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A Novel Photochemical Dimerization of 2-Alkoxy-3-cyanopyridines to Pyridoazocines and Mixed Photodimers

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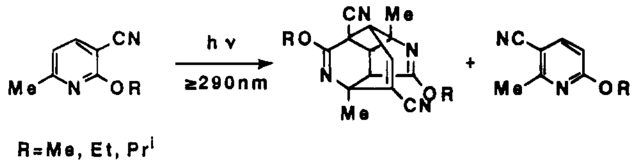
Summary: Irradiation of 3-cyano-2-alkoxypyridines gave dehydrogenated dimers, 1,8-dialkoxy-6,9-dicyanopyrido[3,2-*c*]azocines, and heterophotodimers, 3,12-dicyano-4,8-dialkoxy-5,9-diazatetracyclo$[4.3.3.0^{2,7}.0^{3,10}]$dodeca-4,8,11-trienes, in the presence of different pyridines.

Aromatic rings, known for their rigidity in the ground state, become exceedingly flexible upon excitation with a quantum of light. The photochemistry that results from this flexibility has evolved rapidly and dramatically during the past three decades into a synthetically valuable and mechanistically exciting area of contemporary research.[1] It has been shown that benzene and its derivatives undergo a number of important photoreactions such as photoisomerization and photoadditions with various alkenes. Furthermore, a great deal of attention has been paid to dimerization processes. For example, photolysis of substituted naphthalenes[2] and anthracenes[3] leads to $4\pi + 4\pi$ dimerization, and benzene rings incorporated in a rigid scaffold photocyclize intramolecularly.[4] In contrast to the photochemistry of hydrocarbon aromatics, pyridines show quite poor photoreactivities. The photoaddition of pyridines to alkenes is generally sluggish, and only a few photoreactions of this type have been reported, such as the isomerizations to Dewar pyridines and azaprismanes.[5] Recently, we reported a photodimerization of 2-alkoxy-3-cyano-6-methylpyridines involving a $2\pi + 2\pi$ cyclobutane formation, followed by a novel $2\pi + 2\pi + 2\pi + 2\sigma$ rearrangement (Scheme 1).[6] We now find that irradiation of 2-alkoxy-3-cyanopyridines promotes $2\pi + 2\pi$ photocyclodimerization, leading to pyrido[3,2-*c*]azocines and to mixed photodimer formation.

Scheme 1



Pyridines **1a−c** were prepared by standard S_N2 reactions from 2-chloro-3-cyanopyridines and the corresponding alkoxides.[7] Other pyridines **3a,b** were obtained by alkylation of the corresponding pyridones with alkyl iodide in the presence of silver carbonate.[8] The structures of these compounds were assigned on the basis of elemental analysis and spectral data. Irradiation of an acetonitrile solution of **1a** (0.04 M) in a Quartz vessel with a high pressure mercury lamp, under a nitrogen atmosphere, gave a yellow solid as the photoproduct. The mass spectrum (*m/e*) of the photoproduct showed a molecular ion peak at 266 (M^+), which indicated that this adduct was a dehydrogenated dimer with the molecular formula $C_{14}H_{10}N_4O_2$. The ^{1}H-NMR spectrum ($CDCl_3$) exhibited four olefinic protons at δ 5.29 (dd, $J = 4.6$ and 9.0 Hz, 1H, 4-CH), 6.77 (d, $J = 9.0$ Hz, 1H, 3-CH), 7.00 (d, $J = 4.6$ Hz, 1H, 5-CH), and 7.82 (s, 1H, 10-CH), in addition to two peaks derived from methoxy protons at 3.89 and 4.11. The ^{13}C-NMR ($CDCl_3$) spectrum displayed sp^2 carbon peaks at δ 97.2 (s, 6-C), 109.5 (d, 4-C), 113.7 (s, 9-C), 123.1 (s, 11-C), 142.1 (d, 3-C), 143.5 (d, 10-C), 146.6 (d, 5-C), 152.6 (s, 12-C), 157.8 (s, 8-C), and 163.8 (s, 1-C) in addition to the peaks derived from the methyl and cyano groups.[9] Furthermore, the structure of **2a** was unequivocally established by X-ray crystallographic analysis as a dehydrogenated dimer, 6,9-dicyano-1,8-dimethoxypyrido[3,2-*c*]azocine **2a** (Figure 1).[10] Photolysis of other pyridines **1b** and **1c** gave similar results (Scheme 2).

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(9) The assignment was performed by COSY technics.

(10) Crystal and experimental data for **2a**: $C_{14}H_{10}N_4O_2$, MW = 266, yellow rod crystal, monoclinic space group $P2_1/n$ with $a = 10.997(3)$ Å, $b = 14.382(2)$ Å, $c = 8.356(2)$ Å, $\beta = 103.80(1)°$, $\bar{v} = 1372.6$ Å^3, $Z = 4$, $\varrho = 1.22$ g/cm^3, and $\mu = 0.8$ cm^{-1}. Data were collected with Mo Kα radiation on an Enraf-Nonius CAD-4. The structure was solved by the direct method of full-matrix least-squares. Final R and Rw were 0.057 and 0.062 for 1918 reflections. The author has deposited atomic coordinates for **2** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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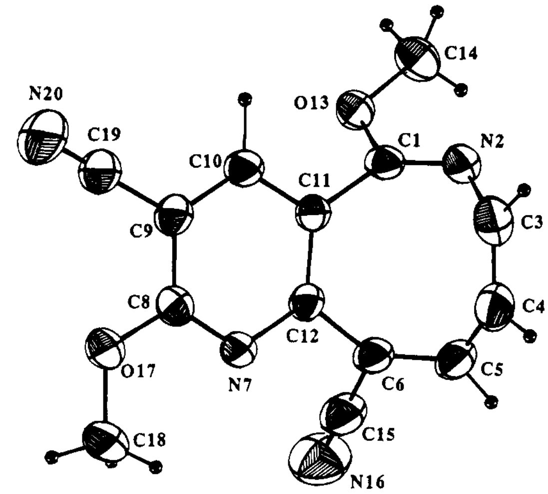


Figure 1. ORTEP diagram of the dimer **2a**.

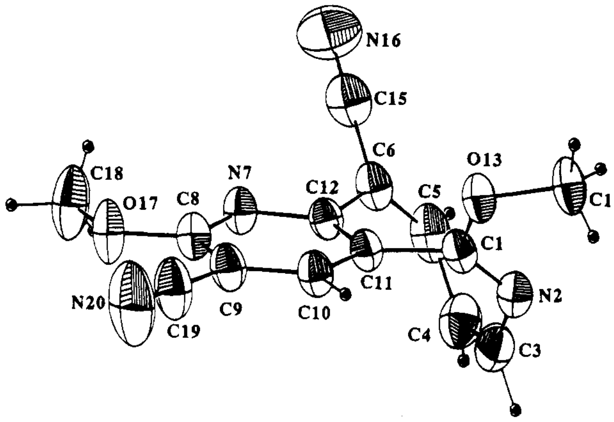
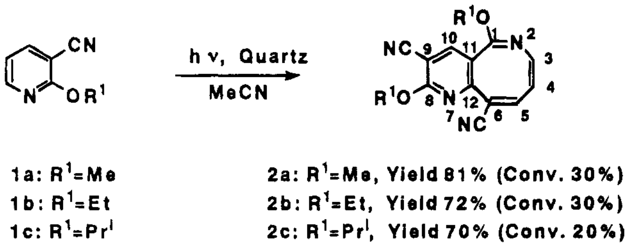


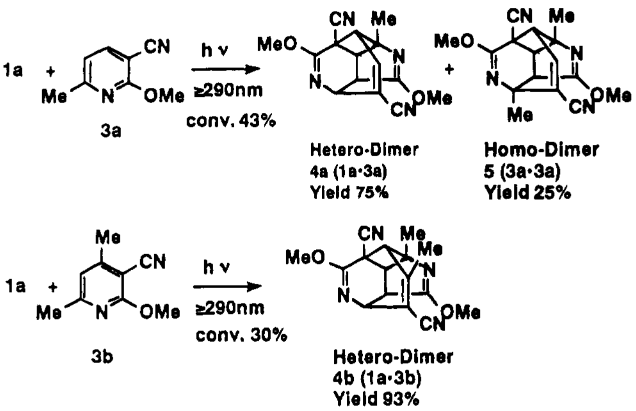
Figure 2. ORTEP diagram of the dimer **2a**.

Scheme 2

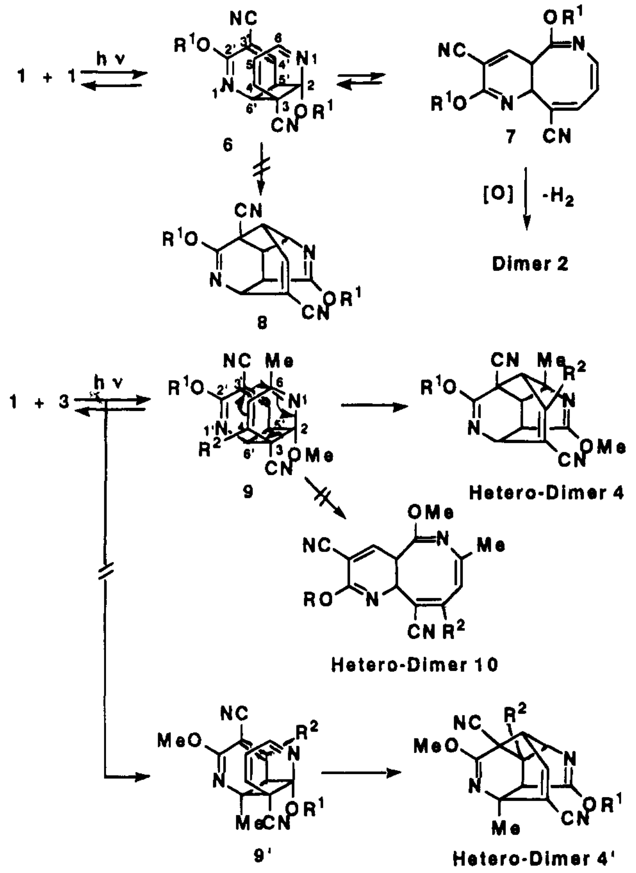


The pyrido[3,2-*c*]azocine **2a** is isoelectronic (12π-electrons) with the antiaromatic benzocyclooctatetraene ring system. Paquette et al. have reported the unique character of azocines and benzazocines and also suggest that these heterocyclooctatetraenes exist in strain-free puckered "tub" conformations, on the basis of spectroscopic data.[11] The existence of this conformation is confirmed for the first time by X-ray crystallographic analysis as shown in Figure 2. The two planes containing the pyridine ring and N2—C3—C4—C5 atoms are inclined at angles of 60.5° and 52.0°, respectively, to the plane containing the C1, N2, C5, and C6 atoms.[12] This structure is consistent with the azadiene fragment of the azocine ring being conjugated through the C3—C4 double bond rather than through the pyridine ring.

Scheme 3



Scheme 4



In contrast to the photolysis of **1a**—**1c**, 4-cyano-2-methoxypyridine, 3-cyano-2-(ethylthio)pyridine, and 3-cyano-2-(dimethylamino)pyridine were inert under the same photolytic conditions.

Next we tried the mixed photodimerization of **1a** with **3a** or **3b**. When a benzene solution of **1a** (0.04 M) and **3a** (0.04 M) was irradiated through a Pyrex filter under nitrogen, heterodimer **4a**(**1a**·**3a**), 3,12-dicyano-4,8-dimethoxy-1-methyl-5,9-diazatetracyclo[4.3.3.0^{2,7}.0^{3,10}]dodeca-4,8,11-triene, and a homodimer **5**(**3a**·**3a**) of **3a**, 3,12-dicyano-4,8-dimethoxy-1,6-dimethyl-5,9-diazatetracyclo-[4.3.3.0^{2,7}.0^{3,10}]dodeca-4,8,11-triene, were obtained in 75% and 25% yields, respectively, at 43% conversion of **3a**. Irradiation of a benzene solution of **1a** and **3b** (0.04 M in each) gave only a mixed photodimer **4b**(**1a**·**3b**) in 93% yield at 30% conversion of **3b**. The structures of the mixed photodimers were determined by the comparison

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[11] (a) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 11. (b) Paquette, L. A.; Anderson, L. B.; Hansen, J. F.; Lang, S. A., Jr.; Berk, H. *J. Am. Chem. Soc.* **1972**, *94*, 4907.

[12] Dihedral angles were defined as follows: $\omega = 1/2(\omega_1 + \omega_2)$, where ω_1 and ω_2 were dihedral angles N2—C1—C11—C12 and C5—C6—C12—C11, respectively. The dihedral angle of the C3—C4 bond was determined in the same manner.

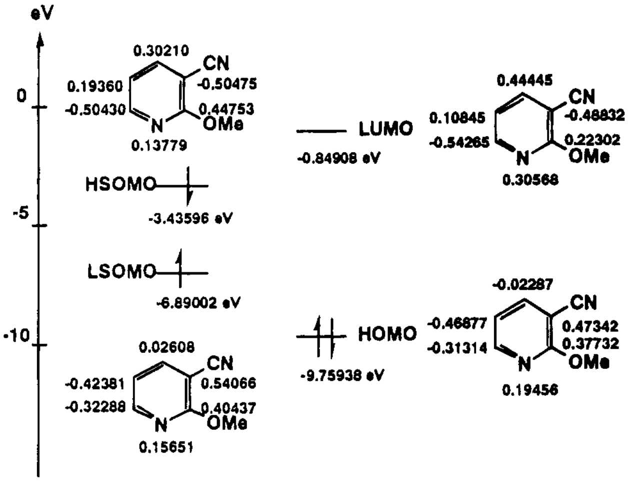

Figure 3. Estimated energies and coefficients of 3-cyano-2-methoxypyridines **1a** obtained from the PM3 Hamiltonian contained within the MOPAC program.

of spectral data of a photodimer of 3-cyano-2-ethoxy-6-methylpyridine, whose structure was unequivocally confirmed by X-ray crystallographic analysis[6] (Scheme 3).

For the formation of the dimer **2**, a mechanism is postulated that involves $2\pi + 2\pi$ photodimerization between the C2—C3 and C5′—C6′ bonds leading to cyclobutane **6**, which easily produces azacyclooctatriene **7** because of the influence of the electron-donating methoxy group and electron-withdrawing cyano group (Scheme 4). Finally, the dimer **7** is dehydrogenated to pyridoazocine **2**, the driving force being aromatization to the pyridine ring. In this photoreaction, formation of isomeric dimer **8** was not observed. We demonstrated that atmospheric oxygen is necessary to oxidize **7** to **2**. If **1a** is irradiated in degassed solution, a quantitative recovery of starting material occurs.

The formation of the mixed photodimer **4** can be explained by cyclobutane formation between the C2—C3 bond of alkylated pyridine (**3a** or **3b**) and the C5—C6 bond of the less substituted 2-alkoxy-3-cyanopyridine **1** leading to cyclobutane **9** followed by $2\pi + 2\pi + 2\pi + 2\sigma$ rearrangement. While two types of heterophotodimers (**4** and **4′**) are possible in the mixed photodimerization, only a single heterodimer, **4**, was observed. The reaction path from cyclobutane **9** to an azacyclooctatriene-type heterophotodimer **10** was not observed either.

The high regioselectivity for the dimerization is supported by Frontier-MO calculations using the PM3 Hamiltonian contained within the MOPAC program. The orbital energies and coefficients of the singlet excited state for **1a** (HSOMO and LSOMO) and those of the ground state of **1a** (LUMO and HOMO) were obtained[13] (Figure 3). The energy gap (ΔE) between HSOMO and LUMO is smaller than that between LSOMO and HOMO, and this frontier orbital interaction is the most important in this photodimerization. The coefficients at the 3-position in the HSOMO of the excited state and those at the 6′-position of the LUMO in the ground state are larger than those at any other positions. It is concluded that the initial bond formation between the C2—C3 and the C5′—C6′ bonds occurs and leads to dimers (**2**, **4**, and **5**).[14]

What determines the selectivity of the rearrangement from the cyclobutane intermediate **6** or **9** to dimer **2** or **4**? In the case of the reaction of **1a** with **3a** or **3b**, mixed photodimer **4** was obtained exclusively; nevertheless, the steric interaction between the methyl and cyano groups in the cyclobutane intermediate **9** prevent the formation of dimer **4**. There is no satisfactory explanation for this regioselectivity. But it seems that the electronic effect of the methyl group is an important factor in determining the path to dimers **2** or **4**. That is, the rearrangement to the dimer **4** from the intermediate **9** should be accelerated by the electron-donating methyl group.

In conclusion, the photoreaction of 2-alkoxy-3-cyanopyridines leads to unprecedented cyclodimerizations followed by novel rearrangements whose paths are dependent on the substituents. This provides a rare example of the photodimerization of heteroaromatic compounds. We are continuing to explore the scope and limitations of the photoreactions of these unusually photoreactive heteroaromatics.

Supplementary Material Available: Experimental data of new compounds (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) These results are calculated by "PASOCON MOPAC/386", which is based on the MOPAC (V6.0 QCPE No. 455) of Toray System Center.

(14) The HSOMO coefficient on C-6 position is almost as large as the coefficient on C-3 position (−0.504 30 vs. −0.504 75). For a more accurate approach, the predicted $\Delta\Delta E$ of the reaction was calculated using the Salem–Klopman equation (see, for example: Fleming, I. *Frontier Orbital and Organic Chemical Reactions*: Wiley-Interscience: New York, 1976). The $\Delta\Delta E$ is proportional to $(c_{a1}c_{b1})^2 + (c_{a2} + c_{b2})^2$ where c_X is the orbital coefficient in the reactive site for the addition reaction of the a1—a2 and the b1—b2 bonds. The value of $(c_{C3}c_{C6'})^2 + (c_{C2}c_{C5'})^2$ is 7.7380×10^{-2} and 7.5330×10^{-2}, respectively, to that of $(c_{C6}c_{C6'})^2 + (c_{C5}c_{C5'})^2$ for the alternative pathway. This results also supports that the initial bond formation occurs between C2—C3 and C5—C6 bonds leading to the experimentally observed product.