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The Reactions of Nitrile Oxide–Quinone Cycloadducts. I. Base-Induced Rearrangement of the 1 : 1 -C=C- Adducts of Aromatic Nitrile Oxides with Dialkyl-Substituted *p*-Benzoquinones

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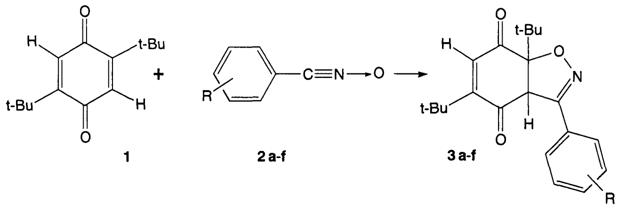
The 1,3-dipolar cycloadducts, 9-aryl-7-oxa-8-azabicyclo[4.3.0]nona-3,8-diene-2,5-diones, which were obtained from the reactions of aromatic nitrile oxides with dialkyl-substituted *p*-benzoquinones, underwent an interesting rearrangement on the action of bases. The reactions exhibited incomprehensible substituent effect. The structure elucidation of the rearranged products and the reaction mechanism are described and discussed.

In the previous papers,[1,2] we reported that alkyl- and alkyl-halo-substituted *p*-benzoquinones except for tetra-substituted ones, react with aromatic nitrile oxides to give cycloaddition products at one of the carbon–carbon double bonds of the quinones, 9-aryl-7-oxa-8-azabicyclo[4.3.0]nona-3,8-diene-2,5-diones in good yields.

These cycloadducts have 4,5-dihydroisoxazole (2-isoxazoline) structure possessing an activated proton due to the adjacent carbonyl group at 4-position of isoxazoline ring. It is known that such a ring system reacts with bases in various ways, e.g. isomerization, ring cleavage, etc.[3]



Scheme 1. The reactions of aromatic nitrile oxides with 2,5-di-*t*-butyl-*p*-benzoquinone.

The cycloadducts show unusual behaviors by the action of some bases and some of the adducts are found to undergo isomerization reaction. In the reactions, the bases are found to act as a catalyst. In the present paper, the structural determination of the isomers obtained and the reaction mechanism are described and discussed.

Results and Discussion

Ethanolic solutions of 1 : 1-C=C-cycloadducts (**3a**—**f**) of aromatic nitrile *N*-oxides (**2a**—**f**) and 2,5-di-*t*-butyl-*p*-benzoquinone (**1**), 9-aryl-3,6-di-*t*-butyl-7-oxa-8-azabicyclo[4.3.0]nona-3,8-diene-2,5-diones, showed instantaneous color change from yellow to successively blue, purple, and colorless on addition of an aqueous solution of sodium hydroxide or neat triethylamine. From the resultant colorless solution, white solid products were obtained as precipitate by neutralization with dilute hydrochloric acid. The amount of the product was almost the same as that of the starting cycloadduct. The product was shown to have the same composition formula and the same molecular weight from the elementary analyses and mass spectral data, showing that the product is an isomer of the starting cycloadduct. The yields and the characterization data of the isomerized products (**4a**—**f**) are summarized in

Table 1. Yields and Characterization Data of **4a**—**f**

Compd	R	Mp	Yields	MS Found (Calcd)	Found (Calcd)/%		
		°C	%		H	C	N
4a	H	178—180	98	339.1793	7.42	74.36	4.40
				(339.1835)	(7.42)	(74.31)	(4.13)
4b	4-Chloro-	175—176	96	373	6.59	67.35	3.75
				(373)	(6.47)	(67.46)	(3.75)
4c	4-Bromo-	168—170	96	417	5.88	60.55	3.24
				(417)	(5.78)	(60.29)	(3.35)
4d	2,4,6-Trimethyl-	167—168	98	395	8.45	75.65	3.95
				(395)	(8.19)	(75.56)	(3.67)
4e	2,3,5,6-Tetramethyl-	170—172	92	381.2310	8.17	75.54	3.83
				(381.2305)	(8.41)	(75.92)	(3.54)
4f	2,6-Dichloro-	209—210	96	407	5.85	62.02	3.61
				(407)	(5.68)	(61.77)	(3.43)

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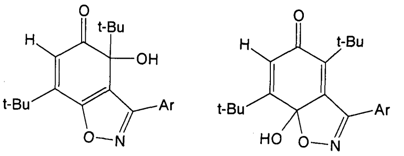
Table 1. All of the reactions proceeded quantitatively. The structures of the isomers were investigated. The IR spectra of the products had a broad absorption at around 3400 cm^{-1}, implying the presence of hydroxyl group. The relative intensity of the carbonyl absorption band compared with that of *t*-butyl at 2960 cm^{-1} of the isomers was much weaker than that of the starting cycloadducts, suggesting that one of the carbonyl groups was missing. ^{1}H NMR spectra gave similar information. As a typical example, the spectrum of the starting adduct **3a**[1] was compared with that of the isomerized product **4a**. The isomer **4a** had a hydroxyl peak at δ=2.74, which disappeared upon addition of D_2O. The methine proton signal at δ=4.69 in the starting **3a** disappeared in the spectrum of the isomer **4a**. The two signals due to *t*-butyl groups were observed in each spectrum (at δ=0.98 and 1.00 for **3a**, and at 1.08 and 1.28 for **4a**), showing that one of the *t*-butyl groups, at higher magnetic field in **3a**, shifted downfield by about 0.3 ppm. This suggests that the one of the *t*-butyl groups may be affected by strong magnetic anisotropic effect due to the change of chemical environment. The other isomers (**4b**—**f**) also showed a similar spectral change. The data are summarized in Table 2.



4 4'

Scheme 2. Possible structures of the products.

From the spectral data described above, the structures of the isomerized products are assumed to be either 9-aryl-2-hydroxyl-2,5-di-*t*-butyl-7-oxa-8-azabicyclo[4.3.0]nona-1(6),4,8-trien-3-one (**4**) or 9-aryl-6-hydroxyl-2,5-di-*t*-butyl-7-oxa-8-azabicyclo[4.3.0]nona-1,4,8-trien-3-one (**4'**). Other structures where the hydroxyl group attached to other positions might be ruled out from the consideration of the stability of the intermediate carbanion. The distinct difference in the two possible structures is that the latter (**4'**) has a hemiacetal carbon atom (7a-carbon atom). The acetal carbon atom is known to be appeared at around δ=100 in ^{13}C NMR spectrum. Any of the isomerized products have no signals in the acetal carbon region and the ^{13}C NMR data is consistent with the structure **4** (Table 3). Their chemical shifts were compared with that of 3-phenyl-1,2-benzisoxazole (**5**) which has the same ring skeleton as **4**. The comparison of the chemical shifts of C-3, C-3a, and C-7a of the isomers with the corresponding carbon atoms of 3-phenylisoxazole supports the proposed structure. The shifts of the other carbons are entirely consistent

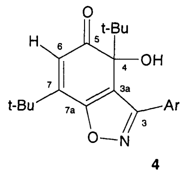
Table 2. ^{1}H NMR Data of **4a**—**f**

Compd	Quinone moiety		Aromatic moiety	
4a	1.08 (s, 9H, *t*-Bu)	1.28 (s, 9H, *t*-Bu)	7.46 (m, 3H, *m*-, *p*-)	7.98 (m, 2H, *o*-)
	2.74 (s, 1H, OH)	6.64 (s, 1H, vinyl)		
4b	1.09 (s, 9H, *t*-Bu)	1.30 (s, 9H, *t*-Bu)	7.44 (d, 2H, *m*-)	7.99 (d, 2H, *o*-)
	2.77 (s, 1H, OH)	6.67 (s, 1H, vinyl)		
4c	1.09 (s, 9H, *t*-Bu)	1.32 (s, 9H, *t*-Bu)	7.58 (d, 2H, *m*-)	7.90 (d, 2H, *o*-)
	2.80 (s, 1H, OH)	6.66 (s, 1H, vinyl)		
4d	1.08 (s, 9H, *t*-Bu)	1.24 (s, 9H, *t*-Bu)	2.06 (s, 6H, Me)	2.35 (s, 3H, Me)
	2.61 (s, 1H, OH)	6.66 (s, 1H, vinyl)	6.94 (s, 2H, *m*-)	
4e	1.15 (s, 9H, *t*-Bu)	1.29 (s, 9H, *t*-Bu)	1.98 (s, 6H, Me)	2.34 (s, 6H, Me)
	2.71 (b, 1H, OH)	6.83 (s, 1H, vinyl)	7.47 (s, 1H, *p*-)	
4f	1.11 (s, 9H, *t*-Bu)	1.26 (s, 9H, *t*-Bu)	7.40 (s, 3H, *m*-, *p*-)	
	2.64 (s, 1H, OH)	6.68 (s, 1H, vinyl)		

^{1}H NMR were measured with $CDCl_3$ as the solvent and Me_4Si as the internal reference. Abbreviation in the NMR data: s=singlet; d=doublet; m=multiplet; b=broad.

Table 3. ^{13}C NMR Spectra of Rearranged Products

Compd	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	*t*-Butyl group			
4a	157.8	125.1	72.6	179.3	145.7	112.2	177.0	24.5	33.6	38.3	
4b	156.9	123.7	72.6	179.3	145.8	112.2	177.2	23.4	27.9	33.6	38.3
4c	157.0	123.3	72.6	179.3	145.8	112.2	177.2	25.9	33.6	38.3	
5	157.2	120.4	(122.1)	(122.1)	130.2	110.1	163.8	—	—	—	



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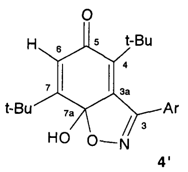

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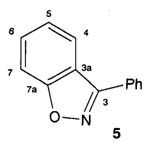

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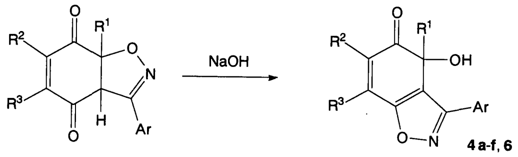
Table 4. Reaction Characteristics of the Adducts with Base. Isomerizable Adducts Depending on the Substituents on Quinone Moiety

R^1	Me	Me	Me	Me	*i*-Pr	*t*-Bu	*t*-Bu
R^2	Me	H	Me	Me	*i*-Pr	*t*-Bu	H
R^3	H	Me	Me	Cl	H	H	*t*-Bu
Compds No. of the rearranged products	—	—	—	—	**6**	—	**4a**—**f**
Rearrangement[a)]	No	No	No	No	Yes	No	Yes

a) Yes means that the starting adducts undergo rearrangement. No indicates that the adducts undergo color change on addition of a base but the starting adducts are recovered on neutralization.



4a-f, 6

with the proposed structure. The structures of the rearranged products (**4a**—**f**) were thus determined to be **4**.

The action of bases was investigated. It was shown that they act as a catalyst. Sodium hydroxide of less than 10 mol% of the substrate effected quantitative isomerization of the starting cycloadduct though the rate of the reaction was slower than when a larger amount of a base was used. Triethylamine also effected the isomerization with a slower reaction rate. However, pyridine did not effect the reaction even though used as a solvent, the starting material being recovered by subsequent treatment with dilute hydrochloric acid.

The scope and limitation of the reaction as to the structure of the starting cycloadducts (**4a**—**f**) were investigated. In addition to the cycloadducts of 2,5-di-*t*-butyl-*p*-benzoquinone with various aromatic nitrile oxides, those of 2,5-dimethyl-, 2,6-dimethyl-, 2,6-diisopropyl-, 2,6-di-*t*-butyl-, and 2-*t*-butyl-6-methyl-*p*-benzoquinones with 2,6-dichlorobenzonitrile *N*-oxide were subjected to the base-induced reaction. On addition of an aqueous solution of sodium hydroxide into an ethanolic solution of the cycloadduct, all of the cycloadducts underwent similar color change from yellow to blue at the initial stage of the reaction. Some of them subsequently followed apparently a similar color change as that of **4a**—**f**, while the other ones showed no more color change and remained deep blue for a prolonged period. The classification of the cycloadducts owing to their reaction characteristics is summarized in Table 4. The former group of the cycloadducts gave the isomerized products structure similar to those from **4a**—**f**. This comprises **3a**—**f** and 4,6-diisopropyl-8-azabicyclo[4.3.0]nona-3,8-diene-2,5-diones (adduct of 2,6-diisopropyl-*p*-benzoquinone). The other cycloadducts are included in the latter group and afforded the starting cycloadducts on neutralization of the deep blue solutions with dilute hydrochloric acid. The characterization data of the product **6** are listed in Tables 5 and 6. The signal due to one of the alkyl groups (alkyl group at 6-position of the starting cycloadduct) was shifted to downfield by about 0.3 ppm by isomerization. This pattern of spectral change is the same as observed for **4a**—**f**.

The reaction mechanism still remained unsolved. In particular, the reason why 3,6-di-*t*-butyl and 4,6-diisopropyl derivatives do undergo isomerization and 4,6-di-*t*-butyl one does not is still uncertain.

The color change of the solution from yellow to blue, however, might be considered due to the formation of nitroso group by proton abstraction at 1-position (4-position of the isoxazoline ring) with a base. 9-Aryl-1,3,4,6-tetramethyl-7-oxa-8-azabicyclo[4.3.0]nona-3,8-diene-2,5-dione, which is the cycloadduct of 2,3,5,6-tetramethyl-*p*-benzoquinone with an aromatic nitrile oxide and has no hydrogen at 1-position, does not show any change upon treating with a base, supporting the mechanism of the initial stage of the reaction. After the formation of the carbanion, the isomerization might be considered to take place via isoxazoline ring opening, recyclization, and then hydroxide anion rearrangement

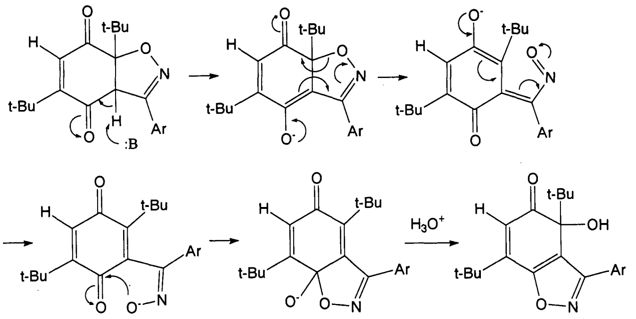
Table 5. The Characterization Data of **6**

Compd	θ	Yield	Found (Calcd)/%		
	°C	%	H	C	N
6	188—190	93	4.90 (5.04)	59.85 (60.01)	3.40 (3.68)

Table 6. ^{1}H NMR Spectra of **6**

Compd	Quinone moiety	Aromatic moiety
6	0.58 (d, 3H, *i*-Pr), 1.17 (d, 6H, *i*-Pr), 1.32 (d, 3H, *i*-Pr), 2.38 (h, 1H, *i*-Pr), 2.90 (h, 1H, *i*-Pr), 2.95 (b, 1H, OH), 6.15 (s, 1H, vinyl)	7.35 (m, 3H, *m*-, *p*-)

^{1}H NMR were measured with $CDCl_3$ as the solvent and Me_4Si as the internal reference. Abbreviation in the NMR data: s=singlet; d=doublet; h=heptet; m=multiplet; b=broad.



Scheme 3. Possible reaction mechanism of the rearrangement.

as illustrated in Scheme 3.

Experimental

Melting points were measured using a micro-melting-point measuring apparatus (Yazawa Co., Ltd.) and are uncorrected. IR spectra were recorded with a JASCO IRA-1 spectrophotometer. Mass spectra were recorded with a Hitachi RMU-7L high resolution mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with JEOL JNM-MH100 and FX-60 spectrometers respectively, and chemical shifts were reported in ppm from internal tetramethylsilane (TMS), unless otherwise cited. Column chromatography was conducted on silica gel (Wako-gel C-100 or C-200) with benzene as an eluent.

Materials. 2,5-Di-*t*-butyl-*p*-benzoquinone was obtained commercially (Tokyo Kasei Industry, Ltd.) and recrystallized from hexane. The other dialkyl-substituted *p*-benzoquinones were prepared by Liotta's procedures.[4] 2,4,6-Trimethylbenzonitrile *N*-oxide, 2,3,5,6-tetramethylbenzonitrile *N*-oxide, and 2,6-dichlorobenzonitrile *N*-oxide were synthesized according to the Grundmann's procedures.[5] Benzonitrile *N*-oxide, *p*-chlorobenzonitrile *N*-oxide, and *p*-bromobenzonitrile *N*-oxide were generated from the corresponding hydroximoyl chlorides by dehydrochlorination with triethylamine at temperature below 0 °C and allowed to react with quinones.

Preparation of Cycloadducts. All the reactions of dialkyl-substituted *p*-benzoquinones with various aromatic nitrile oxides were according to the procedures described in the previous paper.[1]

Treatment of the Cycloadducts with Bases. General Procedures: To a solution of 500 mg of a cycloadduct in 100 ml of ethanol, 10% sodium hydroxide aqueous solution was added dropwise under stirring and the mixture was stirred for an hour at room temperature. On addition of sodium hydroxide solution, the solution of the cycloadduct instantaneously turned into blue in color, subsequently into purple and then colorless within a few minutes. After that, stirring was continued for an hour. Then the colorless solution was poured into 100 ml of ice-water and the mixture was neutralized with dilute hydrochloric acid. Colorless solid precipitate was collected by filtration and recrystallized from a mixture of hexane and benzene. Yields and characterization data are summarized in Table 1. Triethylamine was also used as neat in place of aqueous sodium hydroxide. The following procedures were similar to that described above.

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