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Configuration of 1,3-Dipolar Cycloaddition Products of Nitrones with *N*-Phenylmaleimide

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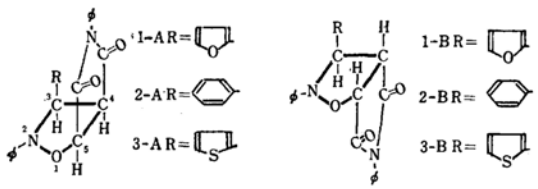
1,3-Dipolar cycloaddition reaction of aldonitrones such as *C*-2-furyl-*N*-phenyl-, *C,N*-diphenyl-, and *C*-2-thienyl-*N*-phenylnitrone with *N*-phenylmaleimide was carried out. The product was separated into two stereo isomers, *cis* and *trans* isoxazolidines with respect to H_3 and H_4, which were identified by NMR spectra. Spin-spin coupling of protons on C_3 and C_4 of isoxazolidine ring was found to be 8.4—9.0 cps for *cis* isomers and to be zero for *trans* isomers.

In a series of studies on the synthesis of new polymers, we have reported syntheses of polymers through 1,3-dipolar cycloaddition reaction.[1] As a basic study of these polymer formation reaction, the reaction of nitrones with *N*-phenylmaleimide was examined. There are some reports on the synthesis of isoxazolidines by 1,3-dipolar cycloaddition reaction of nitrones with C-C double bond.[2-6] However, few studies were carried out from a structural viewpoint. Recently, Huisgen reported the reaction of nitrones with norbornene, and two stereo isomers were isolated in the reaction of *C,N*-diphenylnitrone with norbornene.[7]

We found that *C,N*-diphenylnitrone, *C*-2-furyl- and *C*-2-thienyl-*N*-phenylnitrone gave two kinds of stero isomers, *cis*- and *trans*-isoxazolidines, in each reaction with *N*-phenylmaleimide. NMR spectra of these compounds confirmed their configurations. Details are described in this paper.

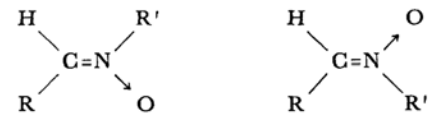


A *cis* B *trans*

Scheme 1

Results and Discussion

Two configurations, *syn* and *anti* forms, are expected for the structure of nitrone.



anti form *syn* form

However, only an *anti* form has been shown to actually exist for aldonitrone by UV and NMR spectroscopy by Hamer and Macaluso.[4] Analytical and physical data of nitrones used are shown in Table 1.

Only one signal was observed as a methine proton in the NMR spectrum of each nitrone. The nitrones used in the present study can therefore be considered to be pure and their configurations *anti* according to Hamer and Macaluso.

The reaction of nitrones with *N*-phenylmaleimide was carried out by heating a mixture of both reagents in anhydrous tetrahydrofuran (THF). The results, analytical and physical data of these products are summarized in Table 2.

Elemental analysis for the paired products gave the same values in spite of their different melting points. Therefore, it is reasonable that these paired compounds are isomers with each other. The ratio of the isomers was determined by comparing the weight of the separated product, and the value obtained was in good agreement with the ratio determined by NMR. Some NMR spectra are shown in Figs. 1 and 2.

Signals observed in lower magnetic fields than $\tau 3$ were assigned to protons on benzene and hetero-

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2) Y. Iwakura, K. Uno, S. Shiraishi and T. Hongu, The 20th Annual Meeting of the Chemical Society of Japan, April, 1967, Tokyo.

3) R. Huisgen, R. Grashey and J. Sauer, "Cycloaddition Reaction of Alkenes," in "The Chemistry of Alkenes," ed. by S. Patai, Interscience Publishers, New York, N. Y. (1946), p. 739.

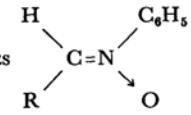
4) J. Hamer and Macaluso, *Chem. Revs.*, **64**, 473 (1964).

5) G. H. Delpierre and M. Lamchen, *Quart. Revs. (London)*, **19**, 329 (1965).

6) Y. Nomura, F. Furusaki and Y. Takeuchi, This Bulletin, **40**, 1740 (1967).

7) R. Huisgen, R. Grashey, H. Hauch and H. Seidl, *Chem. Ber.*, **101**, 2043 (1968).

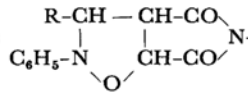
TABLE 1. PHYSICAL DATA OF NITRONES



R	Mp °C	Yield %	Recrystal.	NMR* Methine proton (τ)	NMR* Proton ratio aromatic : methine	Anal. (Calcd) C%	H%	N%
	89	63	Petroleum ether	1.02 (singlet)	8 : 1	70.58 (70.58	4.95 4.85	7.52 7.48)
	111—112	95	Benzene-*n*-hexane	1.43 (singlet)	10 : 1	80.01 (79.16	5.58 5.62	7.21 7.10)
	90	87	Petroleum ether	0.85 (singlet)	8 : 1	64.99 (65.05	4.49 4.47	6.39 6.59)

* NMR spectra were observed in 10 wt% DMSO-d_6 solution at 26°C.

TABLE 2. PHYSICAL DATA OF PRODUCTS



A (*cis*) AND B (*trans*)

	Mp °C	NMR Chemical shift (τ) H_3	H_5	H_4	NMR Coupling constant (cps) J_{3-4}	J_{4-5}	Solvent	Anal. (Calcd) C%	H%	N%
1-A	185—186	5.14(d)	4.65(d)	5.95(q)	8.4**	7.2**	DMSO-d_6	69.80 (69.99	4.61 4.48	7.72 7.77)
2-A	197—199	4.96(d)	4.57(d)	5.84(q)	9.0**	7.2**	DMSO-d_6	74.30 (74.59	4.48 4.96	7.44 7.56)
3-A	171.5	4.35(d) 4.95(d)	4.45(d) 4.85(d)	5.73(q) 6.16(q)	9.0** 9.0**	7.2** 7.2**	DMSO-d_6 $CDCl_3$	66.93 (67.01	4.21 4.29	7.71 7.44)
1-B	140—141	4.43(s)	4.86(d)	5.87(d)	0	7.2	$CDCl_3$	69.77	4.45	7.75
2-B	153—155	4.32(s) 4.07(s)	5.08(d) 4.54(d)	6.31(d) 5.84(d)	0 0	7.2 7.2	$CDCl_3$ DMSO-d_6	75.01	5.08	7.75
3-B	174—175	3.88(s)	4.66(d)	5.84(d)	0	7.2	DMSO-d_6	67.11	4.32	7.50

* NMR spectra were observed in 10 wt% solution at 26°C.
** Values were obtained by first order analysis.
s: singlet, d: doublet, q: quartet.

aromatic rings. Signals of protons on isoxazolidine ring were observed as three groups in a field from τ4 to 6. The ratios of the integrated intensities of signals of protons on aromatic rings and those of isoxazolidine rings were 13/3 for 1-A, 13/3 for 1-B, 15/3 for 2-A, 15/3 for 2-B, 13/3 for 3-A, and 13/3 for 3-B. These values were the same as theoretical values 13/3, 15/3, and 13/3 for compounds 1, 2, and 3, respectively.

Signals observed around τ6 could be assigned to the protons on C_4 of isoxazolidine ring as the atoms of both sides of C_4 are carbon. It is generally accepted that the spin-spin coupling of protons in *cis* position is larger than that in *trans*. In oxazolidine obtained here, the relative position of protons on C_4 and C_5 is to be *cis* position because C_4 and C_5 are also ring members of succinimide at the same time. Therefore, it is reasonable to consider that coupling constants of protons on C_4 and C_5 are comparatively large, and their values are the same independent of the position and kind of substituent on the isoxazolidine ring.

As shown in Table 2 and Fig. 1, compounds obtained could be divided into two groups by the figure of the signal (H_3) of isoxazolidine which was observed in the lowest magnetic field. Compounds 1-B, 2-B, and 3-B belong to group B only, in which signals (H_3) appear as a singlet. On the other hand, compounds 1-A, 2-A, and 3-A form another group A in which signals (H_3) are observed as a doublet.

In group B, signals (H_3) were assigned to those of protons on C_3, because protons on C_4 and C_5 should be *cis* and give doublet signals. Signals (H_4) observed around τ6 were assigned to those of protons on C_4 on the assumption described above,

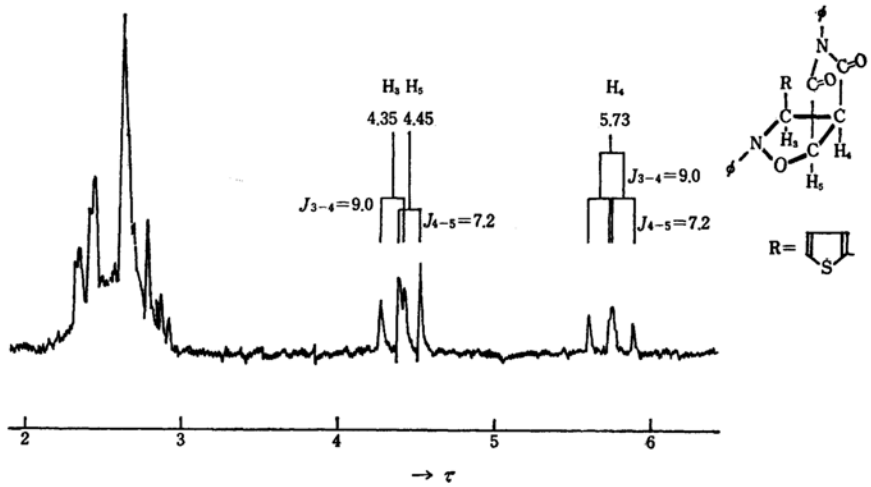


Fig. 1. NMR spectrum of cycloadduct 3-A in DMSO-d_6 by 60 Mc.

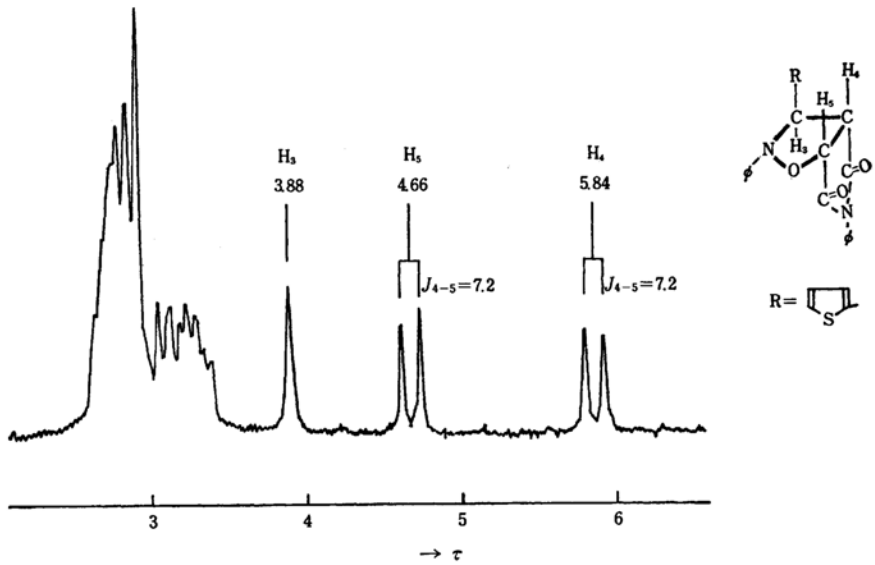


Fig. 2. NMR spectrum of cycloadduct 3-B in DMSO-d_6 by 60 Mc.

and were observed as doublets with spacing of 7.2 cps. The residual signals (H_5) which were observed around τ4.5 were assigned to those of protons on C_5 and were observed as doublets with spacing of 7.2 cps. The same spacing (7.2 cps) of H_4 and H_5 appeared to confirm the above consideration. As the protons on C_4 and C_5 are in *cis*-position, the coupling constants of 7.2 cps are reasonable for the structure. Thus the configuration of compounds in group B was concluded to be *trans* as shown in Scheme I.

In group A, the signals of the protons on isoxazolidine ring were observed as three groups, two doublets and a quartet, as shown in Table 2 and Fig. 2. Coupling constants of these protons were found to be large. Therefore, the relative position of these protons on a ring seems to be *cis*-position. Assignment of the signals in the highest magnetic field to the proton on C_4 may be reasonable because the signals are quartet.

If we assume that the relative position of the protons on C_4 and C_5 is the same, then the coupling constant of the protons on C_4 and C_5 will be independent of the position and the kind of substituent on isoxazolidine ring. Therefore, coupling constants 7.2 cps, which were concluded as that of the protons on C_4 and C_5 in group B may be attributed to the protons on C_4 and C_5 in group A. As shown in Table 2, little variation in values of the chemical shifts of H_5 and H_4 was observed. However, a large variation appeared in the chemical sihft of H_3.

The proton on C_5 is always placed on the opposite side of carbonyl group and far from other groups. Therefore, the difference in relative position between the proton and other groups gave a weak effect on the chemical shift of the proton. On the other hand, the proton on C_3 is located very near the carbonyl group in the compounds of group B, but the distance between the proton and the carbonyl group is great in the compounds of group A. The variation of the distance and relative position between the proton and carbonyl group is known to influence the chemical shift of the proton. Accordingly, the chemical shift of the proton on C_3 was expected to be different according to whether the compound belongs to group A or B. The results obtained were interpreted well by the configuration in Scheme 1.

Experimental

Nitrones. A typical example of the reaction of *C*-2-furyl-*N*-phenylnitrone is as follows. To 150 m*l* of ethanol 22 g (0.23 mol) of 2-furfural and 30 g (0.275 mol) of phenylhydroxylamine were added. The mixture was allowed to react at room temperature over night. The product was obtained by removing the solvent. Recrystallization three times from petroleum ether gave 27 g (63%) of needles, mp 89°C.

1,3-Dipolar Cycloaddition Reaction. The reaction was carried out in a closed tube. To a 30 m*l* of anhydrous THF, 3 g (0.015 mol) of *C*-2-furyl-*N*-phenylnitrone and 2.19 g (0.015 mol) of *N*-phenylmaleimide were dissolved in the presence of a small amount of *β*-naphthylamine which is an inhibitor of radical polymerization. The tube was sealed and heated at 100°C, for 10 hr. The solvent evaporated under reduced pressure to give white mass. It was recrystallized from benzene - hexane to yield white crystals, mp 142—167°C. The crystals were extracted with hot ethanol, and the ethanol solution was cooled to give white needles, mp 142—150°C, which were recrystallized twice from benzene - *n*-hexane to give B, mp 142—144°C. The fraction insoluble in ethanol was recrystallized twice from benzene - *n*-hexane to give A, mp 185—186°C. The reaction of *C*,*N*-diphenylnitrone or *C*-2-thienyl-*N*-phenylnitrone with *N*-phenylmaleimide was carried out by a similar procedure.

NMR Spectra Measurements. The NMR spectra were taken with a Japan Electron Optics C-60 spectrometer at a frequency of 60 Mc using about 10% solution of the sample in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard.