

A Novel [2 + 2] Photodimerization of *N*-[(*E*)-3,4-Methylenedioxcinnamoyl]dopamine in the Solid State

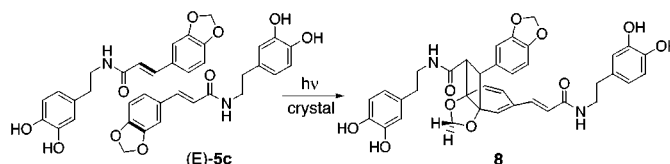
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Received June 7, 2001

ABSTRACT

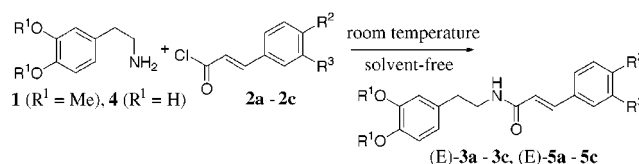


To give photoreactivity to catecholamines, *N*-cinnamoyl-substituted dopamines (*E*-5a–5c and *O,O'*-dimethyldopamines (*E*-3a–3c) were prepared under solvent-free conditions. A particularly interesting observed photoreactivity was that of *N*-[(*E*)-3,4-methylenedioxcinnamoyl]dopamine ((*E*-5c), which underwent a novel type of [2 + 2] photodimerization in the solid state, giving exclusively a tricyclic product 8. This reaction is the first example of solid-state photoaddition of an alkene to the benzene ring.

Catecholamines such as dopamine and dopa are medically and biologically important as neurotransmitters and melanin sources.¹ They are photostable in the absence of oxygen or other oxidants.² To give photoreactivity to them, we prepared *N*-cinnamoyl-substituted dopamines (*E*-5a–5c) and *O,O'*-dimethyldopamines (*E*-3a–3c). Particular cinnamamides are expected to be useful antipsychotic agents that are selective for dopamine D₃ receptor.³ We have found that, in the solid state, cinnamoyldopamines (*E*-3b, (*E*-3c, and (*E*-5c) showed photoreactivity to give dimers 6, 7, and 8, respectively, while other compounds (*E*-3a, (*E*-5a, and (*E*-5b) were virtually photostable. Particularly noteworthy are that (a) the tricyclic product 8 is a product of cycloaddition of an alkene to the benzene ring and (b) formation of α -truxillic dimer 6 is very efficient (100% conversion, 100% yield, $\Phi = 0.75$). By contrast, solution photolyses in methanol resulted in *E*–*Z* isomerization in all cases.

N-[(*E*)-Cinnamoyl]dopamines (*E*-5a–5c) and their *O,O'*-dimethyl derivatives (*E*-3a–3c) were prepared by reactions of amines 1 and 4 with acid chlorides 2a–2c under solvent-free conditions (Scheme 1). After mixing the reactants in a porcelain mill with a pestle for 30 min, the mixture was kept overnight at room temperature.⁴ Reaction products were

Scheme 1

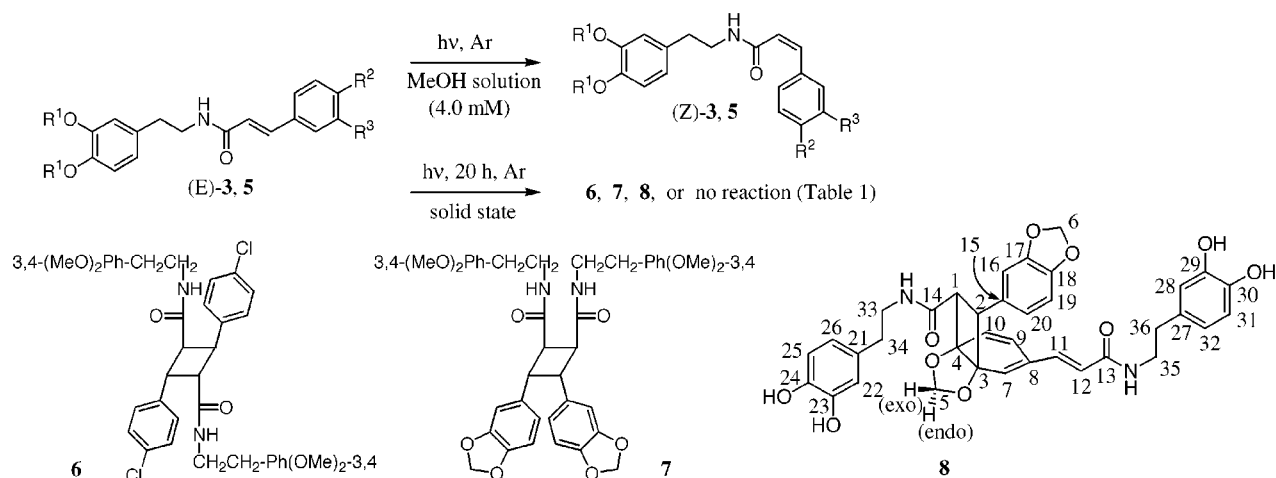


cinnamoyl-dopamine	R ¹	R ²	R ³	yield, mp (recrystallization solvent) ⁵
(<i>E</i>)-3a	Me	H	H	74 %, 124.5–126 °C (acetone)
(<i>E</i>)-3b	Me	Cl	H	100 %, 138.5–140 °C (benzene)
(<i>E</i>)-3c	Me	–OCH ₂ O–		83 %, 166–167 °C (benzene)
(<i>E</i>)-5a	H	H	H	63 %, 164–165 °C (benzene–MeOH) ⁶
(<i>E</i>)-5b	H	Cl	H	26 %, 173.5–174 °C (benzene–MeOH)
(<i>E</i>)-5c	H	–OCH ₂ O–		48 %, 181–183 °C (benzene–acetone)

(1) (a) Pufulete, M. *Chem. Br.* **1997**, 31–35. (b) Martin, C. *Chem. Br.* **1998**, 40–42. (c) *The Pigmentary System*; Nordlund, J. J., Boissy, R. E., Hearing, V. J., King, R. A., Ortonne, J.-P., Eds.; Oxford University Press: New York, 1998; Chapters 24–33.

(2) For example, see: (a) Chedekel, M. R. *Photochem. Photobiol.* **1982**, 35, 881–885. (b) Pandey, G.; Sridhar, M.; Bhalerao, U. T. *Tetrahedron Lett.* **1990**, 31, 5373–5376.

Scheme 2



separated by column or preparative thin-layer chromatography on silica gel (benzene/acetone) or by preparative HPLC on Asahipak GS-320 (MeOH). Isolation yields were reasonable (Scheme 1).⁵

Solution photolyses of cinnamoyldopamines (*E*)-**3a**–**3c** and (*E*)-**5a**–**5c** in methanol resulted in *E*–*Z* isomerization (Scheme 2) and the *E*/*Z* ratio at the photostationary state was around 50/50 in each case.⁷ The irradiation time required to reach the photostationary state was much shorter for 3,4-methylenedioxy derivatives (*E*)-**3c** and (*E*)-**5c** than for other ones. In fact, the photoisomerization quantum yield (estimated at 276 nm⁸) for (*E*)-**3c** (0.45) was much higher than that for (*E*)-**3a** (0.086) or (*E*)-**3b** (0.095). Control experiments on (*E*)-cinnamamide, (*E*)-4-chlorocinnamamide, and (*E*)-3,4-methylenedioxycinnamamide have revealed that the photoisomerization quantum yields for these three amides are not very different (0.24, 0.32, and 0.65, respectively). These results suggest that, when the substituent R² is hydrogen ((*E*)-**3a**, **-5a**) or chlorine ((*E*)-**3b**, **-5b**), the excited states were quenched probably by an intramolecular electron transfer from the catechol moiety to the cinnamoyl moiety.

(3) (a) Austin, N. E.; Avenell, K. Y.; Boyfield, I.; Branch, C. L.; Hadley, M. S.; Jeffrey, P.; Johnson, C. N.; Macdonald, G. J.; Nash, D. J.; Riley, G. J.; Smith, A. B.; Stemp, G.; Thewlis, K. M.; Vong, A. K. K.; Wood, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2553–2555. (b) Stemp, G.; Ashmeade, T.; Branch, C. L.; Hadley, M. S.; Hunter, J. A.; Johnson, C. N.; Nash, D. J.; Thewlis, K. M.; Vong, A. K. K.; Austin, N. E.; Jeffrey, P.; Avenell, K. Y.; Boyfield, I.; Hagan, J. J.; Middlemiss, D. N.; Reavill, C.; Riley, G. J.; Routledge, C.; Wood, M. *J. Med. Chem.* **2000**, *43*, 1878–1885.

(4) For the preparation of **3a**–**3c**, *O,O'*-dimethyldopamine **1** (2 equiv) and acid chloride **2** (1 equiv) were mixed together. For the preparation of **5a**–**5c**, dopamine hydrochloride **4**·HCl (2 equiv), NaOH (2 equiv), and acid chloride **2** (1 equiv) were mixed together.

(5) All new compounds (*E*)-**3b**, (*E*)-**3c**, (*E*)-**5a**, (*E*)-**5b**, (*E*)-**5c**, **6**, **7**, and **8** gave satisfactory NMR, IR, MS, and HRMS spectra. **6**: colorless plates, mp 209–210.5 °C (benzene/acetone). **7**: colorless prisms, mp 189–192 °C (benzene). **8**: white solid, mp 122–127 °C (preparative HPLC). The spectral data for **6**–**8** are given in Supporting Information.

(6) Literature mp 165–166 °C: Tseng, C.-F.; Iwakami, S.; Mikajiri, A.; Shibuya, M.; Hanaoka, F.; Ebizuka, Y.; Padmawinata, K.; Sankawa, U. *Chem. Pharm. Bull.* **1992**, *40*, 396–400.

(7) Irradiations were carried out under an argon atmosphere with a 400-W high-pressure mercury lamp (Pyrex) for several hours (solution) or 20 h (solid), as described previously.⁹

In the solid state, cinnamoyldopamines (*E*)-**3b**, (*E*)-**3c**, and (*E*)-**5c** showed photoreactivity to give dimers **6**, **7**, and **8**, respectively, while other compounds (*E*)-**3a**, (*E*)-**5a**, and (*E*)-**5b** were virtually photostable (Scheme 2, Table 1).^{5,7} The

Table 1. Products from the Solid-State Photolysis

reactant	% conversion	products, % yield
(<i>E</i>)- 3a	0	
(<i>E</i>)- 3b	100	6 , 100 ($\Phi = 0.75$)
(<i>E</i>)- 3c	51	7 , 55
(<i>E</i>)- 5a	~0	
(<i>E</i>)- 5b	~0	
(<i>E</i>)- 5c	66	8 , 100

successful reactivities of the former three compounds appear to support a claimed strategy in crystal engineering, where chloro or methylenedioxy substitution is utilized to steer the crystal packing of cinnamic acids to a parallel array of double bonds.¹⁰ The dimerization of *N*-[(*E*)-4-chlorocinnamoyl]-*O,O'*-dimethyldopamine ((*E*)-**3b**) into the α -truxillic dimer **6** is a very good solid-state photoreaction, because both the conversion and the chemical yield were 100%, the crystalline appearance was intact throughout the reaction,¹¹ and the quantum yield was very high, i.e., $\Phi = 0.75$, which was estimated by a merry-go-round apparatus at 313 nm.¹² This quantum yield is higher than that of the efficient photo-dimerization of (*E*)-cinnamic acid, $\Phi = 0.59$.¹² The solid-

(8) An *E*–*Z* isomerization of methyl cinnamate ($\Phi = 0.32$) was used as a standard: Lewis, F. D.; Quillen, S. L.; Elbert, J. E. *J. Photochem. Photobiol., A* **1989**, *47*, 173–179.

(9) Ito, Y. *Synthesis* **1998**, 1–32. Ito, Y. *Mol. Supramol. Photochem.* **1999**, *3*, 1–70.

(10) Desiraju, G. R. *Crystal Engineering: The Design of Organic Solids*; Materials Science Monographs, Vol. 54; Elsevier: New York, 1989.

(11) The reaction (*E*)-**3b** → **6** has been found to be a perfect single-crystal-to-single-crystal transformation up to 100% conversion. Ohba, S.; Ito, Y. Unpublished work.

(12) Ito, Y.; Matsuura, T. *J. Photochem. Photobiol., A* **1989**, *50*, 141–145.

state photoreaction of (*E*)-**3c** was found to be complex, producing the β -truxinic dimer **7** only in a moderate yield (51% conversion, 55% yield).

The photodimerization of *N*-[(*E*)-3,4-methylenedioxybenzyl]dopamine ((*E*)-**5c**) into the tricyclic product **8** (66% conversion, 100% yield) is novel, since the photoaddition occurred between the double bonds of alkene and benzene. Although it is well-known from the solution photochemistry that photocycloaddition of an alkene to benzene can occur across the ortho, meta, and para positions,¹³ there are no corresponding reactions in the solid state. Indeed, numerous examples of the solid-state [2 + 2] photodimerization of alkenes were reported so far,^{9,14} but the participation of the benzene ring in such photodimerization reactions is unreported.

Product **8** was isolated by preparative HPLC (Asahipak GS-320, MeOH) as a white solid, mp 122–127 °C.⁵ The structure was assigned on the basis of the ¹H and ¹³C NMR including DEPT and 2D NMR (HH COSY, NOESY, HMQC, and HMBC). Figure 1 is the ¹H NMR spectrum of

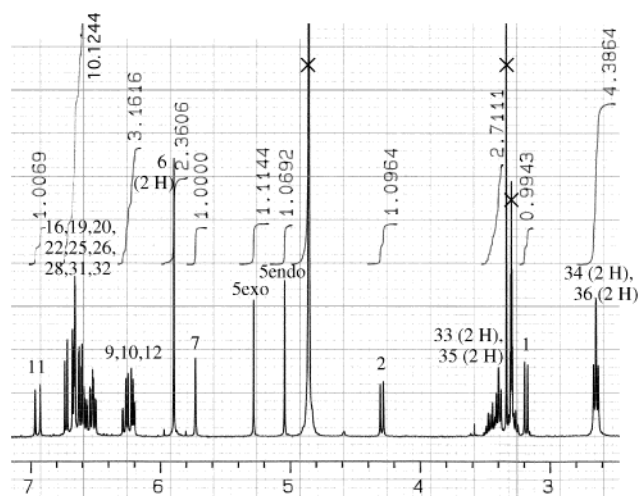


Figure 1. The ¹H NMR spectrum (400 MHz) of **8** in CD₃OD.

the photodimer. Two protons at the methylenedioxy moiety became nonequivalent (H-5_{exo} and H-5_{endo}) as a result of the cycloaddition, and the NOE effect was observed between H-2 and H-5_{exo}. It is noticeable that the methylene protons at C-33 are nonequivalent probably due to the asymmetric environment around the tricyclic structure. On exposure to air, the dimer **8** turned to pale brown in a day or two.

(13) For example, see: Kopecky, J. *Organic Photochemistry; A Visual Approach*; VCH: New York, 1992; Chapter 7.

(14) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, 87, 433–481.

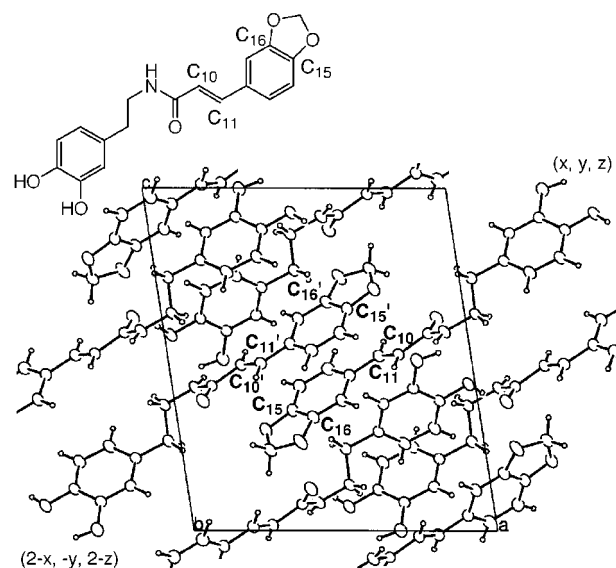


Figure 2. The crystal structure of (*E*)-**5c**.

The stereochemistry of **8** is consistent with the crystal structure of (*E*)-**5c** (Figure 2).¹⁵ Two molecules at positions (*x*, *y*, *z*) and (2 − *x*, −*y*, 2 − *z*) are related by a center of symmetry. The relevant double bonds (C10–C11 vs C15′–C16′, C15–C16 vs C10′–C11′) are almost parallel, and their separation is short (C10⋯C15′ = C10′⋯C15 = 3.36 Å and C11⋯C16′ = C11′⋯C16 = 3.59 Å). These carbon⋯carbon distances are well within the Schmidt's critical distance (4.2 Å).¹⁴ Therefore, the photoaddition must have proceeded topochemically. Finally, we would like to mention that the solid state is a good reaction medium to cause unusual photocycloaddition of biorelevant molecules.¹⁶

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Government (10440215). The authors also acknowledge MacScience Co. for the single crystal X-ray diffraction.

Supporting Information Available: NMR, IR, and MS data of **6–8**; X-ray structural information and an X-ray crystallographic file for (*E*)-**5c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) MacScience DIPlabo (Imaging Plate). Crystal data: C₁₈H₁₇NO₅ (*M*_r = 327.34), colorless prism, monoclinic *P*2₁/*n*, *a* = 12.4020(5), *b* = 8.8690(3), *c* = 14.2710(5) Å, β = 98.761(2)°, *V* = 1551.40(10) Å³, *Z* = 4, *D*_x = 1.401 g/cm³, λ (Cu Kα) = 1.54184 Å, μ = 0.857 mm^{−1}, 3047 measured reflections, *R* = 0.0511, *R*_w = 0.1445 for 2511 reflections [*I* > 2σ(*I*) with 286 parameters].

(16) Ito, Y.; Fujita, H. *Chem. Lett.* **2000**, 288–289. Ito, Y.; Hosomi, H.; Ohba, S. *Tetrahedron* **2000**, 56, 6833–6844.