Photoinduced Intramolecular Substitution. II.[1,2] Absence of *meta*-Favoring Effect in Nucleophilic Photosubstitution of Nitroveratrole Derivatives

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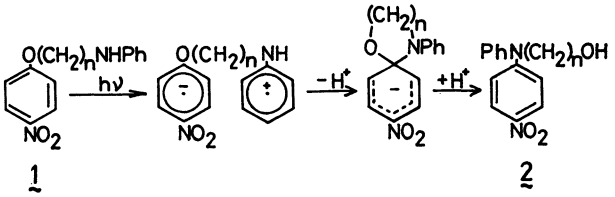
Possible occurrence of the photo-Smiles rearrangement accompanying *meta*-favoring nucleophilic aromatic substitution was examined in a homologous series of 1-(2-methoxy-4-nitrophenoxy)-ω-anilinoalkanes. The structure of reaction products, the reaction kinetics, and absorption spectra of intermediates showed no appreciable alteration of reaction pathway by the introduction of 2-methoxyl group. The photoreaction was exclusively a *para*-directing nucleophilic substitution.

In the previous papers[1,3] we have reported the photo-Smiles rearrangement (intramolecular nucleophilic aromatic substitution) of **1**, along with the reaction mechanism involving a radical ion pair and a *spiro*-type Meisenheimer complex, both ascertained by laser flash photolysis (Scheme 1).

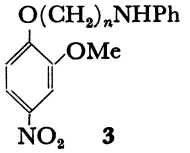


Scheme 1.

The product **2** is also obtained by a catalytic action of strong base such as sodium hydride or sodium ethoxide in DMF. Thus, both the photoinduced and thermal reactions (the Smiles rearrangement) of **1** afford the same product.

On the other hand, intermolecular photoreaction of nitroanisoles and nitroveratrole (3,4-dimethoxynitrobenzene) with nucleophiles shows preference of *meta*- to *para*-substitution.[4,5]

It is worthy of note that the *meta*-orientation observed in the intermolecular photoreactions is not exclusive in contrast with the thermal nucleophilic reactions. Therefore, the coincidence of the product of the photorearrangement with that of the Smiles rearrangement may not be the result of the exclusive photoreaction, but merely due to the lack of an appropriate substituent at the position to undergo the replacement. In other words, the photoreaction of **1** may have several pathways available, the relative importance of which changes according to conditions provided. In this regard, it is interesting to see whether the *meta*-substitution takes place when a methoxyl group is introduced to the *meta* position of the nitro group. Methoxyl is known as a good leaving group in nucleophilic substitution reactions. The present paper is concerned with the photoreaction of the homologs of **3**.

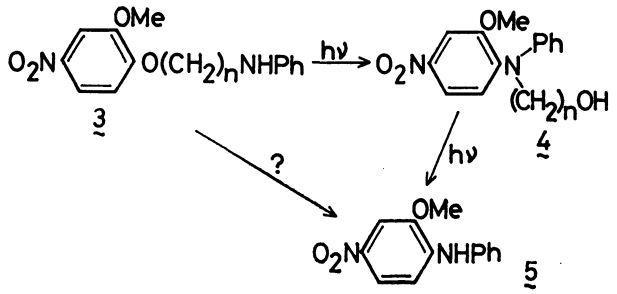


Results and Discussion

Irradiation of **3**. Irradiation of **3** was performed under the same conditions that were applied to **1**.[1] Nitroveratrole type chromophore has UV spectral peaks at *ca.* 300 and 340 nm, and irradiation with any one of 313-, 334-, and 366-nm lines of a high-pressure Hg lamp is plausibly effective for the reaction. However, filter isolation of the longer wavelength lines is accompanied by fairly strong reduction in their intensity, and these lines are also effective for further degradation of photoproducts. For these reasons, only the 313 nm line, isolated through an aqueous solution of $NiSO_4$ (1 cm in path-length), was adopted for the light source.

The photoreaction proceeded with development of yellow color in the solution. The coloration corresponded to the increase in the intensity at *ca.* 410 nm, accompanied by a concomitant decrease in the maxima in the 300—340 nm region in the UV-VIS spectrum. Structures of the products were assigned to **4** on the basis of elemental analysis as well as of the following spectral characteristics: their ^1H NMR spectra showed neither loss of methoxyl group nor remarkable change in the signal patterns of aromatic and polymethylene protons from those of **3**. Appearance of OH group was detected by NMR and IR spectroscopies. Additional evidence was the absorption peak around 410 nm, attributable to *p*-nitroaniline type chromophore.

The $n=2$ and $=3$ homologs dissolved in purified acetonitrile decomposed only to polymeric substances on irradiation, but addition of triethylamine accelerated the photorearrangement to give **4** in high yields. Addition of the amine was unnecessary for the reaction of the $n=4$ homolog. In this case, another nitroaniline derivative (**5**) was obtained as a by-product in a low



yield. The structure of **5** was confirmed by its ^1H NMR spectrum which showed loss of $(CH_2)_4OH$ group and appearance of a broad singlet at δ 6.75. The UV spectrum (λ_{max} at 401 nm in acetonitrile) and mass spectrum also supported the assignment. Since **5** was also obtained on irradiation of the rearranged product **4**, this compound is probably a secondary photolysis product, though direct formation from **3** cannot completely be eliminated.

Photorearrangement rates were obtained in acetonitrile in the absence and presence of triethylamine by the determination of time dependence of the absorption of **4**, and are summarized in Table 1.

Table 1. Relative initial rate constants (k_{rel}) of the photorearrangement of **3** in acetonitrile

	$\frac{Et_3N}{mol\ dm^{-3}}$	$n=2$	$n=3$	$n=4$
k^0_{rel}	0	*ca.* 0[a)]	*ca.* 0[a)]	4.0
k^{TEA}_{rel}	2.84×10^{-2}	4.4	0.9	1.0[b)]

a) A slight but steady increase in absorbance at 410 nm suggested occurrence of the rearrangement, but accompanying decomposition to unidentified polymeric subustances made it difficult to determine unambiguous values. b) k^{TEA}_{rel} ($n=4$) = 1.0.

From Table 1, it is evident that the reaction is catalyzed by base, especially in the lower homologs ($n=2$ and 3). Furthermore, these homologs scarcely showed reactivity in the absence of base, and only the

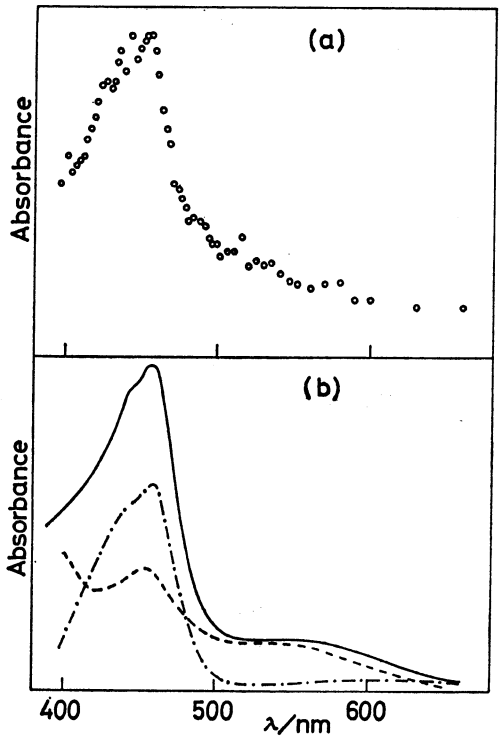


Fig. 1. (a) Transient absorption spectrum of **3** ($n=2$) in CH_3CN (10 ns after excitation). (b) Superposed spectrum (——) of nitroveratrole radical anion (------) and *N*-ethylaniline radical cation (-·-·-).

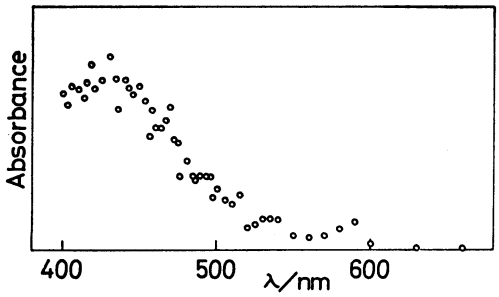


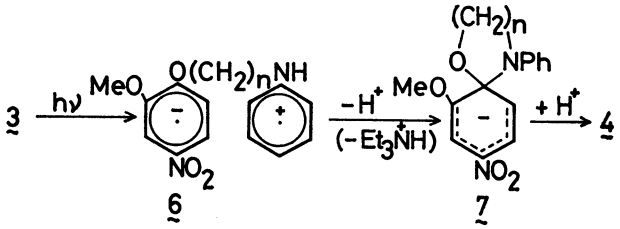
Fig. 2. Transient absorption spectrum of **3** ($n=2$) in CH_3CN–Et_3N (3 μs after excitation).

$n=4$ homolog gave a significant value. These characteristics are similar to those observed in **1**, implying a similar reaction mechanism in the present case.

Intermediates in the Photoreaction. In order to obtain evidence for this mechanism, transient spectra of the solution irradiated with an N_2 laser were observed. The spectra of the $n=2$ homolog observed in the presence of triethylamine at 10 ns and 3 μs after irradiation are reproduced in Figs. 1a and 2, respectively.

The transient species which gave the absorption curve shown in Fig. 1a has a lifetime of *ca.* 75 ns in acetonitrile and 35 ns in the same solvent containing triethylamine, though the spectra in both cases are comparable in shape and peak intensity. The species which gave the spectrum shown in Fig. 2 has a lifetime exceeding 200 μs with no remarkable peak, and its intensity is very low in the absence of triethylamine. These facts seem to suggest that a short-lifetime species formed immediately after the irradiation is converted into a long-lifetime one through a process facilitated by the base.

In all respects these characteristics coincide with the mechanism proposed for the photorearrangement of **1** (Scheme 1). If the same mechanism really works for **3**, the transient species with the shorter lifetime should be a radical ion pair produced by electron transfer from aniline to nitroveratrole moieties, and its spectrum should be a superposition of those of *N*-alkylaniline radical cation and nitroveratrole radical anion.[6] The supposed spectrum is shown in Fig. 1b. Though the peak position is somewhat different, probably due to the difference in the conditions adopted for measurement such as solvent and temperature, other spectral features are almost the same. Therefore, the short-lifetime intermediate is probably the radical ion pair **6**. The long-lived species then should be a *spiro*-type Meisenheimer complex depicted as **7**, but unfortunately any appropriate model anion to be compared has not been known. It may be argued that the spectrum in Fig. 2 is due to the absorption of the triplet state of



Scheme 2.

nitroveratrole chromophore. This T-T transition, however, was observed at 490 nm with a lifetime of *ca.* 250 ns in acetonitrile, which was reduced to 36 ns in an oxygen saturated solution. Thus the Meinsenheimer complex is a more plausible assignment. A supporting evidence for this is the increase in the intensity due to this species in the presence of triethylamine, since the formation of **7** is greatly facilitated by base (Scheme 2).

In conclusion, it can safely be said that the introduction of a methoxyl group to the *meta*-position of the nitro group has little effect on the reaction pathway of Scheme 1. Consequently the mechanism of the photoreaction of **3** could be written as in Scheme 2.

Experimental

^{1}H NMR spectra were recorded on JEOL-60HL (60 MHz) and MH-100 (100 MHz) spectrometers. The chemical shifts are in ppm with TMS as the internal standard. Electronic spectra were recorded on Hitachi EPS-3T and 100-50 spectrophotometers.

Kinetics of the Photoreaction. The rate constants were determined as described in the previous paper.[1] Acetonitrile (Wako, G. R. grade) used for the solvent was distilled from a mixture with phosphorus pentaoxide.

Transient Spectra Measurement. The absorption spectra of the transient species were determined as described previously.[3]

Materials. 2-Methoxy-4-nitrophenol was prepared by the procedure of Drake *et al.*[7]

1-(2-Methoxy-4-nitrophenoxy)-2-bromoethane: To a mixture of 8.40 g (50 mmol) of 2-methoxy-4-nitrophenol, 11.75 g (62.5 mmol) of dibromoethane, and 50 cm^3 of water, stirred and refluxed, was added 1.95 g (48.8 mmol) of sodium hydroxide in 10 cm^3 of water during 1.5 h, and reflux was further continued for 24 h. After cooling the reaction mixture, the organic layer was extracted with three portions of 20 cm^3 dichloromethane. The solvent was removed from the combined extracts, and a remaining solid mass was charged on a column packed with active alumina. Elution with benzene yielded 5.60 g (40%) of pale yellow crystals of mp 82—83 °C: NMR ($CDCl_3$) δ=3.77 (2H, t, J=6 Hz, CH_2Br), 4.03 (3H, s, OCH_3), 4.53 (2H, t, J=6 Hz, OCH_2), 7.13 (1H, d, J=9 Hz), 7.9 and 8.00 (2H, dd, J=9 and 3 Hz). Found: C, 39.31; H, 3.69; N, 5.21%. Calcd for $C_9H_{10}NO_4Br$: C, 39.15; H, 3.65; N, 5.07%.

1-(2-Methoxy-4-nitrophenoxy)-3-chloropropane: This compound was prepared from 2-methoxy-4-nitrophenol and 1,3-dichloropropane in the same method as was applied for the ethane derivative in 52% yield: mp 79—81 °C; NMR ($CDCl_3$) δ= 2.38 (2H, m, C-CH_2-C), 3.86 (2H, t, J=6 Hz, CH_2Cl), 4.01 (3H, s, OCH_3), 4.35 (2H, t, J=6 Hz, OCH_2), 7.10 (1H, d, J=9 Hz), 7.90 (1H, d, J=3 Hz), and 8.02 (1H, dd, J=9 and 3 Hz). Found: C, 49.02; H, 4.89; N, 5.76%. Calcd for $C_{10}H_{12}NO_4Cl$: C, 48.90; H, 4.92; N, 5.70%.

1-(2-Methoxy-4-nitrophenoxy)-4-bromobutane: This compound was prepared from 2-methoxy-4-nitrophenol and 1,4-dibromobutane in 38% yield: mp 51—52 °C; NMR ($CDCl_3$) δ= 2.01 (4H, m, C-CH_2CH_2-C), 3.71 (2H, t, J=6 Hz, CH_2Br), 4.01 (3H, s, OCH_3), 4.18 (2H, t, J=6 Hz, OCH_2), 7.09 (1H, d, J=9 Hz), 7.9 and 8.02 (2H, dd, J=9 and 3 Hz). Found: C, 43.59; H, 4.67; N, 4.63%. Calcd for $C_{11}H_{14}NO_4Br$: C, 43.44; H, 4.64; N, 4.61%.

Preparation of 1-(2-Methoxy-4-nitrophenoxy)-ω-anilinoalkanes (3): A mixture of the halide (30—50 mmol) and aniline (5 cm^3) was heated at 110 °C for 2 h. After cooling, the reaction mixture was neutralized with 10% aqueous sodium carbonate solution, and unreacted aniline removed by steam distillation. From the remaining liquid was isolated the desired aniline derivative by column chromatography (active alumina, with benzene as an eluent).

*1-(2-Methoxy-4-nitrophenoxy)-2-anilinoethane (**3**, n=2)*: This compound was obtained in 64% yield as yellow crystals: mp 133—135 °C; UV_{max} (CH_3CN) 297 (ε 8100)and 340 nm (ε 8700); NMR (DMSO-d_6) δ=3.42 (1H, br s, NH), 3.58 (2H, t, J=5 Hz, CH_2N), 3.93 (3H, s, OCH_3), 4.33 (2H, t, J=5 Hz, OCH_2), and 6.7—8.2 (8H, m). Found: C, 62.75; H, 5.52; N, 9.61%. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72%.

*1-(2-Methoxy-4-nitrophenoxy)-3-anilinopropane (**3**, n=3)*: This compound was obtained in 69% yield as yellow crystals: mp 99—100 °C; UV_{max} (CH_3CN) 298 (ε 8300) and 341 nm (ε 8900); NMR ($CDCl_3$) δ=2.20 (2H, m, C-CH_2-C), 3.43 (2H, t, J=6 Hz, CH_2N), *ca.* 4.0 (1H, br s, NH), 4.00 (3H, s, OCH_3), 4.29 (2H, t, J=6 Hz, OCH_2), 6.6—7.5 (6H, m), 7.87 (1H, d, J=3 Hz), and 8.00 (1H, dd, J=9 and 3 Hz). Found: C, 63.73; H, 6.21; N, 9.28%. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.26%.

*1-(2-Methoxy-4-nitrophenoxy)-4-anilinobutane (**3**, n=4)*: This compound was obtained in 40% yield as yellow crystals: mp 94—95 °C; UV_{max} (CH_3CN) 297 (ε 8600) and 341 nm (ε 9200); NMR ($CDCl_3$) δ=*ca.* 1.9 (4H, m, C-CH_2CH_2-C), 3.28 (2H, t, J=6 Hz, CH_2N), 3.83 (1H, br s, NH), 3.98 (3H, s, OCH_3), 4.20 (2H, t, J=6 Hz, OCH_2), 6.7—7.5 (5H, m), 7.89 (1H, d, J=3 Hz), and 8.03 (1H, dd, J=9 and 3 Hz). Found: C, 64.79; H, 6.67; N, 8.90%. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85%.

N-*(2-Methoxy-4-nitrophenyl)-2-anilinoethanol (**4**, n=2)*: A solution of 12 mg (0.042 mmol) of **3** (n=2) in 200 cm^3 of acetonitrile containing 1 cm^3 of triethylamine was irradiated with a 100-W high-pressure Hg lamp through an aqueous $NiSO_4$ filter under N_2 for 1.5 h. The process was repeated five times. After removing the solvent and amine from the combined solution, the residue was charged on a slica-gel column, and **4** (n=2) was separated by chromatography using benzene–dichlromethane mixture. The alcohol was obtained in 83% (50 mg) as a viscous dark red liquid: UV_{max} (CH_3CN) 256 (ε 11100) and 411 nm (ε 9000); NMR ($CDCl_3$) δ=2.4 (1H, br s, OH), *ca.* 3.95 (4H, m, NCH_2CH_2O), 3.90 (3H, s, OCH_3), 6.8—7.55 (6H, m), and 7.9—8.15 (2H, m). Found: C, 62.71; H, 5.65; N, 9.57%. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72%.

N-*(2-Methoxy-4-nitrophenyl)-3-anilino-1-propanol (**4**, n=3)*: This compound was obtained by the same procedure as has been described for the n=2 homolog in 86% isolated yield as a viscous dark red liquid: UV_{max} (CH_3CN) 256 (ε 11100) and 413 nm (ε 9500); NMR ($CDCl_3$) δ=1.86 (2H, m, C-CH_2-C), 2.77 (1H, br s, OH), 3.73 (2H, t, J=6 Hz, CH_2N), 3.80 (3H, s, OCH_3), 3.84 (2H, t, J=6 Hz, OCH_2), 6.7—7.4 (6H, m), and 7.7—7.9 (2H, m). Found: C, 63.81; H, 6.16; N, 9.12%. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.26%.

N-*(2-Methoxy-4-nitrophenyl)-4-anilino-1-butanol (**4**, n=4)*: A solution of 500 mg (1.58 mmol) of **3** (n=4) in 800 cm^3 of acetonitrile was irradiated with a 100-W high-pressure Hg lamp through an aqueous $NiSO_4$ filter under N_2 for 7.5 h. After removing the solvent, the remaining mass was charged on silica gel and eluted with benzene and benzene–dichloromethane mixture. The alcohol (460 mg, 92%) was obtained as a viscous dark red liquid: UV_{max} (CH_3CN) 255 (ε 11200) and 414 nm (ε 9600); NMR ($CDCl_3$) δ=*ca.* 1.65 (5H, m, C-CH_2CH_2-C+OH), 3.5—4.0 (4H, m, CH_2N+OCH_2), 3.79 (3H, s, OCH_3), 6.8—7.4 (6H, m), and 7.7—8.0 (2H, m).

Found: C, 64.66; H, 6.45; N, 8.78%. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85%.

*2-Methoxy-4-nitro-*N*-phenylaniline (5)*: This compound was obtained as a first eluate by the chromatograph for the separation of **4** ($n=4$) described above in 7% yield: yellow crystals, mp 77—78 °C; UV_{max} (95% EtOH) 251 (ε 9900) and 403 nm (ε 17600); NMR ($CDCl_3$) $\delta=4.01$ (3H, s, OCH_3), 6.75 (1H, br s, NH), and 6.9—8.0 (8H, m); MS (70 eV), *m/e*, 244 (M^+), 229 (M^+-15), 198 (M^+-NO_2), 154, and 148. Found: C, 63.84; H, 4.98; N, 11.63%. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47%.

*Photolysis of **4** (n=4) for the Preparation of **5***: A solution of 23 mg (0.073 mmol) of the alcohol **4** ($n=4$) in 240 cm^3 of acetonitrile was irradiated with a 100-W Hg lamp through a Pyrex filter for 6 h. After removing the solvent *in vacuo*, the residue was extracted with three 2-cm^3 portions of chloroform. From the combined extracts, the solvent was distilled off, and the remaining mass was charged on a silica-gel column, eluted with benzene–dichloromethane (1 : 1) mixture. The product **5** was obtained (4.5 mg, 23% yield) as a first eluate, followed by 13 mg of the unreacted starting material.

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