The Reaction of 2,4,6-Trimethylbenzonitrile *N*-Oxide with Polysubstituted *p*-Benzoquinones

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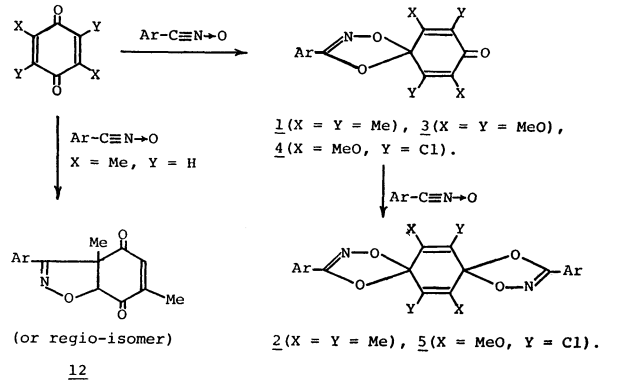
The reaction of 2,4,6-trimethylbenzonitrile *N*-oxide with various di- and tetrasubstituted *p*-benzoquinones and the structures of the products were studied. All of the tetrasubstituted quinones gave dioxazole derivatives through addition at the carbonyl site, whereas the disubstituted quinones gave dioxazoles or isoxazoline derivatives depending on the substituents. The reactivity of the quinone carbonyl toward the nitrile oxide varies with the substituents and with the substitution pattern; this phenomenon is discussed in terms of the resonance and inductive effects of the substituents.

Nitrile *N*-oxide is known to be a typical 1,3-dipole and to undergo 1,3-dipolar cycloaddition reaction with various unsaturated compounds to give heterocycles. *p*-Benzoquinones have two kinds of potential reactive sites, *i.e.*, two C=C and two C=O bonds. Cycloaddition with unsubstituted *p*-benzoquinone is known to occur at the C=C bond to give isoxazoline derivatives, which are then oxidized to isoxazoles.[1] In general, C=C bonds are more reactive than C=O bonds toward 1,3-dipoles, and so cycloaddition preferentially takes place at a C=C bond.[2] In a previous paper,[3] however, we reported that tetrahalo-*p*-benzopuinones (*p*-haloanils) make C=O addition with aromatic nitrile *N*-oxides to form dioxazole derivatives. Recently, cyclobutenediones have been reported to undergo this type of addition with mesitonitrile *N*-oxide.[4] The carbonyl addition has also been reported in the reaction of diazomethane with *p*-benzoquinones having all of the hydrogens replaced by electronegative groups.[5] 2,6-Dimethoxy-*p*-benzoquinone has also been shown to make carbonyl addition with diazomethane.[6] The dependence of the addition site on the substituents and the substitution pattern of the quinone will give a certain clue to the consideration of the exact nature of the cycloaddition reaction. In this respect, the reactions of mesitonitrile *N*-oxide with various polysubstituted *p*-benzoquinones were investigated; the results will be discussed in this paper. The effects of substituents on the reactivity of quinone carbonyls will also be discussed in terms of both inductive and resonance effects.

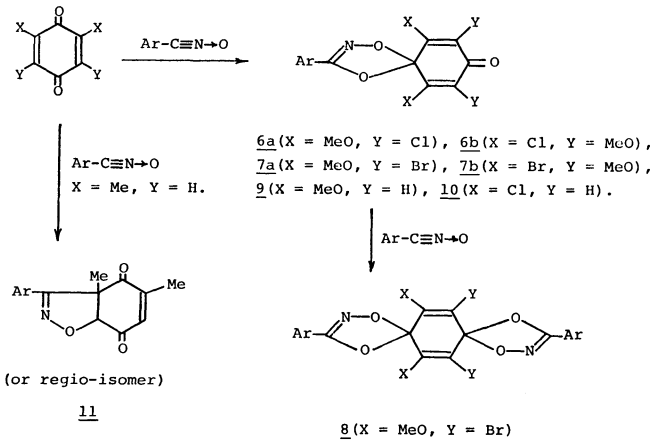
Results and Discussion

Mesitonitrile *N*-oxide (2,4,6-trimethylbenzonitrile *N*-oxide, MNO) was allowed to react with tetramethyl-*p*-benzoquinone (DQ), tetramethoxy-*p*-benzoquinone (TMOQ), 2,5-dichloro-3,6-dimethoxy-*p*-benzoquinone (25DCMOQ), 2,6-dichloro-3,5-dimethoxy-*p*-benzoquinone (26DCMOQ), 2,6-dibromo-3,5-dimethoxy-*p*-benzoquinone (26DBMOQ), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), 2,3-dichloro-1,4-naphthoquinone (23DCNQ), 2,6-dimethyl-*p*-benzoquinone (26DMQ), 2,5-dimethyl-*p*-benzoquinone (25DMQ), 2,6-dimethoxy-*p*-benzoquinone (26DMOQ), 2,5-dimethoxy-*p*-benzoquinone (25DMOQ), and 2,6-dichloro-*p*-benzoquinone (26DCQ) in chloroform at room temperature.

All of the tetrasubstituted quinones gave 1 : 1-carbonyl addition products, some of which added another MNO to give 1 : 2-adducts. The PMR spectrum of the 1 : 1-adduct from DQ and MNO (**1**) shows two singlets, at 1.92 and 2.10 ppm(δ), with a relative area corresponding to each six protons due to methyl groups on the quinone moiety, and that of the 1 : 2-adduct (**2**) shows a singlet resonance signal, at 1.98 ppm, with a relative area corresponding to twelve protons due to four methyl groups on the quinone residue. The IR spectrum of the latter has no absorption band in the $\nu_{C=O}$ region (1650—1750 cm^{-1}). TMOQ gave a 1 : 1-adduct (**3**) and no 1 : 2-adduct because of its very low reactivity. The adduct **3** has two singlet resonance signals in its PMR spectrum due to methoxyl groups on the quinone moiety. 25DCMOQ gave one 1 : 1-adduct and one 1 : 2-adduct. The PMR and IR spectroscopic aspects are substantially similar to those of the corresponding adducts from DQ. Thus, the



Scheme 1.

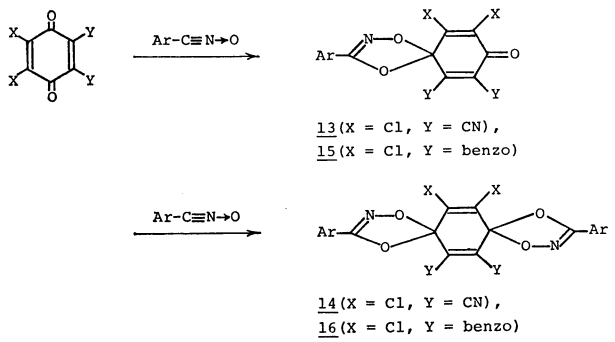


Scheme 2.

Table 1. The reaction products of aromatic nitrile *N*-oxides with substituted *p*-benzoquinones

Product	Compd. No.	Reactants mole ratio[a]	React. time, h	Yield %	Mp, °C[b]	Anal. Found (Calcd) C	H	N	IR, $\nu_{C=O}$ cm^{-1}	MS, *m/e*
C=O adducts										
DQ·MNO	**1**	1/1	20 days	50[c]	98.5—101	74.08 (73.82	6.90 7.12	4.05 4.30)	1675	325(M^+), 164, 161
DQ·MNO_2	**2**	1/2	30 days	51[d]	199—202	84.17 (83.92	6.96 7.04	5.51 5.76)	—	
TMOQ·MNO	**3**	1/1	20 days	82	152—154	61.79 (61.69	5.72 5.95	3.83 3.60)	1655 1675	
25DCMOQ·MNO	**4**	1/1	100	66	176—179	54.70 (54.29	4.48 4.30	3.79 3.52)	1690	
25DCMOQ·MNO_2	**5**	1/2	120	90	182—184	60.32 (60.11	4.75 5.04	5.15 5.01)	—	560, 558(M^+), 397, 236, 208, 193, 161
26DCMOQ·MNO	**6a**	1/1	24	47	116—120	54.08	4.33	3.70	1680	
	6b			11	142—145	54.52 (54.29	4.56 4.30	3.43 3.52)	1680	
26DBMOQ·MNO	**7a**	1/1	24	21	128—130	44.46	3.54	2.73	1680	489, 487, 489(M^+), 324, 296, 281, 253, 225, 161
	7b			13	150—152[e]	44.45 (44.38	3.60 3.52	2.84 2.88)	1680	
26DBMOQ·MNO_2	**8**	1/2	70	75	171—174	51.68 (51.87	4.57 4.35	4.42 4.32)	—	
26DMOQ·MNO	**9**	1/1.1	24	82	169—172	65.36 (65.64	5.76 5.81	4.02 4.25)	1695	329(M^+), 168, 161
26DCQ·MNO	**10**	1/1	15	77	139—141	56.60 (56.83	3.98 3.87	3.96 4.14)	1670	339, 337(M^+), 178, 176, 161
26DCQ·DNO[g]	**17**	1/1	15	78	135—141	58.04 (57.97	4.40 4.29	3.86 3.98)	1680	
26DCQ·BNO	**18**	1/1.2[h]	6	36	168—171	53.00 (52.73	2.51 2.38	4.56 4.73)	1690	
DDQ·MNO	**13**	1/1	6	73	116—119[f]	55.39 (55.69	2.69 2.86	11.09 10.82)	1710	
DDQ·MNO_2	**14**	1/2	10	75	165—169[f]	61.54 (61.21	4.22 4.04	10.48 10.20)	—	
23DCNQ·MNO	**15**	1/1	15	76	149—152	61.67 (61.87	4.08 3.89	3.88 3.61)	1675	
23DCNQ·MNO_2	**16**	1/2	20	83	182—184	65.71 (65.58	4.71 4.76	5.10 5.10)	—	
C=C adducts										
26DMQ·MNO	**11**	1/1	15	33[i]	116—118	73.08 (73.34	6.69 6.59	4.91 4.71)	1680	297(M^+), 282, 254, 202, 186, 161
25DMQ·MNO	**12**	1/1	15	30[i]	59— 62	73.12 (73.34	6.82 6.59	4.88 4.71)	1670	

a) All of the reactions were conducted in chloroform at room temperature, unless otherwise cited. b) All of the products were purified by recrystallization from hexane, unless otherwise noted. c) Unreacted starting materials were recovered. The yields based on the reacted starting materials were almost quantitative. d) The 1 : 1-adduct **1** was also obtained in a 32% yield based on DQ. e) Recrystallized from methanol. f) Recrystallized from a mixture of hexane and chloroform. g) DNO means 2,3,5,6-teramethylbenzonitrile *N*-oxide. h) See the experimental section. i) This reaction gave a complicated mixture of products. Attempts to separate and characterize the other products were not successful.



Scheme 3.

quinones with two carbonyls with equal structural surroundings gave only one 1 : 1-adduct, as is shown in Schemes 1 and 3. On the other hand, some of the quinones with two carbonyls with different structural surroundings, such as 26DCMOQ and 26DBMOQ, gave two 1 : 1-adducts, which then gave the same 1 : 2-adduct upon the addition of another MNO. The addition site of the 1 : 1-adduct was determined by PMR spectroscopy, as will be discussed later. All of the 1 : 2-adducts obtained here may be mixtures of *cis* and *trans* isomers, as was observed for the 1 : 2-adduct from chroranil and MNO.[3] Attempts to separate them, however, have not yet been successful.

Disubstituted quinones also gave 1 : 1-adducts; their structures were also determined to be those of carbonyl addition products except for those from dimethylquinones, 25DMQ and 26DMQ, which gave isoxazoline derivatives as the main products and some other unisolable by-products. Between the C=O and C=C addition products, a distinct difference is observed in their PMR spectra. The resonance signal due to 2- and 6- methyls on the mesityl residue of the C=O adduct appears as a single peak at a lower field than that due to 4-methyl protons, which always appears around 2.3 ppm, independently of the substitution patterns of the starting quinones. On the other hand, the resonance signal of the C=C adduct appears at a higher field than that of 4-methyl, which also appears at about 2.3 ppm. The upper-field shift of the 2- and 6-methyl signals can be interpreted in terms of their increased shielding by the magnetic anisotropy of the carbonyl in the C=C addition product, where the two methyls are located in the vicinity of the carbonyl group and where one methyl is above, and the other below, the plane of the group. Furthermore, some differences are observed in the spectra of the quinone moieties. For example, the methoxyl and methine on the quinone moiety of the adduct from 26DMOQ (**9**) resonate at 3.80 and 5.48 ppm respectively, each as one singlet, whereas those of the adduct from 26DMQ (**11**) each appear at two different positions. This can reasonably be explained only by considering that **9** is a spiro-dioxazole derivative and **11** is an isoxazoline derivative, as is shown in Scheme 2. The two singlets, each with relative areas corresponding to three protons in the PMR spectrum of **11**, are due to aliphatic and olefinic methyls respectively, while the other two singlets, each corresponding to one proton, are due to angular and olefinic hydrogens respectively. The structure of the C=C addition products may be considered to be that shown in Schemes 1 and 2, judging from the chemical shifts of the angular methyl and methine

Table 2. PMR Spectral data of the addition products δ, ppm, in $CDCl_3$ (relative area)

Compound No. of the products	Mesityl residue			Quinone residue	
	2,6-Me	4-Me	3,5-H		
C=O addition					
1	2.46 (6)	2.30 (3)	6.93 (2)	1.92 (6)	2.10 (6)
2	2.46 (12)	2.29 (6)	6.91 (4)	1.98 (12)	
3	2.39 (6)	2.30 (3)	6.89 (2)	3.80 (6)	4.11 (6)
4	2.42 (6)	2.29 (3)	6.92 (2)	3.97 (3)	4.26 (3)
5	2.44 (12)	2.30 (6)	6.92 (4)	4.09 (6)	
6a	2.40 (6)	2.29 (3)	6.92 (2)	4.23 (6)	
6b	2.46 (6)	2.29 (3)	6.89 (2)	3.95 (6)	
7a	2.40 (6)	2.30 (3)	6.93 (2)	4.20 (6)	
7b	2.52 (6)	2.29 (3)	6.91 (2)	3.96 (6)	
8	2.40 (6) 2.53 (6)	2.29 (6)	6.87 (4)	4.04 (6)	
9	2.39 (6)	2.29 (3)	6.89 (2)	3.80 (6)	5.48 (2)
10	2.47 (6)	2.30 (3)	6.92 (2)	6.49 (2)	
15	2.47 (6)	2.28 (3)	6.91 (2)	7·78 (4) m	
16	2.45 (12)	2.27 (6)	6.91 (4)	7.70 (4) m	
C=C addition					
11	2.15 (9) [a]	2.27 (3)	6.88 (2)	1.69 (3) 4.26 (1)	[2.15] 6.62 (1)
12	2.16 (6)	2.29 (3)	6.89 (3) [b]	1.70 (3) 4.35 (1)	1.98 (3) [6.89]

a) Overlapping with the signal due to a methyl on the quinone residue. b) Overlapping with the signal due to olefinic methine proton on the quinone residue.

protons of the adducts. The characterization data for all of the addition products are summarized in Table 1, and the PMR data, in Table 2.

The structures of the 1 : 1-carbonyl addition products from such quinones as are shown in Scheme 2, the carbonyls of which have different structural surroundings, were determined by means of their PMR spectra, as will be described below. A comparison of the chemical shifts of the 2- and 6-methyls on the mesityl residue among the six 1 : 1-adducts, **3**, **6a**, **6b**, **9**, **10**, and the 1 : 1-adduct from MNO and chloranil,[3] reveals that the adduct from chloranil, **6b**, and **10** have the same chemical shift of 2.46—2.47 ppm, while the others have one of 2.39—2.40. This fact can be explained by assuming that the methyls of the former adducts interract with the chlorine atoms on the quinone moieties, and those of the latter, with the methoxyl groups. Thus the structures of the **6a**, **6b**, **9**, and **10** adducts were determined to be such as are shown in Scheme 2. As to the two isomereric adducts from MNO and 26DBMOQ ,the **7a** isomer, the signal due to the 2- and 6-methyls of which appears at 2.40 ppm, is determined to be formed by the addition of MNO to the carbonyl with methoxyl substituents on its α and α' positions, and the **7b** isomer, the signal of which is at 2.52 ppm, by such an addition to the carbonyl on the other side. This assignment was made by the comparison of the chemical shift of the corresponding methyl groups of the adduct from MNO and bromanil, the signal of which appears at 2.53 ppm.[3] This is supported by the fact that **7a** and **7b** gave the same 1 : 2-adduct upon the addition of another MNO and that the 1 : 2-adduct shows two signals, at 2.40 and 2.53 ppm, due to the 2- and 6-methyls on the mesityl residues attached to the two sides.

The structure determination presented above reveals the following facts: 26DMOQ and 26DCQ added MNO at more sterically hindered carbonyl, and made no further addition. DQ gave a 1 : 2-adduct with MNO, but TMOQ gave only a 1 : 1-adduct. 26-DCMOQ and 26DBMOQ gave two isomers of the 1 : 1-adducts, and the major products were those formed by addition to the carbonyls on the methoxyl-substituted side.

These results imply that the carbonyl addition is governed by the resonance and inductive effects of the quinone substituents. The resonance effect reduces the reactivity of the carbonyl on its meta-position, while the positive inductive effect enhances the reactivity of the carbonyl. This conclusion is very qualitative, but it can explain the facts described above and also the fact that the reactivity of tetrasubstituted quinones decreases in the order of; DDQ, tetrahalo-*p*-benzoquinones, 26DCMOQ, and 26DBMOQ. A marked reduction in the reactivity by the resonance effect is clearly seen in the facts that 25DMOQ does not react at all with MNO under the given reaction conditions and that the reactivity of 25DCMOQ is much less than that of 26DCMOQ.

Experimental

All the melting points cited are uncorrected. The characterization data for the products are given in Table 1. The PMR spectra were recorded with a Hitachi R-20A or a R-22 spectrometer. The Mass spectra were determined with a Hitachi RMU-7L high-resolution mass spectrometer.

Materials. The 2,6-dichloro-*p*-benzoquinone (26DCQ) 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), and 2,3-dichloro-1,4-naphthoquinone (23DCNQ) were commercially obtained and were used after recrystallization. The 2,5- and 2,6-dimethyl-*p*-benzoquinones (25 and 26DMQ) were prepared from 2,5- and 3,5- dimethylphenols respectively.[7] The 2,6-dimethoxy-*p*-benzoquinone (26DMOQ) was prepared by the nitric acid oxidation of pyrogallol trimethyl ether, which had itself been obtained by the methylation of pyrogallol with dimethyl sulfate.[8] The 2,6-dichloro- and 2,6-dibromo-3,5-dimethoxy-*p*-benzoquinones (26DCMOQ and 26DBMOQ) were prepared from 26DMOQ by chlorination and bromination respectively.[8] The tetramethoxy-*p*-benzoquinone (TMOQ) was synthesized by treating 26-DBMOQ with sodium methoxide.[8] The tetramethyl-*p*-benzoquinone (DQ) was prepared from durene,[9] and the 2,5-dichloro-3,6-dimethoxy-*p*-benzoquinone (25DCMOQ), from chloranilic acid.[10]

Reaction of Quinones with Mesitonitrile N-*Oxide (MNO).* The reactions were conducted by dissolving the reactants in chloroform in a concentration of about 5 mmol/300 ml and by then allowing the mixture to react at ambient temperatures for a given period. After the reaction, the solvent was evaporated and the residue was treated by means of column chromatography on silica gel (Wako gel C-100), with a benzene or chloroform eluent. The reaction conditions and the results are tabulated in Table 1. Some typical examples follow.

*6,10-Dichloro-3-mesityl-1,4-dioxa-2-azaspiro[4.5]deca-2,6,9-trien-8-one (**10**)*: A solution of 1.00 g (5.65 mmol) of 26DCQ and 0.910 g (5.65 mmol) of MNO in 300 ml of chloroform was stirred for 15 h at room temperature. Then, the solvent was evaporated under a reduced pressure, and the residue was treated with column chromatography on silica gel with benzene. The elute was recrystallized from hexane to give the title compound, which weighed 1.47 g (77%).

*7,9-Dibromo-3-mesityl-6,10-dimethoxy-1,4-dioxa-2-azaspiro[4.5]-deca-2,6,9-trien-8-one (**7a**) and 6,10-Dibromo-3-mesityl-7,9-dimethoxy-1,4-dioxa-2-azaspiro[4.5]deca-2,6,9-trien-8-one (**7b**)*: A solution of 1.60 g (4.91 mmol) of 26DBMOQ and 0.790 g (4.91 mmol) of MNO in 300 ml of chloroform was stirred for 24 h at room temperature. The solvent was then evaporated to complete dryness under a reduced pressure, without heating, to give a reddish brown solid. The solid was treated with hot hexane to separate the hexane-soluble part from the insoluble one. Cooling the hot solution gave 0.50 g (21%) of the crystals of **7a**. The subsequent evaporation of the filtrate gave 1.40 g of the residue, most of which was determined to be **7a**. The hexane-insoluble part weighed 0.30 g (13%) and was recrystallized from methanol to give 0.13 g of **7b**. The PMR spectrum of the reddish-brown solid above showed that the reaction was almost completed; the product composition ratio of **7a** to **7b** was estimated to be about 7 : 1 by a comparison of the intensities of the signals at 4.20 and 3.96, which are due to the methoxyl groups on the quinone moieties of **7a** and **7b** respectively.

*6,14-Dibromo-3,11-dimesityl-7,13-dimethoxy-1,4,9,12-tetraoxa-2,10-diazadispiro[4.2.4.2]tetradeca-2,6,10,13-tetraene (**8**)*: A solution of 1.60 g (4.91 mmol) of 26DBMOQ and 1.58 g

(9.82 mmol) of MNO in 300 ml of chloroform was stirred at room temperature for 70 h. The subsequent evaporation of the solvent and recrystallization of the residue from hexane gave 2.39 g (75%) of the title compound.

*3-Mesityl-6,7,9,10-tetramethyl-1,4-dioxa-2-azaspiro[4.5]deca-2,6,9-trien-8-one (**1**)*: A solution of 1.00 g (6.1 mmol) of DQ and 1.00 g (6.2 mmol) of MNO in 200 ml of chloroform was allowed to stand at an ambient temperature for 20 days, after which the solvent was evaporated to give a yellow viscous oil, which was subsequently treated by means of column chromatography on silica gel with benzene. MNO, DQ, and the title compound were eluted out in that order. The product weighed 1.0 g (50%), and the recovered MNO and DQ weighed 0.5 g each.

*3,11-Dimesityl-6,7,13,14-tetramethyl-1,4,9,12-tetraoxa-2,10-diazadispiro[4.2.4.2]tetradeca-2,6,10,13-tetraene (**2**)*: A reaction of 0.82 g (5.1 mmol) of MNO with 0.40 g (2.5 mmol) of DQ in 150 ml of chloroform at an ambient temperature for 30 days gave 0.62 g (51%) of the title compound and 0.26 g (32%) of the 1 : 1-adduct, **1**, upon the column chromatography of the reaction products.

*3-Mesityl-3a,5(or 6,7a)-dimethyl-3a,4,7,7a-tetrahydrobenzisoxazole-4,7-dione (**11**)*: A solution of 0.70 g (5.1 mmol) of 26DMQ and 0.82 g (5.1 mmol) in 200 ml of chloroform was let stand at room temperature for 15 h; solvent was then evaporated to leave a tan yellow solid, which was washed with hexane to remove the hexane-highly soluble part. The residue was recrystallized from hexane to give 0.50 g (33%) of the title compound. Several components were observed in the hexane washing by TLC, but all attempts at their separation have not yet been successful.

*Reaction of Benzonitrile N-Oxide (BNO) with 26DCQ. 6,10-Dichloro-3-phenyl-1,4-dioxa-2-azaspiro[4.5]deca-2,6,9-trien-8-one (**18**)*: Into a solution of 0.55 g (3.53 mmol) of benzhydroxamoyl chloride in 20 ml of tetrahydrofuran (THF), was added, drop by drop, a solution of 0.36 g (3.54 mmol) of triethylamine in 10 ml of THF at a temperature below 0 °C. The triethylammonium chloride thus precipitated was removed by filtration, and the filtrate was added to a solution of 0.48 g (2.71 mmol) of 26DCQ in 30 ml of THF. The mixture was allowed to react with stirring at room temperature for 6 h, and then the solvent was removed by evaporation. The residue was treated with column chromatography on silica gel with benzene to give 0.10 g (24% based on the starting benzhydroxamoyl chloride) of 3,4-diphenyl-1,2,5-oxadiazole 2-oxide (diphenylfuroxan), 0.40 g of an unidentified oil, and 0.33 g (36% based on the quinone) of the title compound.

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