Redox-Photosensitized Reactions. 13.[1] $Ru(bpy)_3^{2+}$-Photosensitized Reactions of an NADH Model, 1-Benzyl-1,4-dihydronicotinamide, with Aromatic Carbonyl Compounds and Comparison with Thermal Reactions

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Photosensitized reactions of 1-benzyl-1,4-dihydronicotinamide (BNAH) with aromatic carbonyl compounds (**1a–f**) by $Ru(bpy)_3^{2+}$ have been investigated. The reduction to the corresponding alcohols occurs with di-2-pyridyl ketone (**1a**) in a quantitative yield and with methyl benzoylformate (**1b**) in a 18% yield. Noteworthy is the efficient formation of 1:1 adducts **4b–f**, a new class of 4-alkyl-1,4-dihydronicotinamides, in 55–85% isolated yields; **4b** is a single isomer of a condensed bicyclic imide, whereas the other adducts are obtained as diastereomeric mixtures. In the case of trifluoroacetophenone (**1c**), the diastereomeric 6-alkylated 1,6-dihydronicotinamides (**4c'**) are formed as minor 1:1 adducts. The structure of each adduct has been determined by spectroscopic and X-ray crystallographic studies with one exception (**4d**). The mechanism of the photosensitized reactions is discussed in terms of sequential indirect electron–proton transfer from BNAH to **1a–f** followed by electron transfer or cross-coupling between radical intermediates. On the other hand thermal reactions of BNAH with **1a–e** in the dark give neither the adduct nor the half-oxidized dimers of BNAH but the alcohols. It is suggested that electron-transfer mechanisms are not responsible for the thermal reactions.

In previous papers,[1,2] we reported that electron-transfer-induced reactions of 1-benzyl-1,4-dihydronicotinamide (BNAH), a typical NADH model, with olefins are efficiently photosensitized by $Ru(bpy)_3^{2+}$ (bpy = 2,2'-bipyridine) to yield two-electron reduction products of the olefins and 1:1 adducts of the reactants as shown in Scheme I. The $Ru(bpy)_3^{2+}$-photosensitized reactions can therefore exemplify chemical behaviors of BNAH in electron-transfer processes, being thus diagnostic to test controversial mechanisms of electron transfer[3-6] or hydride transfer[7-10] in thermal reactions of NADH models in the dark. Furthermore, the adduct formation is of synthetic and pharmacological interest since preparation of 4-alkyl-1,4-dihydronicotinamide is relatively difficult and since the unique structure of the adducts is reminiscent of 4-arylated Hantzsch esters, which are known to be pharmacologically active.[11] However, isolated yields of the adducts are low or, at best, moderate because of difficulties of the isolation; we obtained only one isomer of the possible diastereoisomers in each case. On the other hand we have found that the $Ru(bpy)_3^{2+}$-photosensitized reactions with aromatic carbonyl compounds give 1:1 adducts in high yields,[12] a finding of synthetic and mechanistic interest. In the present paper we wish to report details of the photosensitized reactions of BNAH with several aromatic ketones and aldehydes.

Scheme I

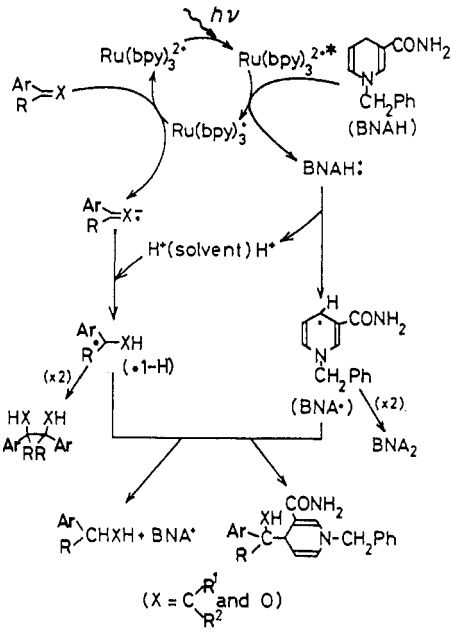

Table I. $Ru(bpy)_3^{2+}$-Photosensitized Reactions of 1 with BNAH[a]

	1		time,	conversn,	yield,[b] %		
	Ar	R	h	%	2	4[c]	5
a	2-pyridyl	2-pyridyl	2	79	95	0	10
b	C_6H_5	$COOCH_3$	7	100	18	60[d]	9
c	C_6H_5	CF_3	6	97	4[e]	86[f]	<1
d	2-pyridyl	H	2	99	12	55	4
e	p-C_6H_5CN	H	3	97	5	63	6
f	C_6H_5	H	15	85	0	85	<1

[a] For methanolic solutions containing of 1 (~50 mM), BNAH (~0.1 M), and $Ru(bpy)_3^{2+}$ (~0.27 mM) irradiated at >470 nm under cooling with water. [b] Isolated yields based on the 1 consumed unless otherwise noted. [c] Mixtures of two diastereoisomers. [d] A single isomer. [e] VP yield. [f] Total yield of **4c** and **4c'**.

Results

Photosensitized Reactions. Methanolic solutions of $Ru(bpy)_3^{2+}$ (~0.27 mM), BNAH (~0.1 M), and **1a–f** (~50

(1) Part 12: Ishitani, O.; Ihama, M.; Miyauchi, Y.; Pac, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1525.
(2) Pac, C.; Miyauci, Y.; Ishitani, O.; Ihama, M.; Yasuda, M.; Sakurai, H. *J. Org. Chem.* **1984**, *49*, 26. Pac, C.; Ihama, M.; Yasuda, M.; Miyauchi, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1981**, *103*, 6495.
(3) Steffens, J. J.; Chipman, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 6694.
(4) Ohnishi, Y.; Ohno, A. *Chem. Lett.* **1976**, 697.
(5) Ohno, A.; Shio, T.; Yamamoto, H.; Oka, S. *J. Am. Chem. Soc.* **1981**, *103*, 2045.
(6) Fukuzumi, S.; Kondo, Y.; Tanaka, T. *Chem. Lett.* **1983**, 751.
(7) Abels, R. H.; Hutton, R. F.; Westhimer, F. H. *J. Am. Chem. Soc.* **1957**, *79*, 712.
(8) Powell, M. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 1014.
(9) Carlson, B. W.; Miller, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 479.
(10) Maltens, F. M.; Verhoeven, J. W.; Gase, R. A.; Pandit, U. K.; Boer, T. J. D. *Tetrahedron* **1978**, *34*, 443.
(11) (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (b) Meyer, H.; Kazda, S.; Belleman, P. *Annual Report of Medicinal Chemistry*; Academic: New York, 1983; Vol. 18.
(12) Ishitani, O.; Pac, C.; Sakurai, H. *J. Org. Chem.* **1983**, *48*, 2941.

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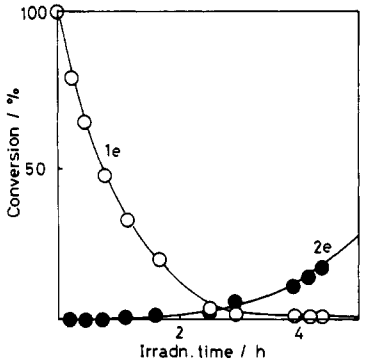
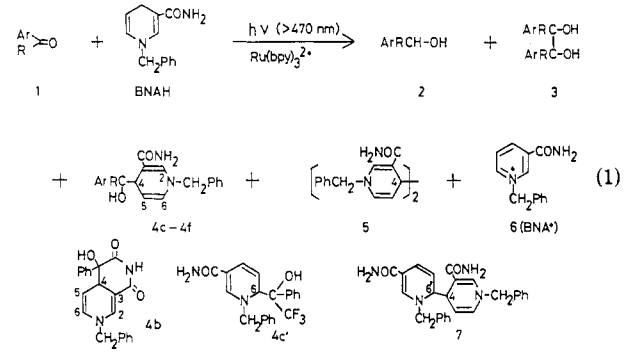


Figure 1. Time-conversion plots for the disappearance of **1e** (–○–) and for the formation of **2e** (–●–) by irradiation of a methanolic solution of **1e** (50 mM), BNAH (0.1 M), and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1 mM) at >470 nm.

mM) were irradiated at >470 nm. Equation 1 shows the products formed, yields of which are summarized in Table I. In the case of di-2-pyridyl ketone (**1a**), the reduction



(1)

to the corresponding alcohol **2a** quantitatively occurred with no formation of any adduct. The photosensitized reaction of methyl benzoylformate (**1b**) mainly gave an adduct as a single isomer of a condensed cyclic imide (**4b**) along with a smaller amount of **2b**. In the other cases 1:1 diastereomeric mixtures of 4-(hydroxyalkyl)-1,4-dihydronicotinamides **4c–f** were mainly formed, which were separated into each isomer by column chromatography on basic alumina. In the case of **1c**, the diastereomeric 6-(hydroxyalkyl)-1,6-dihydronicotinamides **4c'** were isolated in very small amounts of HPLC, while no indication was obtained for the formation of the positional isomers of **4d–f**. Although a half-oxidized dimer of BNAH (**5**) was isolated in a 10% yield in the case of **1a**, control runs showed that **5** and an isomer of **5** (**7**) were not detected at an early stage of the photoreaction but only after substantial consumption of **1a**. In the cases of **1b–f**, on the other hand, HPLC demonstrated that **5** and **7** are primary products.

In either case of 2-pyridinecarboxyaldehyde (**1d**) or *p*-cyanobenzaldehyde (**1e**), the corresponding alcohol **2d** or **2e** was formed in a significant amount at the completion of the photoreaction. However, the alcohol formation can be attributed to the consequences of secondary reactions since an induction period was observed as shown in Figure 1. It was indeed found that irradiation of a methanolic solution of **4d** or **4e** (25 mM) in the presence of BNAH (25 mM) and $Ru(bpy)_3^{2+}$ (1 mM) gave **2d** or **2e** each in 40–50% yield.[13] On the other hand, either **2a** or **2b** was confirmed to be a primary photoproduct. In the case of trifluoroacetophenone (**1c**), the yield of **2c** in the photosensitized reaction was lower than that in a thermal reaction at room temperature, suggesting that the alcohol formation mostly occurs by a thermal reaction.

Table II. Thermal Reactions of BNAH with 1 in the Dark[a]

	1		time,	conversn,	yields of
	Ar	R	h	%	2,[b] %
a	2-pyridyl	2-pyridyl	22	15	70
b	C_6H_5	$COOCH_3$	20	39	53
c	C_6H_5	CF_3	10	33	67
d	2-pyridyl	H	8	40	5
e	*p*-C_6H_4CN	H	22	35	9
f	C_6H_5	H	20	0	0

[a] Methanolic solutions were heated at 60 °C in the dark. [b] Based on the 1 consumed.

It was confirmed by VPC that 1,2-diphenyl-1,2-ethanediol (**3f**) was formed in 13% yield in the photosensitized reaction of **1f**. In the other cases, unfortunately, the corresponding diols **3b–e** which had been prepared by the $TiCl_4$–Zn reduction[14] of **1b–e** revealed no peak in VPC, probably due to decompositions. Furthermore, HPLC analyses of **3b–e** again encountered severe difficulties since the diol peaks were hidden by the huge peak of BNAH or the adduct.

Thermal Reactions. Heating of methanolic solutions of **1a–f** and BNAH at 60 ± 0.5 °C in the dark resulted in the reduction to **2a–e**, while **1f** was not reduced to **2f** at all. It was found that the presence of $Ru(bpy)_3^{2+}$ exerts no effect on the thermal reactions at all. In any case, neither the 1:1 adducts nor the half-oxidized dimers of BNAH could be detected at all. Table II summarizes the results.

Discussion

Isolation and Identification of the Adducts 4b–f and 4c'. Column chromatography on basic alumina was found to be convenient for the isolation of relatively pure, diastereomeric 1:1 mixtures of **4c–f** in good yields as well as for separation of the diastereoisomers in amounts enough for various spectroscopic measurements. Analytically pure samples were thus obtained for the both diastereoisomers of **4c** and for the *RR* + *SS* isomers of **4e** and **4f** whereas the *RS* + *SR* isomers of the latter could not be made free from the contamination of very small amounts of the other isomers. In the case of **4d**, both isomers could not be purified enough for elemental analysis because of decompositions occurring during isolation–purification procedures. However, all the compounds isolated were found to be sufficiently pure for spectroscopic purposes. In the case of **4b**, partial evaporation of an irradiated solution resulted in efficient precipitation of solids, which were then recrystallized to give an analytically pure sample. Either the precipitate or the purified sample of **4b** revealed only a single HPLC peak unlike diastereomeric mixtures of **4c–f**, even though methanol–water mixtures in different ratios were used as the moving phase. Moreover the ^1H NMR spectra show homogeneous resonances independently of solvents. These observations demonstrate that **4b** is homogeneous in the diastereochemistry.

All the isolated adducts commonly reveal similar spectroscopic features characteristic of the 4-substituted 1,4-dihydronicotinamide structure. However, the UV absorption maximum of **4b** (377 nm) is significantly longer than those of the other adducts (335–343 nm), thus reflecting the more conjugated, bicyclic imide structure. Moreover **4b** shows no ^1H NMR signal assignable to the

(13) Ishitani, O.; Yanagida, S.; Takamuku, S.; Pac, C. *Bull. Chem. Soc. Jpn.*, in press.

(14) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

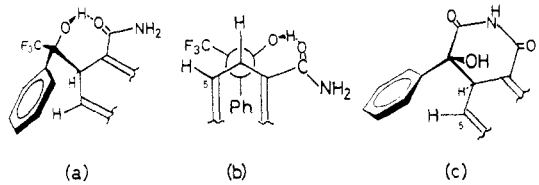


Figure 2. (a) Perspective illustration of (*RS*)- + (*SR*)-**4c** in the most stable conformation; H-5 is located just over the shielding region of the phenyl ring. (b) Newman projection formulas of the *RR* + *SS* configuration of **4c**; the phenyl ring cannot take any conformation for shielding of H-5. (c) Perspective illustration of (*RS*)- + (*SR*)-**4b**.

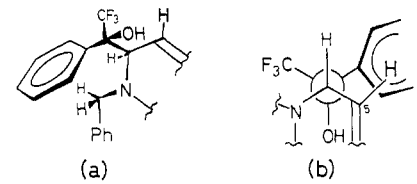


Figure 3. (a) Perspective illustration of (*RR*)- + (*SS*)-**4c**′ in the most stable conformation; the benzylic protons are strongly shielded. (b) Newman projection formulas of (*RS*)- + (*SR*)-**4c**′ which shows the shielding of H-5 by the phenyl ring in the most stable conformation.

CH_3O protons but a broad singlet of imide NH at δ 10.4. The absolute structures of (*RR*)- + (*SS*)-**4e** and (*RR*)- +(*SS*)-**4f** were unambiguously determined by X-ray crystallographic studies (see supplementary material). A preliminary X-ray crystallographic analysis of an isomer of **4c** (**4c**-A) gave a strong support to the assignment of the *RS* + *SR* configuration, which was also made on the basis of ^1H NMR analysis (vide infra). Further refinement of data is now in progress. In cases of the other adducts, however, all attempts failed to obtain crystals suitable for crystallographic measurements.

A notable observation for the structure assignment of **4c** is that H-5 of an isomer (**4c**-A) shows the ^1H NMR resonance at δ 3.88, a chemical shift much higher in field than that of the other isomer (**4c**-B) (δ 4.9). Molecular models of **4c** show that conformations at the two chiral centers are almost frozen because of the remarkable steric bulkiness of the $PhC(OH)CF_3$ group independently of the configurations. With regard to the conformational freezing, it should be noted that the OH proton of the both isomers shows the ^1H NMR signals at very low fields in either $CDCl_3$ or CD_3SOCD_3 (δ 8–9) compared with those of the other adducts (δ 5.6–6.5), an observation demonstrating the formation of relatively strong hydrogen bonding between OH and $CONH_2$ associated with conformational rigidity. With the *RS* + *SR* configuration, therefore, H-5 should be strongly shielded by the phenyl ring at the quaternary chiral center, while such a shielding effect on H-5 can not be expected with the *RR* + *SS* configuration, as shown in Figure 2. On the basis of these arguments, we assign the *RS* + *SR* configuration to **4c**-A and the *RR* + *SS* one to **4c**-B.

With regard to the configuration of **4b**, it should be noted that the chemical shift of H-5 (δ 3.92) is very similar to that of (*RS*)- + (*SR*)-**4c** but much higher in field than that of the (*RR*)- + (*SS*)-**4c**. According to molecular models, **4b** is again conformationally frozen so that H-5 is shielded by the phenyl ring at the quarternary chiral center with the *RS* + *SR* configuration but not at all with the *RR* + *SS* one, as shown in Figure 2. Therefore the *RS* + *SR* configuration is attributable to **4b**. On the other hand the diastereomeric configurations of **4d** are left unidentified since the diastereoisomers reveal very similar spectroscopic properties, perhaps due to free rotation of the ArCH(OH) group.

The other minor isomers of **4c** (**4c**′-A and **4c**′-B) show IR and mass spectra very similar to each other as well as to those of **4c**. In ^1H NMR the benzylic methylene protons of either **4c**′-A or **4c**′-B show an AB quartet which should be the consequence of diastereotopic splitting, thus demonstrating that the minor adducts are the diasteromeric 6-substituted 1,6-dihydronicotinamides. Similar diastereotopic splitting occurs for the benzylic protons of the 4,6′-bonded half-oxidized dimers of BNAH (**7**).[15] Significantly **4c**′-A reveals the ^1H NMR resonance of the benzylic methylene protons at a much higher field (δ 3.33) than either **4c**′-B (δ 4.63) or the diastereomers of **7** (δ 4.38 and 4.42).[15] On the contrary H-5 of **4c**′-B shows the signal at δ 5.98, a higher field compared with the H-5 resonance of **4c**′-A, which is overlapped with the aromatic resonances at δ 6.5–7.8. Molecular models reveal that conformations of these adducts are again freezed to allow specific shielding effects of the phenyl ring on the benzylic methylene protons with the *RR* + *SS* configurations or on H-5 with the *RS* + *SR* configuration as shown in Figure 3. These arguments enable us to assign the *RR* + *SS* configuration to **4c**′-A and the *RS* + *SR* configuration to **4c**′-B.

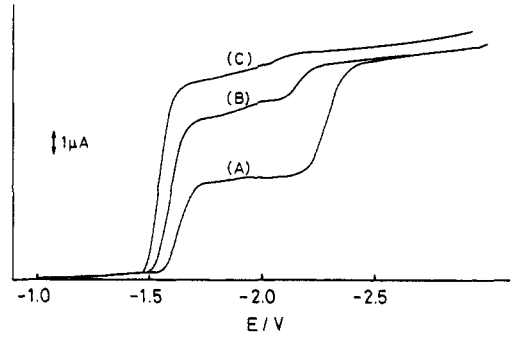


Figure 4. Polarograms of deaerated acetonitrile solutions of **1b** (1.15 mM) (A) in the absence of methanol and in the presence of (B) 1.0 vol % methanol and (C) 3.0 vol % methanol vs. an $Ag/AgNO_3$ reference electrode; $[Et_4NClO_4]$ = 0.1 M; scan rate, 10 mV s^{-1}.

Mechanism. We previously demonstrated that the photosensitized reactions of olefins with BNAH by $Ru(bpy)_3^{2+}$ proceed via indirect electron–proton transfer from BNAH to olefins of $E_{1/2}^{red} > -2.2$ V vs. Ag/Ag^+,[1,2] a unique mechanistic sequence arising from the facile generation of the azacyclohexadienyl radical, BNA$^\bullet$, by the proton loss from very acidic $BNAH^{\bullet+}$ ($pK_a < 1$)[16] following photochemical electron transfer. This radical may undergo electron transfer or radical coupling with the half-reduced olefin radicals depending on the substituents of olefins as shown in Scheme I. This mechanism can reasonably describe the present photosensitised reactions. It was confirmed that the luminescence of $Ru(bpy)_3^{2+}$ is not quenched by **1a–f** at all while the luminescence quenching by BNAH efficiently occurs.[2] Moreover, no photosensitized reaction occurred with acetophenone and benzophenone that has $E_{1/2}^{red} < -2.2$ V, probably the limit for the occurrence of electron transfer from $Ru(bpy)_3^+$ to carbonyl compounds as well as to olefins.

According to this mechanism, reduction potentials of the half-reduced species **1**$^\bullet$-H should be primarily essential in determining the choice of the electron transfer or the radical-coupling reaction with BNA$^\bullet$. Figure 4 shows the

(15) Ohnishi, Y.; Kitami, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2674.

(16) Maltens, F. M.; Verhoeven, J. W. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 228.

Table III. Polarographic Data of 1a–f and Quantum Yields for the Disappearance of 1 (Φ_{-1}) and the Formation of 2 (Φ_2)

	1		$-E_{1/2}^{red}$, V[a] (I_d, μA mM^{-1} mg$^{2/3}$ s$^{-1/2}$)[b]			
	Ar	R	methanol[d]	acetonitrile[e]	Φ_{-1}[c]	Φ_2[c]
a	2-pyridyl	2-pyridyl	1.46 (4.4)	~1.8 (3.9), ~1.9 (2.9)	0.20	0.20
b	C_6H_5	$COOCH_3$	~1.5 (3.8), ~1.6 (2.4)	1.64 (3.6), 2.41 (3.6)	0.49	0.14
c	C_6H_5	CF_3	1.83 (0.5)	1.71 (4.5), 2.38 (3.5)	0.14	0
d	2-pyridyl	H	1.71 (5.4)	1.91 (2.4), 2.48 (0.7)	0.44	0
e	*p*-C_6H_4CN	H	1.52 (3.3), 1.94 (3.0)	1.70 (2.9), 2.28 (0.7)	0.49	0
f	C_6H_5	H	1.86 (3.2), ~2.1 (1.7)	2.17 (3.8)	0.05	0

[a] Polarographic half-wave potentials in volts vs. $Ag/AgNO_3$ using a dropping mercury electrode and $NaClO_4$ (0.1 M) in methanol or Et_4NClO_4 (0.1 M) in acetonitrile as the supporting electrolyte. [b] Diffusion current constant, $I_d = i_d/cm^{2/3}t^{1/6}$. [c] At 520 nm for deaerated methanolic solutions containing a carbonyl compound (50 mM), BNAH (0.1 M), and $Ru(bpy)_3^{2+}$ (2.7 mM). [d] Capillary with $m^{2/3}t^{1/6}$ of 1.13 mg$^{2/3}$ s$^{-1/2}$ and a drop time of 0.5 s (pulse interval) at a 67 cm of pressure. [e] Capillary with $m^{2/3}t^{1/6}$ of 1.15 mg$^{2/3}$ s$^{-1/2}$ and a drop time of 0.5 s (pulse interval) at a 67 cm of pressure.

polarographic behaviors of **1b** in which the first reduction wave grows at the expense of the second one, being accompanied by positive shifts upon addition of methanol to an acetonitrile solution of **1b**. The two reduction waves in acetonitrile have similar diffusion-current constants (I_d), probably corresponding to the reversible, sequential two-electron-transfer processes (eq 2 and 3).[17] The effect of

$$1 + e^- \rightleftarrows 1^{\bullet-} \quad (2)$$

$$1^{\bullet-} + e^- \rightleftarrows 1^{2-} \quad (3)$$

(in acetonitrile)

methanol on the polarographic behaviors can be reasonably interpreted in terms of the ECE processes (eq 4 and 5) occurring in the first reduction wave as discussed for the electrochemical reduction of benzophenone in the presence of a proton donor.[18,19] In other words, the potential of this

$$1 + e^- \rightleftarrows 1^{\bullet-} \overset{H^+}{\rightleftarrows} 1^{\bullet}\text{-H} \quad (4)$$

$$1^{\bullet}\text{-H} + e^- \rightleftarrows \text{1-H}^- \overset{H^+}{\rightleftarrows} \underset{(2)}{\text{H-1-H}} \quad (5)$$

(in methanol)

reduction wave in the presence of methanol is certainly diagnostic for qualitative estimation of the reduction potential of **1b**$^{\bullet}$-H. Table III lists the polarographic reduction potentials of **1a–f** in either methanol or acetonitrile together with quantum yields for the disappearance of **1a–f** and for the formation of **2a,b**. The single waves of **1a** and **1d** in methanol should be due to the ECE processes whereas the second waves of **1e** and **1f**, which correspond to eq 5,[20,21] might provide a probe for the reduction potentials of **1e**$^{\bullet}$-H and **1f**$^{\bullet}$-H.[22]

The reduction wave of BNA^+ in methanol appears at −1.445 V vs. Ag/Ag^+, certainly due to the one-electron reduction process. Although this potential does not necessarily equal the oxidation potential of BNA$^{\bullet}$, it is significant to note that this value is not far from the estimated oxidation potentials of BNA$^{\bullet}$ and related species in acetonitrile (ca. −1.0 to −1.4 V vs. Ag/Ag^+)[23] as well as from the redox potential of the $NAD^+/NAD^{\bullet}$ couple in a buffer solution at pH 9.1 (−1.155 V vs. SCE).[24] The observed reduction potential of BNA^+ is very similar to that of the reduction wave of **1a** in methanol and only slightly positive than that of **1b**, while the reduction potentials of **1d–f** corresponding to eq 5 are much more negative. Namely, BNA$^{\bullet}$ can undergo electron transfer to **1a**$^{\bullet}$-H in a high efficiency and also to **1b**$^{\bullet}$-H (eq 6) competitively with the radical coupling (eq 7), while the latter reaction predominantly occurs with the other half-reduced radicals. The

$$\text{BNA}^{\bullet} + {}^{\bullet}\text{1-H} \begin{cases} \xrightarrow{E > -1.6\ \text{V}} \text{2a,b} + \text{BNA}^+ & (6) \\ \xrightarrow{E < -1.6\ \text{V}} \text{4b-f} & (7) \end{cases}$$

steric bulkiness of **1a**$^{\bullet}$-H perhaps contributes, at least in part, to the exclusive reduction of **1a**$^{\bullet}$-H because of inhibition of eq 7. The essential role of BNA$^{\bullet}$ in the two-electron reduction is demonstrated by the complete lack of the reduction of **1a** to **2a** in the $Ru(bpy)_3^{2+}$-photosensitized reaction of **1a** using a potential one-electron donor, *N*,*N*-dimethyl-*p*-toluidine, in place of BNAH.

Interestingly the cross coupling between BNA$^{\bullet}$ and 1$^{\bullet}$-H (eq 7) is highly regioselective in a sharp contrast to the nonselective dimerization of BNA$^{\bullet}$.[25] This can be explained by assuming important roles of hydrogen bonding between the hydroxyl group of 1$^{\bullet}$-H and carbamoyl carbonyl of BNA$^{\bullet}$ to bring the radicals favorably for the predominant coupling at C4 of BNA$^{\bullet}$. In the case of **1c**$^{\bullet}$-H, however, steric bulkiness of this radical would weaken the hydrogen bonding to allow the competitive coupling at C6 even to a minor extent. According to this interpretation, the low-yield formation of the C4-bonded 1:1 adducts in the photosensitized reactions of olefins with $BNAH^2$ would be, at least in part, due to the consequences of nonselective radical-coupling reactions arising from the lack of such specific hydrogen bonding as well as from steric repulsions in the relevant pathway. By the same reason, such hydrogen bonding might be also kinetically effective to facilitate either electron transfer or the cross-coupling be-

(17) Evans, D. H. *Encyclopedia of Electrochemistry of the Elements*; Bard, A. J., Lund, H., Eds.; Marcel Dekker: New York, 1978; Vol. XII, pp 1–259.
(18) Given, P. H.; Peover, M. E. *J. Chem. Soc.* **1960**, 385.
(19) Michielli, R. F.; Elving, P. J. *J. Am. Chem. Soc.* **1968**, *90*, 1989.
(20) Nadjo, L.; Saveant, J. M. *J. Electroanal. Chem.* **1971**, *33*, 419.
(21) Laviron, E.; Lucy, J. C. *Bull. Soc. Chim. Fr.* **1966**, 2202.
(22) Unfortunately, the polarography of **1c** in methanol showed only a weak, ambiguous wave at ca. −1.8 V which is of little electrochemical significance. A major origin of the polarographic behavior can be attributed to the hemiacetal formation, since the IR band of carbonyl stretching vibrations at 1720 cm^{-1} disappeared upon addition of methanol to an acetonitrile solution of **1e** and since ^1H NMR signals of the ortho aromatic protons in CD_3CN at lower fields (δ 7.90–8.30) moved to higher field upon addition of CD_3OD, finally almost overlapping with those of the other protons at δ 7.26–7.87 in CD_3OD.
(23) Blaedel, W. J.; Haas, R. G. *Anal. Chem.* **1970**, *42*, 918.
(24) Jensen, M. A.; Elving, P. J. *Biochem. Biophys. Acta* **1984**, *764*, 310.
(25) (a) The one-electron reduction of BNA^+ with Zn gives the diastereomers of **5** and **7** in a comparable ratio.[15] We have also found that a diastereoisomer of **5** and the both isomers of **7** are quantitatively formed in a 2:2:1 ratio by the *fac*-$Re(bpy)(CO)_3Br$-photosensitized reduction of BNA^+ by triethylamine which proceeds via photomediated one-electron transfer from the amine to BNA^+.[25b] (b) Pac, C.; Ishitani, O. *Abstracts of Papers, Beijing International* Conference on Photochemistry, Beijing, China; 1985; pp 315–317.

tween BNA• and 1•-H predominating over the homocoupling reaction of each radical.[26] Concerning the formation of **4b**, on the other hand, no significant data are available for a reasonable interpretation of mechanistic details, though interactions of the methoxycarbonyl group of **1b**•-H and the carbamoyl substituent of BNA• are presumed to play important roles in the stereoselective cross coupling of the radicals.

Comparisons between Thermal and Photosensitized Reactions. The thermal reactions of **1a–f** with BNAH in methanol did not give at all the 1:1 adducts **4b–f** nor the half-oxidized dimers of BNAH **5** and **7**, thus revealing quite different behaviors from the $Ru(bpy)_3^{2+}$-photosensitized reactions. It is therefore implied that the photosensitized reactions provide a useful synthetic tool for the preparation of **4b–f**. Moreover, there is little parallelism in the "two-electron" reduction of the carbonyl compounds between the two types of reactions. In particular the efficient reduction of **1c** to **2c** in the dark shows a sharp contrast to the lack of the reduction in the redox-photosensitized reactions.

A mechanistic implication of the entire different behaviors of the thermal reactions is that a simple ECE mechanism involving discrete radical intermediates is probably inadequate to describe the hydride-equivalent transfer from BNAH to **1a–e** in the dark, since the redox-photosensitized reactions indeed involve indirect electron–proton transfer as has been discussed in the previous section. Moreover, the ECE mechanism again disagrees with specific transfer of the C4 deuterium label of NADH models to carbonyl carbon of carbonyl compounds in the dark,[27] unless specific interactions between ion–radical pairs in a solvent cage would operate to allow unique reactions entirely different from those of free ion radicals in which protonation does occur at carbonyl oxygen of **1a–f**. Alternatively sequential transfer of an electron and a hydrogen atom would be another possible candidate for the mechanism of the thermal reduction of **1a–e**. If this were the case, the hydrogen atom transfer following the initial electron transfer from BNAH to **1a–e** should be much faster than the proton transfer from very acidic $BNAH^{\bullet+}$[16] to the very basic anion radical of **1a–e**. Therefore a mechanism involving hydride transfer may be the best choice.

Conclusions

The $Ru(bpy)_3^{2+}$-photosensitized reactions of BNAH with **1b–f** provide a useful synthetic method for the preparation of the 4-hydroxyalkylated 1,4-dihydronicotinamides, **4b–f**, a new class of compounds which cannot be obtained by direct thermal reactions in the dark. The two-electron reduction of carbonyl compounds is predicted to occur upon redox photosensitization by $Ru(bpy)_3^{2+}$ in cases where polarographic reduction waves in methanol appear at more positive potentials than −1.6 V vs. Ag/Ag^+, a formal limit for electron transfer from BNA• to 1•-H to occur. On the other hand, electron-transfer mechanisms involving discrete radical intermediates cannot reasonably interpret chemical behaviors of thermal reactions of BNAH with **1a–e**.

Experimental Section

Melting points were taken on a hot plate and are uncorrected. Vapor-phase chromatography (VPC) was performed on a Shimadzu GC-7A dual column instrument using a 0.5 m × 3.2 mm glass column packed with 5% UCON LB550X on Shimalite W, a 1 m × 3.2 mm column packed with 5% PEG 20M on Shimalite W, a 2 m × 3.2 mm column packed with 3% OV-17 on Chromosorb W, and a 1 m × 3.2 mm column packed with 5% OV-1 on Celite 545. HPLC was carried out on a Toyosoda CCPD dual pump and a Yanaco M-315 spectromonitor using a 25 cm × 4.6 mm column packed with Chemicosorb 7-ODS-H; the mobile phase was 40% methanol in $NaOH–KH_2PO_4$ buffer solution (pH 7) at a flow rate of 0.8 mL/min, and the wavelength of the spectromonitor was set at 355 nm. ^1H NMR spectra were recorded on a JEOL JNM-PMX-100 spectrometer, ^{13}C NMR spectra on a JEOL FX-100 spectrometer, IR spectra on a Hitachi 220-10 spectrometer, UV and visible absorption spectra on a Hitachi 220-A spectrometer, and mass spectra on a Hitachi RMU-6E spectrometer. Luminescence spectra were recorded on a Hitachi 850 spectrofluorometer for deaerated solutions of $Ru(bpy)_3^{2+}$ (0.25 mM) after correction of instrument responses.

All data sets ($I > 30(I)$) in X-ray crystallographic analysis were measured by the ω-2θ method on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71069 Å). The structure was solved by the direct method (MULTAN) and the refinement was made with anisotropic temperature factors for all the non-hydrogen atoms and with isotropic thermal parameters for the hydrogens. For details of the data see supplementary material.

The preparation and purification of BNAH[28] and $Ru(bpy)_3Cl_2·6H_2O$[29] were carried out according to the literature methods. The carbonyl compounds **1a–f** were obtained from Nakarai Chemicals and purified by recrystallization or distillation. Methanol was distilled from magnesium methoxide.

Polarographic measurements were performed for air-free dry solutions containing **1a–f** or BNA^+ (~1 mM) and a supporting electrolyte (0.1 M), sodium perchlorate in methanol or tetraethylammonium perchlorate in acetonitrile, at 20 ± 0.1 °C by using a Yanagimoto P-1100 potentiostat. The reference electrode was an $Ag/AgNO_3$ (0.1 M) in methanol or acetonitrile, and the working electrode was a dropping Hg electrode at a 67 cm of pressure operated at a pulse-regulated dropping time of 0.5 s. The $m^{2/3}t^{1/6}$ values were 1.15 $mg^{2/3}\ s^{1/6}$ in acetonitrile and 1.13 $mg^{2/3}\ s^{1/6}$ in methanol.

Determination of Quantum Yields. Quantum yields were determined for 4-mL Ar-purged solutions containing **1a–f** (50 mM), BNAH (0.1 M), and $Ru(bpy)_3Cl_2·6H_2O$ (3 mM) in quartz cuvettes by using a Reinecke's salt actinometer.[30] The incident light at 520 nm was isolated from an Ushio xenon lamp (300 W) by using a Hitachi high-intensity monochromometer, and the intensity was determined to be 2.57×10^{17} photons/min. All the procedures were performed in a dark room with a safety lamp. Both the disappearance of **1a–f** and the formation of **2a,b** were analyzed by VPC and plotted against time. Quantum yields were calculated from the slopes of initial linear portion of the plots.

Photosensitized Reaction of 1a. A 100-mL methanolic solution of **1a** (0.96 g, 5.1 mmol), BNAH (2.14 g, 10 mmol), and $Ru(bpy)_3Cl_2·6H_2O$ (20 mg, 0.027 mmol) was irradiated at >470 nm for 2 h under cooling with water. Details of the irradiation apparatus and the filter solution were described previously.[2] The irradiated solution was evaporated to 10 mL to give a precipitate, which was filtered and washed with cold methanol (3 mL) to give **5** (0.21 g, 10%) as yellow solids. The filtrate was distilled in vacuo to give **2a** (0.89 g, 97%); bp 105–110 °C (1.1 mmHg). To the residue were added dichloromethane (100 mL) and then cold 0.1 M hydrochloric acid (300 mL). After vigorous shaking, the hy-

(26) (a) The reported rate constants for the homocoupling of ArC(OH)R are (6×10^6)–(7×10^8) $M^{-1}\ s^{-1}$ in 2-propanol[27b] whereas that of NAD• is 3×10^7 $M^{-1}\ s^{-1}$ in water at pH 9.1.[24] These rate data indicate that the rate constants of eq 7 should be $>10^9$ $M^{-1}\ s^{-1}$, very large for sterically bulky radicals unless there are operated specific interactions between 1•-H and BNA•, e.g., hydrogen bonding presumed in text. (b) Ingold, K. U. *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, pp 40–56.

(27) Vennesland, B.; Westheimer, F. H. *The Mechanism of Enzyme Action*; McElroy, W. D., Glass, B., Eds.; Johns Hopkins: Baltimore, 1954.

(28) Mauzarall, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1955**, *77*, 2261.

(29) Broomhead, J. A.; Yaung, C. G. *Inorg. Synth.* **1983**, *22*, 127.

(30) Wagner, E. E.; Adamson, A. W. *J. Am. Chem. Soc.* **1966**, *88*, 394.

drochloric acid layer separated was washed with dichloromethane (100 mL) and then neutralized with cold 0.5 M NaOH to pH 7 under ice cooling. After vacuum evaporation to dryness, the residue was extracted with 300-mL boiling ethanol and then filtered. The filtrate was evaporated to give 1-benzylnicotinamide chloride (**6**) (0.58 g, 23%). A similar treatment of BNAH did not give **6** at all.

Photosensitized Reaction of 1b. Similarly a 140-mL methanolic solution of **1b** (1.25 g, 8.2 mmol), BNAH (3.27 g, 15.3 mmol), and the sensitizer (30 mg, 0.04 mmol) was irradiated for 7 h. The irradiated solution was evaporated to 50 mL to give a precipitate, which was filtered and washed with cold methanol (3 mL) to give **4b** (1.19 g, 60%) as pale yellow solids: mp 223–224 °C dec (DMF–water); IR (KBr) ν_{max} 3445 (OH), 3100 (NH), 1685 (C=O and/or C=C), 1659 (C=O), 1570 cm^{-1} (C=C); UV (MeOH) λ_{max} 377 nm (ϵ 5960); ^1H NMR (CD_3SOCD_3) δ 3.92 (dd, 1 H, J = 1.6, 8.0 Hz, H-5), 4.06 (br s, 1 H, H-4), 4.46 (s, 2 H, CH_2Ph), 6.00 (br d, 1 H, J = 8 Hz, H-6), 6.52 (s, 1 H, exchanged with D_2O, OH), 7.12–7.50 (m, 11 H, H-2, 2 × Ph), 10.36 (s, 1 H, exchanged with D_2O, NH); ^{13}C NMR (CD_3SOCD_3) δ 41.0, 56.0, 76.4, 96.1, 101.0, 125.1, 126.8, 127.0, 127.4, 127.6, 128.2, 128.7, 131.4, 137.9, 140.2, 141.1, 166.5, 172.7; MS, m/e (relative intensity) 346 (13, M^+), 328 (32, M – H_2O), 312 (27, BNA^+), 255 (8, M – $PhCH_2$), 169 (65), 105 (27). 91 (100, $PhCH_2$). Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.56; H, 5.28; N, 8.17. After filtration of **4b**, the filtrate was further evaporated to 10 mL and then cooled to give a precipitate, filtration of which gave **5** (0.31 g, 9%). Vacuum distillation of the filtrate gave **2b** (0.24 g, 18%); bp 75–110 °C (0.3 mmHg).

Photosensitized Reaction of 1c. A 150-mL methanolic solution of **1c** (1.31 g, 7.5 mmol), BNAH (3.24 g, 15.1 mmol), and the sensitizer (30 mg, 0.04 mmol) was irradiated for 6 h. The photolysate was evaporated and then chromatographed on 100 g of basic alumina (70–230 mesh, Merck Art 1076). After elution of BNAH (0.2 g) with 2% methanol in diethyl ether (400 mL), further elution with 4–50% methanol in diethyl ether (7 × 200 mL) gave mixtures of the diastereomers of **4c** and **4c′** in different ratios. The combined yield was 2.52 g (86%). A small amount of **5** (20 mg) was finally eluted with methanol (200 mL).

The first fraction in which an isomer of **4c** had been enriched was subjected to repeated column chromatography to give the *RS* + *SR* isomer of **4c** as pale yellow solids: mp 152.5–154.0 °C dec (Et_2O–MeOH); IR (KBr) ν_{max} 3430 (OH), 3300, 3175 (NH_2), 1667 (C=C), 1640 (C=O), 1565 cm^{-1} (C=C); UV (MeOH) λ_{max} 335 nm (ϵ 4680); ^1H NMR (CD_3SOCD_3) δ 3.72 (br d, 1 H, J = 5.6 Hz, H-4), 3.88 (dd, 1 H, J = 5.6, 7.6 Hz, H-5), 4.45 (s, 2 H, CH_2Ph), 6.13 (d, 1 H, J = 7.6 Hz, H-6), 7.04–7.76 (m, 13 H, H-2, NH_2, 2 × Ph), 9.01 (s, 1 H, exchanged with D_2O, OH); ^{13}C NMR (CD_3SOCD_3) δ 43.4, 56.5, 79.7, 100.3, 101.5, 126.8, 127.5, 128.5, 130.2, 137.6, 140.0, 172.8; MS, m/e (relative intensity) 388 (0.2, M^+), 371 (0.2, M – OH), 213 (18, BNA^+), 174 (0.2, $PhCOCF_3$), 169 (2), 123 (5), 105 (7), 91 (100, $PhCH_2$). Anal. Calcd for $C_{21}H_{19}F_3N_2O_2$: C, 64.94; H, 4.93; N, 7.21. Found: C, 64.73; H, 4.82; N, 7.18.

Similarly, repeated column chromatography of another fraction eluted with 7% methanol in diethyl ether gave the *RR* + *SS* isomer of **4c** as pale yellow solids: mp 176.5–177.5 °C dec (Et_2O–MeOH); IR (KBr) ν_{max} 3475 (OH), 3320, 3180 (NH_2), 1675 (C=C), 1635 (C=O), 1565 cm^{-1} (C=C); UV (MeOH) λ_{max} 338 nm (ϵ 5370); ^1H NMR (CD_3SOCD_3) δ 4.08–4.28 (3 H, m overlaid with s at δ 4.16, H-4, CH_2Ph), 4.75–4.98 (m, 1 H, H-5), 6.16 (d, 1 H, J = 7.9 Hz, H-6), 6.86–7.63 (m, 13 H, H-2, NH_2, 2 × Ph), 8.53 (s, 1 H, exchanged with D_2O, OH); ^{13}C NMR (CD_3SOCD_3) δ 43.3, 56.5, 79.7, 100.1, 101.4, 126.8, 127.4, 127.8, 128.5, 130.2, 137.5, 140.0, 172.8; MS, m/e (relative intensity) 388 (0.6, M^+), 371 (1), 213 (56), 174 (0.5), 169 (11), 123 (32), 105 (7), 91 (100). Anal. Calcd for $C_{21}H_{19}F_3N_2O_2$: C, 64.94; H, 4.93; N, 7.21. Found: C, 65.12; H, 5.06; N, 7.26.

Fractions which had been eluted with 30–50% methanol in diethyl ether were subjected to preparative HPLC to give (*RS*)- + (*SR*)-**4c′** as a yellow oil and (*RR*)- + (*SS*)-**4c′** as pale yellow solids in small amounts. Further treatment for purification resulted in consumptions of the compounds.

(*RS*)- + (*SR*)-**4c′**: IR ($CHCl_3$ solution) ν_{max} 3480, 3350, 3200, 1645, 1590, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2–4.5 (m, 1 H, H-6), 4.6 (br s, 1 H, exchanged with D_2O, OH), 4.63 (AB q, J = 5 Hz, ν_{AB} = 14, CH_2Ph), 5.67 (br d, J = 9 Hz, H-5), 5.4–5.9 (br s, 2 H, exchanged with D_2O, NH_2), 5.98 (d, 1 H, J = 9 Hz, H-4), 7.0–7.7 (m, 11 H, H-2, 2 × Ph); MS, m/e (relative intensity) 388 (0.4, M^+), 371 (0.4), 213 (40), 174 (0.4), 169 (7), 123 (16), 105 (16), 91 (100).

(*RR*)- + (*SS*)-**4c′**: IR ($CHCl_3$ solution) ν_{max} 3560, 3400, 3100, 1642, 1589, 1548 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (AB q, 2 H, J = 16 Hz, ν_{AB} = 49, CH_2Ph), 4.33 (br, 1 H, exchanged with D_2O, OH), 4.63 (d, 1 H, J = 6.0 Hz, H-6), 4.7–5.2 (m, 1 H, H-5), 5.67 (br s, 2 H, exchanged with D_2O, NH_2), 6.5–7.8 (m, 12 H, H-2, H-4, 2 × Ph); MS, m/e (relative intensity) 388 (0.3, M^+), 371 (0.3), 213 (34), 174 (0.3), 169 (7), 123 (11), 105 (11), 91 (100).

Photosensitized Reaction of 1d. After irradiation of a 150-mL methanolic solution of **1d** (0.85 g, 7.9 mmol), BNAH (3.28 g, 15.3 mmol), and the sensitizer (30 mg, 0.04 mmol) for 2 h, the irradiated solution was evaporated and then distilled in vacuo to give **2d** (0.1 g, 12%); bp 50–70 °C (0.1 mmHg). The residue was subjected to column chromatography on basic alumina. Elution with 7% methanol in diethyl ether (400 mL) gave BNAH (0.81 g) and then diastereomeric mixtures of **4d** were eluted with 10% and 20% methanol in diethyl ether (200 mL each); the combined yield of **4d** was 0.82 g (55%). Further elution with 30% methanol in diethyl ether gave **5** (0.13 g, 4%). Repeated column chromatography of the first and second fractions of **4d** resulted in the separation of the diastereoisomers **4d**-A and **4d**-B as yellow solids. Further purification of these compounds could not be made since recrystallization resulted in the deposition of brownish tars.

4d-A: mp 89–92 °C dec (CH_2Cl_2); IR (KBr) ν_{max} 3650, 3330, 3000, 1685, 1648, 1600, 1575, 1440, 1405 cm^{-1}; ^1H NMR (CD_3SOCD_3) δ 3.86 (dd, 1 H, J = 2.4, 5.6 Hz, H-4), 4.22 (dd, 1 H, J = 5.6, 7.8 Hz, H-5), 4.34 (s, 2 H, CH_2Ph), 4.58 (dd, 1 H, J = 2.4, 5.6 Hz, ArC*H*(OH)), 5.67 (d, 1 H, J = 5.6 Hz, exchanged with D_2O, OH), 6.03 (d, 1 H, J = 8.0 Hz, H-6), 6.79 (br s, 2 H, exchanged with D_2O, NH_2), 7.04–8.60 (m, 10 H, H-2, Ph, C_5H_4N); ^{13}C NMR (CD_3SOCD_3) δ 38.1, 56.0, 76.5, 100.7, 101.6, 120.9, 121.4, 126.8, 128.3, 130.6, 135.5, 138.3, 138.9, 147.8, 162.2, 170.2; MS, m/e (relative intensity) 321 (0.5, M^+), 303 (2, M – H_2O), 213 (13, BNA^+), 107 (26, C_5H_4NCHO), 105 (21), 91 (100).

4d-B: mp 161–162 °C dec (CH_2Cl_2–MeCN); IR (KBr) ν_{max} 3680, 3330, 3000, 1680, 1665, 1602, 1598, 1574, 1435, 1405 cm^{-1}; UV (MeOH) λ_{max} 338 nm (ϵ 6599); ^1H NMR (CD_3SOCD_3) δ 3.74 (q, 1 H, J = 5.8 Hz, H-4), 4.24–4.40 (3 H, m overlaid with s at δ 4.28, H-5, CH_2Ph), 4.49 (dd, 1 H, J = 4.4, 5.8 Hz, ArC*H*(OH)), 5.74 (d, 1 H, J = 4.4 Hz, exchanged with D_2O, OH), 5.92 (d, 1 H, J = 7.6 Hz, H-6), 6.84 (br s, 2 H, exchanged with D_2O, NH_2), 6.96–8.54 (m, 10 H, H-2, Ph, C_5H_4N); ^{13}C NMR (CD_3SOCD_3) δ 38.1, 56.1, 78.1, 101.2, 102.4, 121.9, 122.1, 126.8, 127.2, 128.5, 129.9, 135.6, 138.3, 147.8, 162.0, 170.8; MS, m/e (relative invensity) 321 (0.5, M^+), 303 (2), 213 (11), 107 (22), 105 (23), 91 (100). Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 70.56; H, 5.88; N, 13.03.

Photosensitized Reaction of 1e. A 150-mL methanolic solution of **1e** (0.90 g, 6.8 mmol), BNAH (3.35 g, 15.6 mmol), and the sensitizer (30 mg, 0.04 mmol) was irradiated for 5 h, evaporated, and then distilled in vacuo to give **2e** (50 mg, 5%); bp 140–150 °C (10 mmHg). The residue was chromatographed on basic alumina as described above to give BNAH (0.82 g), diastereomeric mixtures of **4e** (1.35 g, 63%), and **5** (0.16 g, 6%). Repeated column chromatography of each fraction of **4e** gave a pure sample of the *RR* + *SS* isomer and a sample of the other isomer contaminated with small amounts of the former and another unknown component. The latter could not be made free from the contamination.

(*RR*) + (*SS*)-**4e**: mp 156.5–157.5 °C dec ($CHCl_3$–MeOH); IR (KBr) ν_{max} 3460, 3305, 3175, 2260 (C≡N), 1675, 1635, 1550 cm^{-1}; UV (MeOH) λ_{max} 343 nm (ϵ 7590); ^1H NMR (CD_3SOCD_3) δ 3.72 (dd, 1 H, J = 3.2, 5.0 Hz, H-4), 4.20 (s, 2 H, CH_2Ph), 4.47 (dd, 1 H, J = 3.2, 5.0 Hz, ArC*H*(OH)), 4.52 (dd, 1 H, J = 5.0, 9.0 Hz, H-5), 6.01 (br d, 1 H, J = 9 Hz, H-6), 6.38 (br d, 1 H, J = 5 Hz, exchanged with D_2O, OH), 6.67–7.80 (m, 12 H, H-2, NH_2, C_6H_4CN, Ph); ^{13}C NMR (CD_3SOCD_3) δ 40.9, 56.1, 76.8, 100.8, 101.5, 108.9, 119.3, 127.0, 127.2, 127.6, 128.3, 130.6, 131.0, 137.9, 139.3, 149.3, 171.0; MS, m/e (relative intensity) 345 (0.5, M^+), 327 (1), 213 (32), 131 (25, NCC_6H_4CHO), 130 (40, NCC_6H_4CO), 123 (11), 122 (16), 105 (14), 102 (16, NCC_6H_4), 91 (100). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.02; H, 5.55; N, 12.17. Found: C, 72.87, H, 5.34; N, 12.14.

(*RS*)- + (*SR*)-**4e**: mp 158–159 °C dec ($CHCl_3$–MeOH); IR (KBr) ν_{max} 3480, 3380, 3200, 2230, 1680, 1640, 1565 cm^{-1}; UV (MeOH)

λ_{max} 343 nm (ϵ 6250); ^{1}H NMR (CD_3SOCD_3) δ 3.82 (q, 1 H, J = 4.8 Hz, H-4), 4.15 (s, 2 H, CH_2Ph), 4.52 (dd, 1 H, J = 3.0, 4.8 Hz, ArC*H*(OH)), 4.65 (dd, 1 H, J = 4.8, 9.8 Hz, H-5), 5.60 (d, 1 H, J = 3.0 Hz, exchanged with D_2O, OH), 5.83 (br d, 1 H, J = 9.8 Hz, H-6), 6.57-7.80 (m, 12 H, H-2, NH_2, C_6H_4, Ph); ^{13}C NMR (CD_3SOCD_3) δ 40.7, 56.0, 75.1, 100.7, 101.8, 109.1, 119.2, 126.7, 127.1, 128.3, 130.1, 130.7, 138.0, 138.5, 149.0, 170.2; MS, *m/e* (relative intensity) 345 (1, M^+), 327 (1), 213 (33), 131 (26), 130 (40), 123 (11), 122 (16), 105 (14), 102 (16), 91 (100).

Photosensitized Reaction of 1f. A 150-mL methanolic solution of **1f** (0.72 g, 6.8 mmol), BNAH (3.31 g, 15.5 mmol), and the sensitizer (30 mg, 0.04 mmol) was irradiated for 15 h, evaporated, and then chromatographed on basic alumina as described above to give BNAH (0.5 g), diastereomeric mixtures of **4f** (2.0 g, 85%), and **5** (< 20 mg). The diastereoisomers of **4f** were separated by repeated column chromatography. A pure sample of the *RR* + *SS* isomer was thus obtained whereas the *RS* + *SR* isomer could not be made free from contamination of small amounts of others.

(*RR*)- + (*SS*)-**4f**: mp 171.5-172.5 °C dec ($CHCl_3$-MeOH); IR (KBr) ν_{max} 3270, 3115, 1669, 1640, 1554 cm^{-1}; UV (MeOH) λ_{max} 342 nm (ϵ 4750); ^{1}H NMR (CD_3SOCD_3) δ 3.70 (dd, 1 H, J = 3.2, 5.8 Hz, H-4), 4.23 (s, 2 H, CH_2Ph), 4.43 (dd, 1 H, J = 2.2, 5.8 Hz, ArC*H*(OH)), 4.47 (dd, 1 H, J = 3.2, 6.0 Hz, H-5), 6.01 (dd, 1 H, J = 2.2, 6.0 Hz, H-6), 6.06 (br s, exchanged with D_2O, OH), 6.78-7.50 (m, 13 H, H-6, NH_2, 2 × Ph); ^{13}C NMR (CD_3SOCD_3) δ 40.9, 56.0, 76.9, 101.6, 126.2, 126.8, 127.1, 128.4, 130.5, 138.1, 139.2, 143.3, 170.9; MS, *m/e* (relative intensity) 320 (0.5, M^+), 302 (2, M - H_2O), 213 (57), 123 (5), 106 (5, PhCHO), 105 (4), 91 (100). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.97; H, 6.29; N, 8.74. Found: C, 74.70; H, 6.21; N, 8.77.

(*RS*)- + (*SR*)-**4f**: mp 162-163 °C dec ($CHCl_3$-MeOH); IR (KBr) ν_{max} 3460, 3340, 3170, 1665, 1635, 1560 cm^{-1}; UV (MeOH) λ_{max} 342 nm (ϵ 6170); ^{1}H NMR (CD_3SOCD_3) δ 3.62 (q, 1 H, J = 5.6 Hz, H-4), 4.23 (s, 2 H, CH_2Ph), 4.38 (dd, 1 H, J = 5.6, 7.8 Hz, H-5), 4.45 (dd, 1 H, J = 3.8, 5.6 Hz, ArC*H*(OH)), 5.64 (d, 1 H, J = 3.8 Hz, exchanged with D_2O, OH), 5.99 (br d, 1 H, J = 7.8 Hz, H-6), 6.74-7.60 (m, 13 H, H-2, NH_2, 2 × Ph); ^{13}C NMR (CD_3SOCD_3) δ 40.4, 56.0, 77.1, 101.6, 102.7, 126.7, 127.1, 127.5, 128.5, 129.7, 138.3, 143.1, 170.7; MS, *m/e* (relative intensity) 320 (0.5, M^+), 302 (1), 213 (33), 123 (6), 106 (5), 105 (7), 91 (100).

Thermal Reactions. Each 3-mL methanolic solution containing **1a-f** (50 mM) and BNAH (0.2 M) in a Pyrex tube was bubbled with a gentle stream of Ar for 15 min and then heated at 60 ± 0.5 °C in a dark room. All the experimental procedures were performed in the dark in order to avoid exposure of reaction solutions to scattering light. The progress of the reactions was followed by both VPC and HPLC.

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Supplementary Material Available: X-ray crystallographic data including positional parameters, temperature factors, bond distances and angles, torsional angles, weighted least-squares planes, and an ORTEP drawing for (*RR*)- + (*SS*)-**4e** and (*RR*)- + (*SS*)-**4f** (32 pages). Ordering information is given on any current masthead page.

$S_{RN}1$ Reactions in Nitrofuran Derivatives[1]

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The reaction of the sterically hindered neopentylic chloride 2-(1′-chloro-2′,2′-dimethylpropyl)-5-nitrofuran (1) with *p*-toluenesulfinate, azide, and *p*-toluenethiolate ions and the salts derived from 2-methylmalononitrile and 2-nitropropane proceed by the $S_{RN}1$ mechanism. The operation of this mechanism is confirmed by the inhibitory effect of oxygen, di-*tert*-butyl nitroxide, and galvinoxyl and the catalytic effect of irradiation by white light. Methoxide and thiocyanate ions do not bring about substitution on 1, and this and other evidence confirms that substitution is not occurring by either the S_N1 or S_N2 mechanisms.

Nucleophilic substitution at the benzylic carbon in *p*- and *m*-nitrobenzylic substrates has been demonstrated to occur, in many cases, by the $S_{RN}1$ mechanism[2] which is given in Scheme I. Our particular interest in this reaction

Scheme I

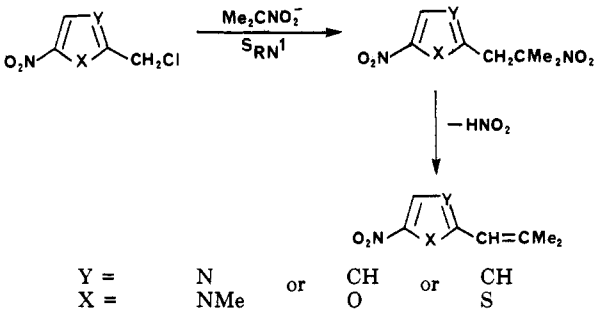
$$ArCR^1R^2X + Y^- \rightarrow [ArCR^1R^2X]^{\bullet -} + Y^{\bullet}$$

$$[ArCR^1R^2X]^{\bullet -} \rightarrow Ar\dot{C}R^1R^2 + X^-$$

$$Ar\dot{C}R^1R^2 + Y^- \rightarrow [ArCR^1R^2Y]^{\bullet -}$$

$$[ArCR^1R^2Y]^{\bullet -} + [ArCR^1R^2X] \rightarrow ArCR^1R^2Y + [ArCR^1R^2X]^{\bullet -}$$

Scheme II



Y =	N	or	CH	or	CH
X =	NMe		O		S

has been in the reactivity of systems which are neopentylic (Scheme I, Ar = *p*- or *m*-$O_2NC_6H_4$, R^1 = *t*-Bu).[3,4] We have shown that substitution by the $S_{RN}1$ mechanism at neopentyl positions also takes place with nitro heteroaromatic

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(2) For reviews, see: Kornblum, N. In *The Chemistry of the Functional Groups*; Patai, S., Ed.; Wiley: Chichester, 1982; Supplement F, Chapter 10. Norris, R. K. In *The Chemistry of the Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1983; Supplement D, Chapter 16.

(3) Jacobs, B. D.; Kwon, S.-J.; Field, L. D.; Norris, R. K.; Randles, D.; Wilson, K.; Wright, T. A. *Tetrahedron Lett.* **1985**, *26*, 3495-3498, and references cited therein.

(4) Barker, S. D.; Norris, R. K. *Aust. J. Chem.* **1983**, *36*, 81-95.

0022-3263/87/1952-2796$01.50/0