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

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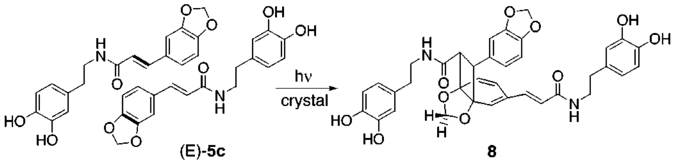
ABSTRACT

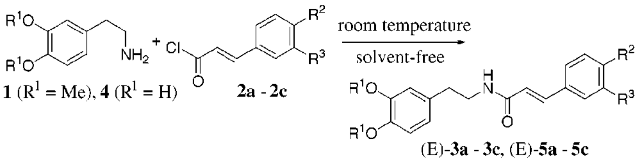


To give photoreactivity to catecholamines, *N*-cinnamoyl-substituted dopamines (*E*)-5a–5c and *O*,*O*′-dimethyldopamines (*E*)-3a–3c were prepared under solvent-free conditions. A particularly interesting observed photoreactivity was that of *N*-[(*E*)-3,4-methylenedioxycinnamoyl]dopamine ((*E*)-5c), 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 D_3 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]
(E)-**3a**	Me	H	H	74 %, 124.5-126 °C (acetone)
(E)-**3b**	Me	Cl	H	100 %, 138.5-140 °C (benzene)
(E)-**3c**	Me	$-OCH_2O-$		83 %, 166-167 °C (benzene)
(E)-**5a**	H	H	H	63 %, 164-165 °C (benzene-MeOH)[6]
(E)-**5b**	H	Cl	H	26 %, 173.5-174 °C (benzene-MeOH)
(E)-**5c**	H	$-OCH_2O-$		48 %, 181-183 °C (benzene-acetone)

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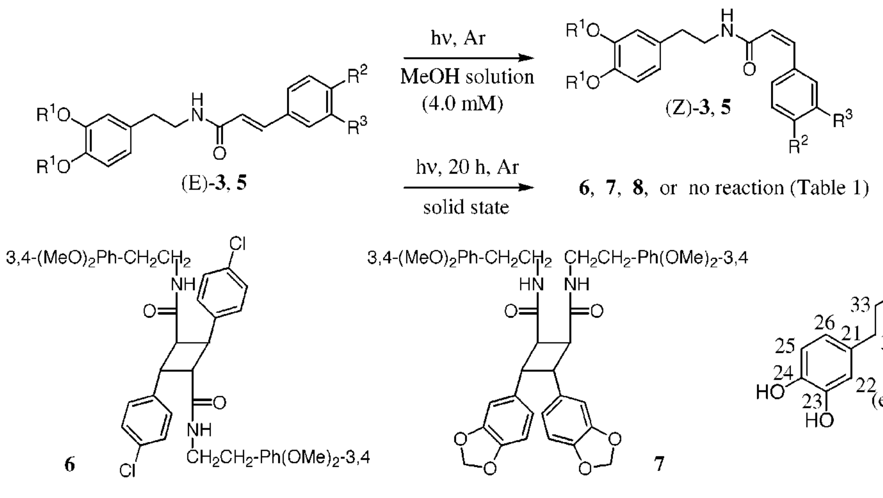
[1] (a) Pufulete, M. *Chem. Br.* **1997**, 31−35. (b) Martin, C. *Chem. Br.* **1998**, 40−42. (c) *The Pigmentary System*; Nordlund, J. J., Boissy, R. E., Hearing, V. J., King, R. A., Ortonne, J.-P., Eds.; Oxford University Press: New York, 1998; Chapters 24−33.

[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.

10.1021/ol0162419 CCC: $20.00

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 nm[8]) 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 R^2 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.

Table 1. Products from the Solid-State Photolysis

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

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 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 photodimerization of (*E*)-cinnamic acid, $\Phi = 0.59$.[12] The solid-

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(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]

(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-methylenedioxycinnamoyl]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 ^{1}H and ^{13}C NMR including DEPT and 2D NMR (HH COSY, NOESY, HMQC, and HMBC). Figure 1 is the ^{1}H NMR spectrum of 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.

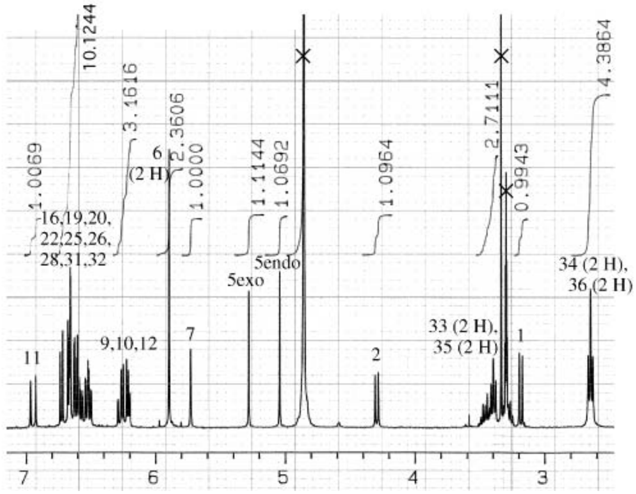

Figure 1. The ^{1}H NMR spectrum (400 MHz) of **8** in CD_3OD.

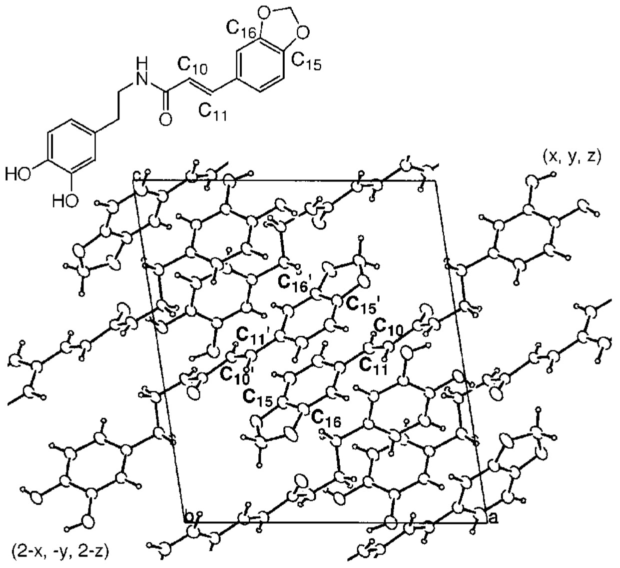

Figure 2. The crystal structure of (*E*)-**5c**.

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 wthin 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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[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.

[15] MacScience DIPlabo (Imaging Plate). Crystal data: $C_{18}H_{17}NO_5$ (M_r = 327.34), colorless prism, monoclinic $P2_1/n$, $a = 12.4020(5)$, $b = 8.8690(3)$, $c = 14.2710(5)$ Å, $\beta = 98.761(2)°$, $V = 1551.40(10)$ Å^3, $Z = 4$, $D_x = 1.401$ g/cm^3, λ (Cu Kα) = 1.54184 Å, $\mu = 0.857$ mm^{-1}, 3047 measured reflections, $R = 0.0511$, $R_w = 0.1445$ for 2511 reflections [$I > 2\sigma(I)$ with 286 parameters].

[16] Ito, Y.; Fujita, H. *Chem. Lett.* **2000**, 288−289. Ito, Y.; Hosomi, H.; Ohba, S. *Tetrahedron* **2000**, *56*, 6833−6844.