopentadiene reacts under acidic conditions with proton donors to give products possessing the *exo*-configuration. At the same time, the possibility of the *endo*- and *exo*-attack of I on dicyclopentadiene should be considered, since a similar type of attack has been observed in the 1,3-dipolar cycloaddition of diphenylnitrilimine to

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6) R. Huisgen, R. Grashey and Sauer, "Cycloaddition Reactions of Alkenes" in 'The Chemistry of Alkenes,' S. Patai, ed., Interscience Publishers, New York, N. Y. (1964), p. 865.

7) 5.27τ for C–3-H and 4.85 for C–5-H of 3-(6-uracilyl)-2,5-diphenylisoxazolidine.²⁾ 5.01τ for C–3-H and 4.55 for C–5-H of 3-(2-benzimidazolyl)-2,5-diphenylisoxazolidine. T. Sasaki and T. Ohishi, This Bulletin, **41**, 3012 (1968).

8) R. Huisgen, L. Feiler and G. Binsch, *Angew. Chem. Intern. Ed. Engl.*, **3**, 753 (1964).

9) K. Alder and G. Stein, *Liebigs Ann.*, **504**, 216 (1933).

10) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **67**, 723, 1178 (1945); P. D. Bartlett and A. Schneider, *ibid.*, **68**, 6 (1946); F. Bergman and H. Japhe, *ibid.*, **69**, 1826 (1947).

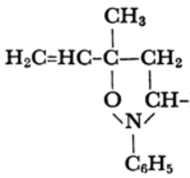
TABLE 2. NMR OF ISOXAZOLIDINES (τ)

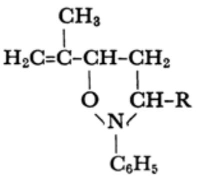
	C-3-H	C-4-H	C-5-H	Solvent	Remark
Va	4.90(q)	7.10(m)	4.76(q)	$CDCl_3$	*Cf.* Fig. 1
Vb	4.89(q)	6.85(q) 7.36(q)	4.72(q)	$CDCl_3$	
Vc	5.00(m)	7.36(m)		$CDCl_3$	4.92(d) (J=8.0 cps) 5.32(t) (J=8.0 cps) } for -CH=CH_2
Ve	4.48(q)	7.17(q) 7.40(q)	5.40(m)	$CDCl_3$	
Vf	4.71(q)	7.00(m)	5.30(q)	DMSO-d_6	
Vg	4.88(q)	5.99(q)	4.73(d)	$CDCl_3$	
Vh	4.95(q)	7.10(m)	5.70(m)	$CDCl_3$	
Vh'	5.59(q)	7.40(m)	6.00(m)	$CDCl_3$	
Vj	5.04(q)	6.98(q) (J=13 and 8 cps) 7.53(q) (J=5 and 13 cps)		$CDCl_3$	

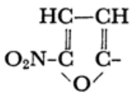
d: doublet, q: quartet, m: multiplet (τ-values are given by that of its center)

norbornene.[11] As is shown in Table 2, the shift of a C–3-H signal for Vh' to a higher magnetic field than that for Vh, which is located in the normal region of 4.95 τ, may be explained by postulating for Vh' the structure of an adduct produced by the *endo*-attack of I on *endo*-dicyclopentadiene,[12] in which the anisotropy effect of a neighboring ethylenic linkage of the cyclopropene ring caused a shift of C–3-H to a higher magnetic field.

The conversion of the 1,3-dipolar cycloaddition reaction of I with isoprene was as high as 95% after their purification by column chromatography; it was found on TLC[13] to be a mixture of two products, which were separated by fractional crystallization to Vc as a high-melting-point fraction and Vc' as a low one. The presence of a vinyl absorption in the infrared spectrum of Vc at 990 and 910 cm^{-1}[14] and that of a terminal methylene in Vc' at 890 cm^{-1}[14] suggest that their structures are as follows:


Vc

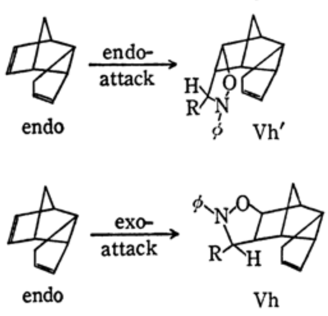

Vc'

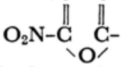
R: 

The validity of Vc structure was further confirmed by the nmr spectrum, as is illustrated in Table 2.

So far the 1,3-dipolar cycloaddition of nitrones has been reported mainly with olefins,[15] and only a few times with acetylenic compounds.[2] I was treated with phenylacetylene, propargyl bromide, and propargyl alcohol, but instead of the expected isoxazolines, an anil, II, and amide, IV, were isolated, as is shown in Table 3: the main product was a black polymer with a mp of over 300°C.

Similarly, the reactions of I with heterocumulenes such as carbon disulfide, dicyclohexylcarbodiimide, and phenyl isocyanate gave only II as an isolated crystalline product; the main product was a black polymer, as is indicated in Table 3. It is noteworthy that in the latter reactions, no amide (IV) formation could be observed. The similar treatment of I in the absence of any dipolarophile resulted only in the formation of black tars. The



R: 

ϕ: C_6H_5–

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[11] R. Huisgen, H. Knupfer, R. Sustman, G. Wallbillich and V. Weberdorfer, *Chem. Ber.*, **100**, 1580 (1967).

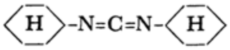
[12] The commerical dicyclopentadiene is known to possess the *endo*-configuration mainly. Therefore, two possible structures can most reasonably assigned to the products depending on the *endo*- and *exo*-attack of I on *endo*-dicyclopentadiene. About their absolute configuration, a more detailed investigation is necessary.

[13] Thin layer chromatograghy on silica-gel, using chloroform as the eluent.

[14] K. Nakanishi, "Sekigaisen Kyushu Spectrum," Nankodo, Tokyo (1960). p. 30.

[15] N. A. Le Bel and J. J. Whang, *J. Am. Chem. Soc.*, **81**, 6334 (1959); N. A. Le Bel, C. M. J. Slusarczuk and L. A. Spurlock, *ibid.*, **84**, 4360 (1962); C. W. Brown, K. Marsden, M. A. T. Rogers, C. M. B. Raylor and R. Wright, *Proc. Chem. Soc.* (*London*), 254 (1960); R. Grashey, R. Huisgen and H. Leitermann, *Tetrahedron Letters*, **12**, 9 (1960).

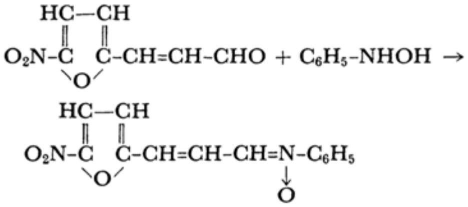
TABLE 3. 1,3-CYCLOADDITION WITH ACETYLENES AND HETEROCUMULENES

	Reaction temp., °C	Reaction time, hr	Anil	Amide	Polymer*
Acetylene					
C_6H_5-C≡CH	90	20	13	39	39
Br-CH_2-C≡CH	120	4	3	3	50
OH-CH_2-C≡CH	120	6	3	3	90
Heterocumulene					Recovered I
CS_2	120	12	61	—	27
	120	22	18	—	77
C_6H_5-N=C=O	120	13	33	—	57

* resin-like, deep-colored substance of mp >300°C

mechanism of the formation of II and IV from I in the above reactions is uncertain at present. However, I was treated with deoxygenator like triphenylphosphine to afford II, as expected.

Similarly, *C*-2-(5-nitro-2-furyl)vinyl-*N*-phenylnitrone (VI) was prepared from β-(5-nitro-2-furyl)acrolein¹⁹⁾ and phenylhydroxylamine; VI was very stable and did not react at all with triphenylphosphine under refluxing in toluene; furthermore, all attempts at the intermolecular cyclization of VI were unsuccessful.



VI

Experimental

All the melting points were determined on a Yanagimoto micromelting-point apparatus and are uncorrected. The microanalyses were carried out on a Yanagimoto C. H. N. Corder, Model MT-1. The infrared spectra were recorded on a JASCO Model IR-S infrared spectrometer, while the nmr spectra were obtained with a Hitachi high resolution NMR spectrometer, Model H-6031, at 60 Mc, and the chemical shifts are reported in τ-values relative to tetramethylsilane as the internal standard. The ultraviolet spectra were measured with a JASCO Model ORD/UV-5 optical rotatry dispersion recorder.

***C*-(5-Nitro-2-furyl)-*N*-phenylnitrone (I).** A solution of 2.8 g (20 mmol) of 5-nitro-2-furfural and 2.2 g (20 mmol) of phenylhydroxylamine in 50 m*l* of ethanol was refluxed at 80°C for 5 min. After cooling, the precipitated yellow crystals were collected and recrystallized from ethanol to give 3.8 g (80%) of I as yellow crystals, mp 184°C (decomp). IR (KBr) cm^{-1}: 1603 ($\nu_{C=N}$), 1096 ($\nu_{N\rightarrow O}$).

Found: C, 57.19; H, 3.49; N, 12.18%. Calcd for $C_{11}H_8O_4N_2$: C, 56.90; H, 3.47; N, 12.07%.

Attempts at Synthesizing I. *N*-(5-Nitro-2-furfurylidene)aniline,¹⁶⁾ (II) (0.5 g (2.3 mmol)) was dissolved in 15 m*l* of dichloromethane, and to this solution there was added a solution of peracetic acid, prepared from 0.5 m*l* of 60% hydrogen peroxide and 2.5 g of acetic acid. After the addition of a catalytic amount of 98% sulfuric acid, the reaction mixture was kept standing at room temperature for 12 hr. The mixture was then poured into 250 m*l* of water and extracted with chloroform. The chloroform layer was washed with 5% aqueous ammonia, and then with 10% sulfuric acid, and dried over magnesium sulfate. The removal of the chloroform at room temperature under reduced pressure afforded an oil, whichw as purified by chromatography (silica-gel, chloroform). Yellow needles with a mp of 177°C were separateed from the second fraction, which was characterized as 5-nitro-2-furanilide (II) by a comparison of its IR spectrum with a specimen prepared by a known method.¹⁷⁾

1,3-Dipolar Cycloaddition of I with Styrene. A mixture of 0.5 g (2 mmol) of I, 1 m*l* of styrene, and 30 m*l* of toluene was refluxed for 2 hr after the addition of five drops of triethylamine as a catalyst. After the distillable parts had been removed under reduced pressure, the residue was dissolved in chloroform and purified on a silica-gel column. Va was obtained as yellow crystals from the first fraction. Similarly, Vb—j were obtained; their yields, UV spectra, and microanalyses are summarized in Table 1.

Reaction of I with Triphenylphosphine. A solution of 0.4 g (1.2 mmol) of I and 0.45 g (1.2 mmol) of triphenylphosphine in 16 m*l* of dry benzene was heated at 90°C in a sealed tube for 2 hr. After the solvent had then been removed under reduced pressure, the residue was purified on a silica-gel column, using chloroform as the eluent. From the first fraction there was obtained a small amount of an oil, which was discarded. 0.15 g (40%) of yellow crystals (mp 124—128°C) was obtained from the second fraction; this substance was identified as II by a comparison of its IR spectrum with that of a specimen¹⁶⁾ and by a mixed-melting-point determination. From the third fraction, 40 mg (10%) of I were recovered, while from the fourth fraction, 0.25 g (60%) of triphenylphosphine oxide, mp 156°C,¹⁸⁾ was obtained.

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16) T. Takahashi, H. Saikachi, S. Yoshina and C. Mizuno, *Yakugaku Zasshi* (*J. Pharm. Soc. Japan*), **69**, 284 (1949).

17) L. Marquis, *Ann. Chim.*, **4**, 196 (1905).

18) Mp 155°C; V. K. Kucherov, *Zhur. Obshchei Khim.*, **19**, 126 (1949).

Reaction of I with Acetic Anhydride. I (0.4 g (1.7 mmol)) was dissolved in 10 m*l* of acetic anhydride, and the reaction mixture was heated at 140°C for 8 hr.[*1] After the excess amount of acetic anhydride had been removed under reduced pressure, water was added to the residue. The resulting precipitates were collected and recrystallized from ethanol to give 0.3 g (75%) of IV, which was confirmed by a comparison of its IR spectrum with a specimen.[16]

***C*-2-(5-Nitro-2-furyl)vinyl-*N*-phenylnitrone (VI).** A solution of 0.34 g (2 mmol) of β-(5-nitro-2-furyl) acrolein[19] and 0.31 g (2 mmol) of phenylhydroxylamine in 10 m*l* of ethanol was refluxed for half an hour; the resulting crystals were collected after cooling and recrystallized from dimethylformamide-ethanol to give 0.42 g (75%) of VI as red crystals, mp 195°C (decomp). IR (KBr): 1070 cm^{-1} ($\nu_{N\rightarrow O}$). UV λ_{max}^{EtOH}: 406 mμ (ε 26000).

Found: C, 60.81; H, 3.96; N, 10.98%. Calcd for $C_{13}H_{10}O_4N_3$: C, 60.46; H, 3.90; N, 10.85%.

[*1] As has been described before, I did not react at all with acetic anhydride when heated at 80°C.

19) H. Saikachi and H. Ogawa, *J. Am. Chem. Soc.*, **81**, 3642 (1958).