Regioselectivity of Photochemical and Thermal Smiles Rearrangements and Related Reactions of β-(Nitrophenoxy)ethylamines[1]

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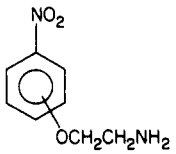
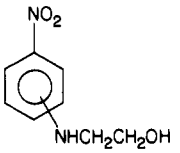
The ortho, meta, and para isomers of β-(nitrophenoxy)ethylamine (**1**, **2**, and **3**, respectively) have been synthesized as hydrochloride salts. The corresponding ortho, meta, or para isomer of β-(nitrophenoxy)ethyl alcohol (**4**, **5**, or **6**, respectively), the Smiles rearrangement product, is formed cleanly in alkaline water by a thermal reaction from **1** or **3** and by a photochemical reaction from the triplet state of **2**. Photolysis of **1** or **3** does not cause Smiles rearrangement; photoproducts recovered from **1** and **3** show that the β-amino group in both cases bonds at the ring carbon atom adjacent to the side chain and meta to the nitro group. The contrast of these results with those reported for photo-Smiles rearrangements of similar systems containing NHPh as the attacking nucleophile and for intermolecular aromatic photosubstitution by alkylamines is discussed. The results support the recently proposed "energy gap" model for predicting regioselectivity in heterolytic nucleophilic aromatic photosubstitution.

Photochemical Smiles rearrangements were first reported in 1970 for a 2,4-dinitrophenyl ether and a series of *s*-triazinyl ethers.[2] Subsequent exploratory[3] and mechanistic[4-7] studies have been reported on photo-Smiles rearrangements of *p*-(nitrophenoxy)-ω-anilinoalkanes. We have synthesized the ortho, meta, and para isomers of β-(nitrophenoxy)ethylamine and wish to report their thermal and photochemical Smiles rearrangements.[8]



1, ortho
2, meta
3, para

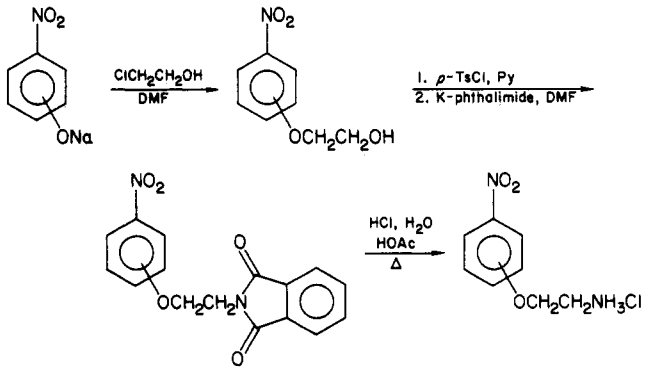


4, ortho
5, meta
6, para

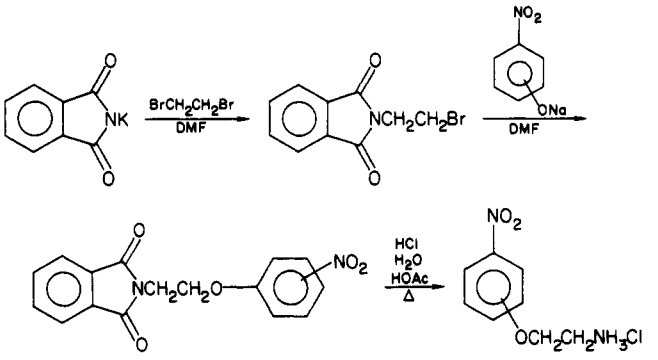
Results

Two methods were developed for synthesizing β-(nitrophenoxy)ethylamines (**1**–**3**) as hydrochlorides. The first, outlined in Scheme I, uses 2-chloroethanol to alkylate a nitrophenol; the hydroxyl group of the product is activated by conversion to a tosylate, and replaced by phthalimide. Hydrolysis of the phthalimide is best done in acid; use of hydrazine to cleave the ortho and para precursors of **1** and **3** results in some attack on the nitrophenyl ring. Moreover, **1** or **3** in alkaline media undergoes thermal Smiles rearrangement that diminishes the yield of the desired material.[9-11] Acid hydrolysis of the phthalimide and isolation

Scheme I



Scheme II



of the amine as the hydrochloride solved both of these problems. Whereas the meta isomer **2** resists hydrazine side reactions, we found it easier to purify the hydrochloride of **2** when it was generated by hydrolysis with HCl rather than by hydrazine cleavage.

A procedure we found more convenient than that in Scheme I is shown by Scheme II. The phthalimido group confers crystallinity on its derivatives, which makes the intermediates of Scheme II easier to isolate than those of Scheme I.

The ortho and para isomers **1** and **3** underwent clean Smiles rearrangements in aqueous sodium hydroxide to give the corresponding β-(nitroanilino)ethyl alcohols **4** and **6**. The reaction of **1** showed isosbestic points at 373, 313, 275, and 262 nm, and the product absorptions at 441 (ε

(1) Reported in part at the Second Chemical Congress of the North American Continent, 180th National Meeting of the American Chemical Society, Las Vegas, Aug 27, 1980; ORGN 165.
(2) (a) Matsui, K.; Maeno, N.; Suzuki, S. *Tetrahedron Lett.* **1970**, 1467–1469. (b) Shizuka, H.; Maeno, N.; Matsui, K. *Mol. Photochem.* **1972**, *4*, 335–351.
(3) Mutai, K.; Kanno, S.; Kobayashi, K. *Tetrahedron Lett.* **1978**, 1273–1276.
(4) Yokoyama, K.; Nakagaki, R.; Nakamura, J.; Mutai, K.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2472–2475.
(5) Mutai, K.; Kobayashi, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 462–465.
(6) (a) Yokoyama, K.; Nakamura, J.; Mutai, K.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 317–318. (b) Mutai, K.; Yokoyama, K.; Kanno, S.; Kobayashi, K. *Ibid.* **1982**, *55*, 1112–1115.
(7) Mutai, K.; Kobayashi, K.; Yokoyama, K. *Tetrahedron* **1984**, *40*, 1755–1759.
(8) A preliminary report has appeared: Wubbels, G. G.; Halverson, A. M.; Oxman, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 4848–4849.
(9) Kleb, G. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 291.
(10) Bernasconi, C. F.; de Rossi, R. H.; Gehriger, C. L. *J. Org. Chem.* **1973**, *38*, 2838–2842.
(11) Caldwell, W. T.; Schwieker, G. C. *J. Am. Chem. Soc.* **1952**, *74*, 5187–5189.

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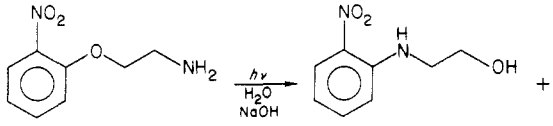
6140) and 287 nm (ε 5140) were identical with those of an authentic sample of **4**. Similarly, the reaction of **3** showed isosbestic points at 349 and 266 nm, and product λ_{max} values at 404 (ε 13 300) and 230 nm (ε 5480) were identical with those of an authentic sample of **6**. The first-order rate constants at 33 °C in the presence of 0.01 M NaOH were 1.5×10^{-4} and 4.2×10^{-5} s^{-1}, respectively.[12] Heating the meta isomer **2** at 99 °C for 15 min in 0.01 M NaOH caused no change in its UV spectrum, and we conclude that it is thermally quite unreactive.

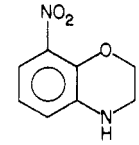
The thermal Smiles rearrangements of **1** and **3** show half-lives on the order of days at 0 °C. Thus their photochemistries could be investigated at 0 °C with little interference from the thermal reaction. We studied these reactions on spectral and preparative scales.

Photolysis of the ortho isomer **1** (1.6×10^{-4} M) in aqueous 0.01 M sodium hydroxide with Pyrex-filtered light from a medium-pressure Hg lamp (GE UA-11) at 0 °C caused complete loss of reactant absorptions [λ_{max} 335 (A = 0.43) and 264 nm (A = 0.65)] in 2 minutes and formation of an intermediate absorbing at 287 nm (A = 0.98). Further irradiation and standing at 33 °C led to product absorptions at 335, 300, and 229 nm. The strong absorption of the Smiles product [λ_{max} 441 nm (ε 6140)] could not be seen among the photoproduct absorptions. The Smiles product was stable under the irradiation conditions.

A preparative photoreaction of **1** in aqueous NaOH (pH 12) was carried out at ca. 0 °C. Thick-layer chromatography of the extracted products on silica gel showed that at least 10 compounds were present. The two major products were isolated and identified as the Smiles product, **4** (8–14%) and 3,4-dihydro-8-nitro-2*H*-1,4-benzoxazine (**7**) (5–8%). The photolysis also generated much intractable material. The possibility that photodisplacement of the nitro group by the amino group occurred was examined by subjecting an ether extract of the photolyzed solution to GC/MS analysis. No trace of a peak corresponding to 3,4-dihydro-2*H*-1,4-benzoxazine (m/e 135) was detected.



1 4



7

The low yield of **7** prompted concern about whether it represents the major photoreaction pathway of **1**. When the preparative photoreaction was conducted at lower pH (9.5) in the presence of 3,5-dinitrobenzoate (to absorb the hydride equivalent), the isolated yields of **4** and **7** based on reacted starting material were 18% and 57%, respectively.

Irradiation of the para isomer **3** (1.56×10^{-4} M) at 0 °C in aqueous 0.01 M NaOH caused rapid replacement of reactant absorptions at 317 (A = 1.25) and 225 nm (A = 0.76) by product absorptions at 323 (A = 1.0), 263 (A = 0.78), and 223 nm (A = 0.94). Extended irradiation and standing at 33 °C caused the 323-nm product peak to decrease in intensity by ca. 40% while the other product absorptions remained stable. As in the case of **1**, an intense absorption by the Smiles product, **6** [404 nm (ε 13 300)], was not observable in the UV spectrum of the photoproducts of **3**; **6** was shown independently to be stable under the irradiation conditions.

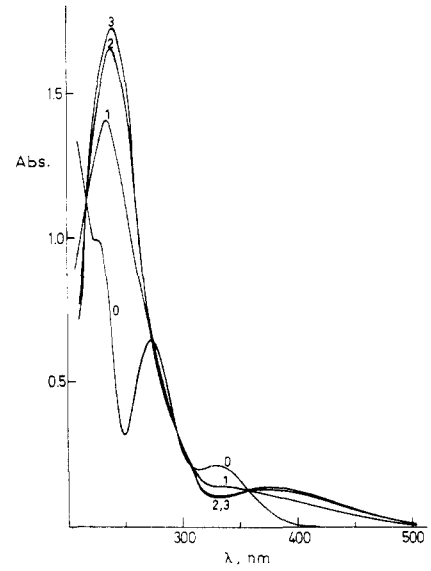
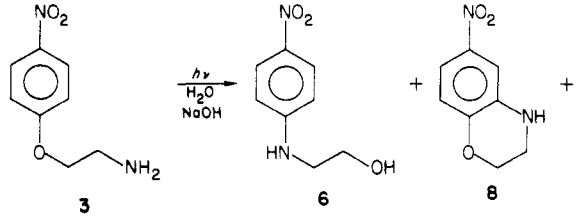
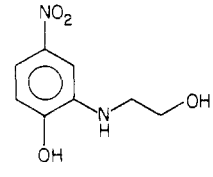


Figure 1. Electronic spectra for photo-Smiles rearrangement of **2** (1.1×10^{-4} M) in water containing 0.01 M NaOH at irradiation times as indicated: 0 = 0 min, 1 = 1 min, 2 = 2 min, 3 = 5 min.

A preparative photolysis of **3** in aqueous 0.04 M Na_2CO_3 was run to completion, and the extracted products were isolated by chromatography on alumina. The major constituents were Smiles product **6** (11%), 3,4-dihydro-6-nitro-2*H*-1,4-benzoxazine (**8**) (14%), and *N*-(2-hydroxyethyl)-2-hydroxy-5-nitroaniline, (**9**) (25%). Each of these was identified by comparison to an authentic sample. Extended irradiation of the benzoxazine in 0.01 M NaOH caused no reaction.



3 6 8



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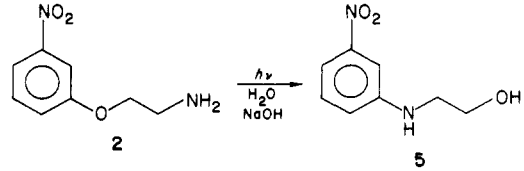
Photolysis of the meta isomer **2** (1.1×10^{-4} M) through Pyrex caused clean and efficient conversion to the Smiles rearrangement product **5**. The spectral changes accompanying the reaction are shown in Figure 1. The final spectrum is identical with that of an authentic sample of



2 5

(12) Kinetics of base-catalyzed Smiles rearrangement of **3** have been reported: (a) Knipe, A. C.; Lound-Keast, J.; Sridhar, N. J. *J. Chem. Soc., Chem. Commun.* **1976**, 765–766. (b) Knipe, A. C.; Lound-Keast, J.; Sridhar, N. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1885–1891.

5 at 1.1×10^{-4} M. A preparative photoreaction of 2 in aqueous 0.01 M NaOH gave pure 5 (75%) after one recrystallization.

Smiles photorearrangement of 2 was efficiently sensitized by triplets and was insensitive to quenching by atmospheric oxygen. Absorption at 405 nm (ϵ_{405} of 5 1110) was used to monitor reactions conducted in a merry-go-round at 313 nm. Bubbling prepurified nitrogen for 40 min through a solution of 2 (1.1×10^{-3} M) and NaOH (0.005 M) in 50% CH_3CN/H_2O had no effect (±5%) on the quantum yield relative to an air-saturated control solution. Irradiation of nitrogen-saturated solutions of 2 in 50% CH_3CN/H_2O containing 0.005 M NaOH and acetophenone (0.333 M) or *p*-methoxyacetophenone (4.32×10^{-2} M) caused Smiles rearrangements to occur with quantum yields 82% and 109%, respectively, of that of the direct photoreaction. The sensitizers in these solutions absorbed 90% of the light at 313 nm.

Irradiation of the free amine 2 in neat acetonitrile caused changes in the UV spectrum similar to those shown in Figure 1. When pyridine (0.01 M) was present in acetonitrile, the photoreaction appeared to take a different course. Extended irradiation of 2 in ether caused no change in the UV spectrum.

That the Smiles photorearrangement of 2 in water is subject to general base catalysis has been previously communicated.[13] The quantum yield of photorearrangement of 2 at 0.010 M NaOH in water is 0.29.

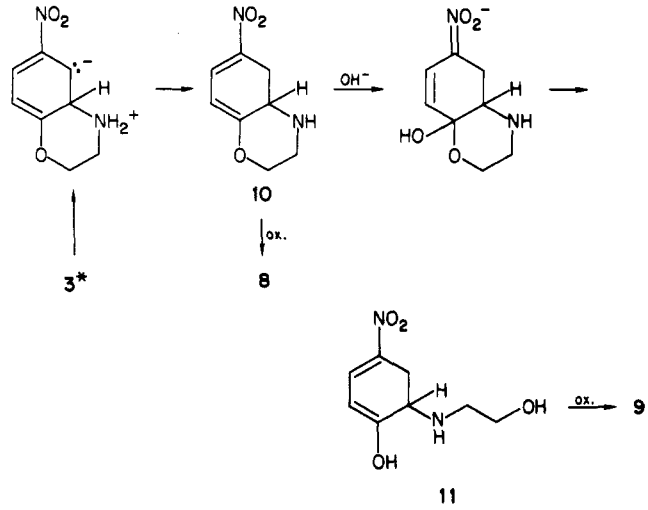
Discussion

A striking finding of this study is the apparent preference for an internal primary amine nucleophile to attack the excited *o*-, *m*-, and *p*-nitrophenyl ethers at the ring position meta to the nitro group. Small yields of the Smiles products of 1 and 3 were recovered from the preparative photoreactions, but we attribute these to thermal rather than photochemical rearrangements because the preparative reaction solutions could not be kept cold enough during irradiation to halt the thermal reaction and because traces of starting materials remain after photolysis that rearrange during workup. The spectral scale reactions, which were subject to better temperature control and could be irradiated to completion, showed that a negligible amount of Smiles product (<2%) is formed photochemically from 1 or 3 in water.

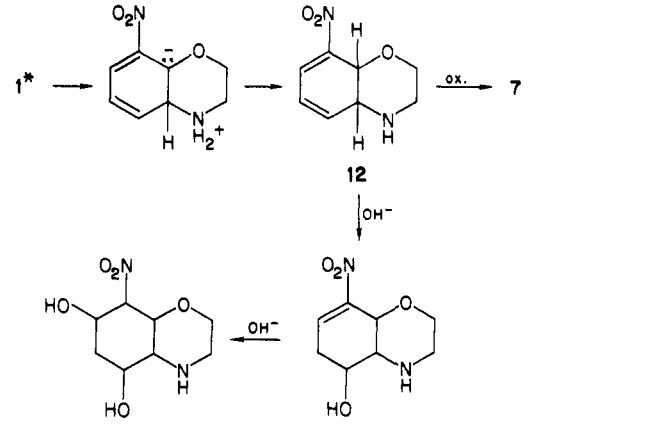
The major products isolated from the photoreactions of 1 and 3 require generation of a hydride equivalent. That reducing equivalent is apparently not taken up by a reaction with dissolved oxygen. As monitored by the changes in the UV spectrum, the efficiency of photoreaction of 3 was increased slightly when the solution was degassed, but the product absorptions were not affected. The reducing equivalent is probably received by the nitro group of ground-state starting material, the reduction products contributing to the rich mixture of colored products that we observe from 1 and 3. That the presence of 3,5-dinitrobenzoate, a good hydrogen acceptor, during the photolysis of 1 sharply increases the yield of 7 corroborates this view.

That benzoxazine 8 is not an intermediate on the pathway to aminophenol 9 in the photolysis of 3 can be explained by an addition–elimination reaction of the putative σ-complex formed from 3, as shown in Scheme III. The observed λ_{max} value (323 nm) of the intermediate formed photochemically from 3 is consistent with that

Scheme III



Scheme IV



expected for intermediate 10 in Scheme III;[14] the λ_{max} is inconsistent with the absorption expected[14] for the isomers of 10 that could in principle also be formed from the zwitterion. That the product analogous to 9 was not observed from photolysis of the ortho isomer 1 is understandable on the basis of Scheme IV. The observed λ_{max} of the photointermediate from 1 (287 nm) is consistent with that expected for 12;[14] that the λ_{max} of 10 is 36-nm red-shifted from that of 12 is attributable to the electron donor–acceptor conjugation of 10 that is absent in 12. The conjugated π-systems of 10 and 12 should cause them to be favored thermodynamically over the less conjugated intermediates that could also form by ring protonation of the initially formed zwitterions.

That the para isomer gives higher product yields than the ortho isomer may be attributed to structural differences between 10 and 12. Conjugate addition of hydroxide ion to 10 generates 11, which may be protected from nucleophilic attack by ionization of the vinyl hydroxyl group. Conjugate addition of hydroxide ion to 12 should be faster than to 10 because 12 lacks the electron-donating ether substituent; a sequence of two such additions is possible for 12 that would generate products unlikely to be isolable by our workup procedures.[15]

(13) Wubbels, G. G.; Celander, D. W. *J. Am. Chem. Soc.* **1981**, *103*, 7669–7670.

(14) Braude, E. A.; Jones, E. R. H.; Ross, G. G. *J. Chem. Soc.* **1946**, 1104–1105. They report ($\lambda_{max\ EtOH}$ (log ε)) $CH_3CH{=}C(NO_2)CH_3$, 242 nm (3.75), and $CH_3CH{=}CHCH{=}CHNO_2$, 298 (4.08) and 226 nm (3.74).

(15) Nitroethylene derivatives are known to be susceptible to nucleophilic conjugate addition and to decomposition and polymerization in aqueous or alcoholic alkali; Warrall, D. E. *J. Am. Chem. Soc.* **1927**, *49*, 1598–1605.

Table I. Charges at Ring Carbons of Triplet π,π^* Nitroanisoles Calculated by PPP-SCF-CI[a]

	C-1	C-2	C-6	intramolecular reactn site
2 nitroanisole	+0.146	+0.046	−0.035	C-6
3-nitroanisole	+0.185	−0.070	−0.062	C-1
4-nitroanisole	+0.160	−0.026	−0.034	C-2 or -6

[a] From ref 16.

A rationalization of the regioselectivity of intermolecular nucleophilic aromatic photosubstitution on nitroanisoles was recently advanced by van Riel, Lodder, and Havinga.[16] According to this view, the charge distribution in the triplet π,π^* state as calculated by CNDO/2 or PPP–SCF–CI methods is not an accurate guide to the ring position of nucleophilic attack. The proposed model postulates that the regioselectivity is controlled by the size of the energy gap between the excited-state nucleophile encounter complex and the ground-state σ-comples: the smaller the energy gap, the more favored the reaction is. In general for nitrophenyl ethers, the σ-complex resulting from attack meta to the nitro group lies 15–18 kcal/mol higher in energy than that from para (or ortho) attack. Moreover, the triplet of the meta σ-complex was calculated to have substantially lower energy than that of the para σ-complex. Thus, the preferred photosubstitution meta to nitro in methoxide photoexchange was found to agree with the qualitative predictions of the model.[16]

The results reported here support this model, and they disagree sharply with the predictions of regiochemistry based on calculated charge distribution. As shown in Table I, the carbon atom bearing the alkoxy group is markedly electron deficient relative to the adjacent carbons in each of the nitroanisoles, yet it is the site of excited-state nucleophilic displacement only for **2** among the β-(nitrophenoxy)ethylamines. For photoexcited **1** and **3**, reaction at the ipso vs. the adjacent position would appear to be favored, as it is for the ground-state Smiles rearrangement, by ring-size considerations, resonance stabilization of the intermediate σ-complex, leaving group abilities of OR^- vs. H^-, and charge density, yet virtually no Smiles reaction occurs for these photoexcited molecules. Indeed, a new regioselection effect that overwhelms the previously recognized effects appears to be at work. The results are predictable on the basis of the energy gap model.[16]

Epiotis[17] has suggested that "the preferred regioselectivity of nucleophilic photosubstitutions will be one which simultaneously maximizes the $HOMO^D$–$HOMO^A$ matrix element and minimizes the $HOMO^D$–$LUMO^A$ matrix element," where D designates the nucleophile and A the aromatic. The photoreactions reported here do not furnish an optimal test of this theory because the nucleophile is constrained to attack either the ring carbon atom bearing the side chain or an atom adjacent to it. Nonetheless, a comparison with this theory is possible within the limits noted. Taking the maximum difference of the HOMO and LUMO coefficients for the ring carbons of nitrophenols[18] as diagnostic for the site of preferred attack, the observed regioselectivities of the meta and para isomers **2** and **3** agree with prediction. For the ortho case **1**, however, Epiotis's model by a fairly narrow margin predicts ipso attack (photo-Smiles rearrangement) rather than the observed attack at C-6. The energy gap model[16] gives the right prediction for this case.

The Smiles and related photoreactions of a variety of nitrophenyl ethers such as p-$O_2NC_6H_4OCH_2CH_2NHPh$[3-7] contrast sharply with the reactions reported here in showing exclusive para regioselectivity. In those cases the attacking nucleophilic group is NHPh instead of NH_2. Nanosecond flash photolysis evidence[4-7] indicates that these reactions proceed through electron transfer from the anilino group to the excited nitrophenoxy group, followed by radical coupling to produce the σ-complex. The regiochemistry is decided by the odd electron distribution in the nitrophenoxy anion radical, which would favor σ-bond formation at ring carbons ortho and para to nitro but not meta. That we see meta regioselectivity indicates that the analogous electron transfer is not involved in our systems. Indeed the gas-phase vertical ionization potentials of methylamine and *N*-methylaniline, which should reflect the ease of ionization of the internal nucleophiles in each case, differ by 1.8 eV (9.45 and 7.65 eV, respectively).[19]

Finally, the regioselectivities of excited **2** and **3** differ from those reported for intermolecular reactions of excited 3- and 4-nitroanisoles with alkylamines. Cornelisse and Havinga[20] note that photodisplacements of methoxide from 4-nitroanisole in water by methyl-, dimethyl-, or ethylamine to give 4-nitroanilines are clean and efficient reactions. The analogous displacements on 3-nitroanisole are clean but inefficient relative to the para isomer. The intramolecular analogue of the para case shows excited-state reactivity at the carbon atom meta to nitro but little if any at the para carbon atom. The intramolecular meta case contrasts with the intermolecular case by showing high efficiency.

We attribute these differences of behavior to the restricted movement of the intramolecular amino group, which among other things denies it close approach to the nitro group. It is well established that triplet π,π^* and n,π^* states lie close enough in energy in nitrophenyl ethers that both states are populated, the π,π^* state usually being of lower energy in polar media. The electron hole of the n,π^* state is localized on the nitro group, whereas that of the π,π^* state is on the ring. Heterolytic nucleophilic aromatic photosubstitution is associated with the π,π^* state whereas photoreduction resulting from electron or hydrogen atom transfer is associated with the n,π^* state.[21] The intramolecular amino group in **1**, **2**, and **3** may be either unable to achieve the right geometry for electron donation to the valence hole on a nitro oxygen or unable to do so before competing excited-state processes occur. For the intermolecular meta case, we suggest that the n,π^* photochemistry leads to quenching, which reduces the efficiency of photosubstitution via the π,π^* state. For the intermolecular para case, we suggest that the observed photosubstitution is the result of the n,π^* photochemistry, the reaction occurring through geminate radical intermediates. Thus we attribute the lack of photo-Smiles reactivity of **3** to its inability to enter the electron-transfer radical coupling pathway that has been established for the para-specific *N*-phenyl photo-Smiles systems of Mutai.[3-7]

Experimental Section

The following instrumentation was used: ^1H NMR, Perkin-Elmer R-600 (60 MHz); IR, Beckman IR20A; UV–vis, Beckman 5260; GC/MS, Hewlett-Packard 5992B; GC, Gow-Mac 750 fid.

(16) van Riel, H. C. H. A.; Lodder, G.; Havinga, E. *J. Am. Chem. Soc.* **1981**, *103*, 7257–7262.
(17) Epiotis, N. D. "Theory of Organic Reactions"; Springer-Verlag: New York, 1978; p 180.
(18) Reference 17, p 276.
(19) Maier, J. P.; Turner, D. W. *J. Chem. Soc., Faraday Trans. 2* **1973**, *69*, 521–531.
(20) Cornelisse, J.; Havinga, E. *Chem. Rev.* **1975**, *75*, 353–403.
(21) Petersen, W. C.; Letsinger, R. L. *Tetrahedron Lett.* **1971**, 2197–2200.

Spectral scale irradiations were conducted in glass-stoppered 1.00-cm cuvettes using Pyrex-filtered light from a 1200-W General Electric UA-11 medium-pressure mercury lamp or chromate-filtered light at 313 nm from a 450-W Hanovia medium-pressure mercury lamp. Preparative scale irradiations were conducted with a 200-W or 450-W Hanovia lamp and a Pyrex filter in a tap-water-cooled immersion reactor. Preparative irradiations below room temperature were conducted either with ice-cooled tap water coolant for the well and immersion of the vessel in ice or by pumping cold ethylene glycol–water through the immersion well with a Neslab RTE-4 refrigerated bath. The preparative reactions were monitored by UV spectra of diluted aliquots. Quantum yields and relative quantum yields were determined at 313 nm in a Rayonet MGR-500 merry-go-round; the light source was a 200-W Hanovia lamp surrounded by 1 cm of 0.002 M K_2CrO_4 in 5% aqueous K_2CO_3 and 3 mm of Pyrex 7740 glass. The actinometer was degassed 0.100 M valerophenone in benzene, which was analyzed with a dodecane internal standard by gas chromatography. Samples of 5.0 mL were contained in 15-mm o.d. Pyrex tubes closed with a double O-ring seal.[22]

All chemicals were obtained from the Aldrich Chemical Co. unless otherwise noted. TLC was carried out on microscope slides coated with a CH_2Cl_2 slurry of Merck PF 254 silica gel. Preparative TLC was carried out on 20 cm × 20 cm Analabs 1000-μm Anasil GF plates.

Satisfactory spectral data (IR and ^1H NMR) were obtained for all intermediates in the syntheses of the hydrochlorides. The following were prepared by reported procedures: **4**, **5**, and **6**;[23] **8**;[24] **9**;[25] 2-(4-nitrophenoxy)ethyl tosylate.[26]

***N*-(2-(4-Nitrophenoxy)ethyl)phthalimide.** 2-(4-Nitrophenoxy)ethyl tosylate (9.72 g, 0.029 mol) and potassium phthalimide (21.9 g, 0.12 mol) were stirred in dry DMF at 100 °C for 1 h. The solution was cooled, and water was added until precipitation ceased. The precipitate was filtered and recrystallized from 95% EtOH (8.25 g, 93%, mp 152.5–153.5 °C).

1-Amino-2-(4-nitrophenoxy)ethane Hydrochloride. *N*-(2-(4-Nitrophenoxy)ethyl)phthalimide (10.0 g, 0.032 mol) was refluxed for 16 h in a mixture of concentrated hydrochloric acid (300 mL) and acetic acid (100 mL). The solution was distilled to about 200 mL and cooled in ice, and the precipitated phthalic acid was filtered off and washed with ice-cold water. The filtrate was reduced to 100 mL by boiling, and the crystals of hydrochloride which formed on cooling were collected. Acetic acid was removed from the filtrate by azeotropic distillation with toluene. Cooling the remaining 30 mL of aqueous solution yielded additional product. Recrystallization of the combined products from absolute EtOH gave pale tan crystals (6.1 g, 0.028 mol, 87%, mp 218–221 °C): ^1H NMR (D_2O) δ 8.17 (d, 2 H), 7.13 (d, 2 H), 4.7 (HDO), 4.45 (t, 2 H), 3.55 (t, 2 H); IR (KBr) 3000, 1610, 1505, 1345, 1270, 1180, 1115, 1080, 1020, 860, 760, 660 cm^{-1}. Anal. Calcd for $C_8H_{11}N_2O_3Cl$: C, 43.95; H, 5.07. Found: C, 44.06; H, 5.11.

2-(3-Nitrophenoxy)ethanol. Sodium 3-nitrophenoxide (8.2 g, 0.051 mol) and 2-chloroethanol (4.03 g, 0.052 mol) were refluxed in dry DMF (25 mL) for 11 h; the solution was cooled and poured in small portions into 300 mL of stirred ice and water. The precipitate was collected and recrystallized from benzene to give almost colorless crystals (4.18 g, 45%, mp 86.5–88 °C).

2-(3-Nitrophenoxy)ethyl Tosylate. 2-(3-Nitrophenoxy)-ethanol (3.37 g, 0.018 mol) dissolved in a minimal volume of chilled pyridine was added to *p*-toluenesulfonyl chloride (3.51 g, 0.018 mol) also in a minimal volume of chilled pyridine. The solution was refrigerated for 24 h whereupon yellow crystals had appeared. These were collected by filtration, and the supernatant was slowly poured into a 10-fold excess volume of ice and water. The precipitate was collected, combined with the above crystals, and recrystallized from benzene–hexane (4.35 g, 72%, mp 96.5–97.5 °C).

***N*-(2-(3-Nitrophenoxy)ethyl)phthalimide.** 2-(3-Nitrophenoxy)ethyl tosylate (25.6 g, 0.076 mol) and potassium phthalimide (28.1 g, 0.152 mol) were stirred at 100 °C for 1 h in dry DMF (140 mL). The solution was cooled, and water was added until precipitation ceased. The precipitated product was collected and recrystallized from 95% EtOH (17.1 g, 72%, mp 130–133 °C).

1-Amino-2-(3-nitrophenoxy)ethane Hydrochloride. The procedure indicated above for the para isomer was used to hydrolyze *N*-(2-(3-nitrophenoxy)ethyl)phthalimide (17.1 g, 0.055 mol). Recrystallization of the product from absolute EtOH gave almost colorless crystals (7.3 g, 61%, mp 218–220 °C): ^1H NMR (D_2O) δ 7.75 (d, 1 H), 7.5 (m, 3 H), 4.7 (HDO), 4.45 (t, 2 H), 3.55 (t, 2 H); IR (KBr) 2980, 1620, 1535, 1495, 1420, 1355, 1295, 1252, 1065, 1025, 850, 800, 740, 675 cm^{-1}. Anal. Calcd for $C_8H_{11}N_2O_3Cl$: C, 43.95; H, 5.07. Found: C, 43.91; H, 5.06.

***N*-(2-Bromoethyl)phthalimide.** Potassium phthalimide (30.8 g, 0.17 mol) was stirred at room temperature for 48 h with 1,2-dibromoethane (63.9 g, 0.34 mol) and dry DMF (375 mL). The precipitated KBr was filtered off, and the liquids were removed from the filtrate by distillation. The brown, solid residue was recrystallized from cyclohexane–heptane (10:1) to give nearly colorless crystals (32.3 g, 72.3%, mp 73–75 °C).

***N*-(2-(2-Nitrophenoxy)ethyl)phthalimide.** Sodium 2-nitrophenoxide (8.0 g, 0.050 mol) and *N*-(2-bromoethyl)phthalimide (12.6 g, 0.050 mol) were refluxed for 4 h in dry DMF (130 mL). The cooled solution was diluted with water until no further precipitation occurred, and the precipitate was collected by filtration. Recrystallization from 95% EtOH gave almost colorless crystals (6.95 g, 45%, mp 115–116 °C).

1-Amino-2-(2-nitrophenoxy)ethane Hydrochloride. The procedure indicated above for the para isomer was used to hydrolyze *N*-(2-(2-nitrophenoxy)ethyl)phthalimide (8.0 g, 0.026 mol). Recrystallization of the product from absolute EtOH gave almost colorless crystals (3.98 g, 71%, mp 175–178 °C): ^1H NMR (D_2O) δ 8.0 (d, 1 H), 7.76 (t, 1 H), 7.3 (m, 2 H), 4.7 (HDO), 4.5 (t, 2 H), 3.55 (t, 2 H); IR (KBr) 3280, 2850, 1620, 1510, 1360, 1290, 1260, 1180, 1010, 785, 755 cm^{-1}. Anal. Calcd for $C_8H_{11}N_2O_3Cl$: C, 43.95; H, 5.07. Found: C, 43.97; H, 5.08.

Preparative Irradiation of 1-Amino-2-(3-nitrophenoxy)-ethane (2). The hydrochloride of **2** (0.301 g) in 0.01 M aqueous NaOH (250 mL) was irradiated through a Pyrex filter in an immersion reactor for 6 h with a 200-W mercury lamp. Scans of diluted aliquots showed that the photoreaction on a preparative scale was identical with that on a spectral scale (Figure 1). The orange reaction solution was extracted with ether (3 × 100 mL), and the ether was dried over $MgSO_4$ and evaporated to dryness giving an orange-red solid (0.267 g). This material was recrystallized once from benzene–hexane to give orange crystals identified as *N*-(2-hydroxyethyl)-3-nitroaniline (170 mg, 75%) by IR and NMR spectra, which were identical with those of an authentic sample.[23]

Preparative Irradiation of 1-Amino-2-(2-nitrophenoxy)-ethane (1). The hydrochloride of **1** (0.650 g, 2.97 mmol) in 0.02 M aqueous NaOH (250 mL) containing NaCl (30 g) to enable subzero cooling was irradiated with a 200-W mercury lamp for 4 h at −10 to +6 °C. The dark brown reaction solution was acidified to pH 6 and extracted with EtOAc (4 × 100 mL). The aqueous layer was basified (pH 11) and refluxed for 1 h to effect Smiles rearrangement of unreacted **1**. This solution was cooled and extracted with EtOAc (3 × 100 mL). The combined extracts were dried over Na_2SO_4 and concentrated to dryness, giving 0.125 g (0.69 mmol, 23%) of **4**, identified by comparison of the IR spectrum with that of an authentic sample.[23] The EtOAc extract from the acidified solution was dried over Na_2SO_4 and evaporated to dryness. The residue was applied in ether to a preparative TLC plate and developed by two elutions with CH_2Cl_2. The final chromatogram showed at least 10 components. The orange band (R_f 0.20 on silica gel in CH_2Cl_2) seventh in mobility was removed and eluted with ether. The orange solid isolated by evaporation of the ether (44 mg) was identified as **4** (10.6%) by comparison with an authentic sample.[23] Collection and isolation of the material contained in a bright yellow band fourth in mobility rank gave 29 mg of an orange solid (mp 77.5–80 °C) identified as 8-nitro-3,4-dihydro-2*H*-1,4-benzoxazine (**7**) (7.1%) by the following spectral data: GC/MS (single chromatogram peak), *m/e* (relative

(22) Wubbels, G. G. *J. Chem. Educ.* **1977**, *54*, 49.
(23) Oprzadek, B. *Soc. Sci. Lodz., Acta Chim.* **1962**, *8*, 83–94; *Chem. Abstr.* **1963**, *59*, 7402e.
(24) Bugaut, A.; Estradier, F. Ger. Offen. 1940085, 1970; *Chem. Abstr.* **1970**, *73*, 36576p.
(25) Eckhardt, W. Ger. Offen. 928909, 1955; *Chem. Abstr.* **1958**, *52*, 4197f.
(26) Steller, K. E.; Letsinger, R. L. *J. Org. Chem.* **1970**, *35*, 311.

intensity) 51.1 (100), 77.1 (57), 78.1 (77), 106.1 (83), 180.1 (74); ^{1}H NMR ($CDCl_3$) δ 7.16 (d, 1 H), 6.74 (m, 2 H), 4.35 (t, 2 H), 4.15 (br s, 1 H), 3.49 (t, 2 H); IR (KBr) 3400, 1550, 1352, 1325, 1221, 1120, 1042, 840, 731, 720 cm^{-1}. Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48. Found: C, 52.87; H, 4.49. The several other products observed by TLC were present in insufficient quantity to enable identification. Several other runs were conducted with longer irradiation times and different workup procedures, but the results did not differ substantially from those reported above. The yield of **7** observed in two other runs was 7.8%, and those of **4** were 9.2% and 13.8%. A portion (1.0 mL) of the final irradiated solution was extracted with ether (1.0 mL), and the extract was subjected to GC/MS analysis; no trace of a peak appeared having a molecular ion at *m/e* 135, which would correspond to 3,4-dihydro-2*H*-1,4-benzoxazine.

A run conducted as above at pH 9.5 on the hydrochloride of **1** (0.917 mmol) in the presence of 1 equiv of 3,5-dinitrobenzoic acid gave 0.357 mmol of unreacted **1** (as thermal Smiles product **4**), 0.010 mmol of reaction product **4**, and 0.318 mmol of **7**. The yields of **4** and **7** based on 0.560 mmol of reacted **1** are 18% and 57%, respectively.

Preparative Irradiation of 1-Amino-2-(4-nitrophenoxy)-ethane (3). The hydrochloride of **3** (0.600 g, 2.74 mmol), dissolved in 550 mL of Na_2CO_3 (0.04 M) which had been adjusted to pH 10, was irradiated through a Pyrex filter for 1.5 h with a 450-W mercury lamp. The temperature initially was maintained at 0 °C by immersing the reactor in an ice bath; the temperature rose to 16 °C during the first 0.5 h of irradiation and stabilized at about 18 °C. The final reaction solution was neutralized (pH 7) and extracted with six 100-mL portions of EtOAc. The organic phases were combined, dried over $MgSO_4$, and concentrated to a reddish brown oil (0.392 g), which was applied in EtOAc to a column of alumina (15 g) packed in ether. Fractions of 30 mL were collected as the eluting solvent was gradually changed to EtOAc, then MeOH, and then water. Fractions 1 and 2 (ether eluant) contained a red solid (0.067 g, mp 100–107 °C) identified as 6-nitro-3,4-dihydro-2*H*-1,4-benzoxazine (**8**) (14%) by comparison with an authentic sample.[24] Fractions 4 and 5 (ether eluant) contained a yellow solid (0.055 g, mp 110.5 °C) identified as *N*-2-hydroxyethyl)-4-nitroaniline (**6**) (11%) by comparison with an authentic sample.[23] Fractions 13 and 14 (methanol–water eluant) contained a red solid (0.148 g) identified as the sodium salt of *N*-(2-hydroxyethyl)-2-hydroxy-5-nitroaniline (25%) by comparison with an authentic sample.[25] Other runs of this preparative reaction which used slightly different irradiation conditions and workup procedures gave results similar to those noted above.

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Registry No. **1**·HCl, 98395-65-4; **2**·HCl, 61711-97-5; **3**·HCl, 98395-62-1; **4**, 4926-55-0; **5**, 55131-09-4; **6**, 1965-54-4; **7**, 98395-66-5; **8**, 28226-22-4; **9**, 74032-78-3; 4-$NO_2C_6H_4OCH_2CH_2OTs$, 22483-44-9; 3-$NO_2C_6H_4OCH_2CH_2OH$, 16365-26-7; 3-$NO_2C_6H_4OH$·Na, 3019-85-0; $ClCH_2CH_2OH$, 107-07-3; 3-$NO_2C_6H_4OCH_2CH_2OTs$, 98395-63-2; $BrCH_2CH_2Br$, 106-93-4; 2-$NO_2C_6H_4OH$·Na, 824395; potassium phthalimide, 1074-82-4; *N*-(2-(4-nitrophenoxy)ethyl)-pthalimide, 98395-61-0; *N*-(2-(3-nitrophenoxy)ethyl)phthalimide, 58910-41-1; *N*-(2-bromoethyl)phthalimide, 574-98-1; *N*-(2-(2-nitrophenoxy)ethyl)phthalimide, 98395-64-3.

Thermal Rearrangement and Decomposition Products of Artemisinin (Qinghaosu)[1]

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Artemisinin (qinghaosu, **1**), a clinically useful antimalarial agent isolated from the plant *Artemisia annua*, is an unusual sesquiterpene lactone which contains an epidioxide (peroxide) function. It is surprisingly stable in neutral solvents heated up to 150 °C or neat, up to 50 °C above its melting point (156–157 °C) for 2.5 min. Extensive changes are detected, however, after 10 min at 190 °C. One decomposition (**2**, 4%) and two rearrangement (**3**, 12%, **4**, 10%) products were isolated by silica gel column chromatography. The structures of the products were characterized by IR spectroscopy, CIMS, ^{1}H NMR, ^{13}C NMR, and X-ray crystallography. The mechanism that accounts for the formation of these products involves the homolytic cleavage of epidioxide to generate a free radical intermediate which rearranges or decomposes to give the observed products.

Artemisinin (qinghaosu, **1**), a clinically useful antimalarial agent isolated from *Artemisia annua*, is an unusual sesquiterpene lactone which contains an epidioxide (peroxide) function.[2-6] In the course of developing a GC/MS assay method to be used in pharmacokinetic studies, it was necessary to examine the thermal stability of the com-

(1) Lin, A. J.; Klayman, D. L.; Hoch, J. M., Abstracts of Papers, 189th National Meeting of the American Chemical Society, Miami, FL, April 1985, ORGN 47.

(2) Liu, J.; Ni, M.; Fan, J.; Tu, Y.; Wu, Z.; Qu, Y.; Chou, W. *Acta Chim. Sin.* **1979**, *37*, 129.

(3) Klayman, D. L. *Science (Washington, D.C.)* **1985**, *228*, 1049.

(4) Qinghaosu Research Group, Inst. Biophy. Acad. Sinica, *Sci. Sin.* **1980**, *23*, 380.