

Exothermic thermal reaction of dopamine with 3,5-dinitrobenzoic acid

Yoshikatsu Ito* and Satoru Arimoto

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501, Japan

Received 19 January 2003; revised 14 March 2003; accepted 10 April 2003

ABSTRACT: Pyrolysis of the crystalline 1 : 1 molecular complex **DA•dnba**, which was prepared from cocrystallization of dopamine (**DA**) and 3,5-dinitrobenzoic acid (**dnba**), was studied. This cocrystal decomposed violently at the melting-point, leading to the formation of a black solid along with a tiny amount of 3-amino-5-nitrobenzoic acid (**1**). The pyrolysis reaction was followed by differential scanning calorimetry (DSC) and one large exothermic peak was observed at the decomposition temperature. In view of the DSC patterns for cocrystal **DA•dnba** and other compounds, it seems that both a catechol moiety and an amino group of **DA** in addition to a strong electron acceptor such as **dnba** are required for the appearance of the exothermic peak. On the basis of (a) elemental analysis of the black solid and (b) other pyrolysis experiments for cocrystals **PA•dnba** (**PA**: β -phenylethylamine), **BA•dnba** (**BA**: benzylamine), **DMDA•dnba** (**DMDA**: O,O'-dimethyldopamine) and **DHBA•dnba** (**DHBA**: 3,4-dihydroxybenzylamine), it is assumed that the black solid was formed mainly through elimination of more than one molecule of water from one molecule of **DA•dnba**. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: dopamine; 3,5-dinitrobenzoic acid; pyrolysis; differential scanning calorimetry; cocrystal

INTRODUCTION

Because dopamine (**DA**) is an important neurotransmitter in the brain,^{1,2} its chemical reactivity has an inherent interest. For example, it reacts with an aldehyde to form a tetrahydroisoquinoline (Pictet–Spengler condensation).³ This reaction and also *N*-acylation of a β -phenylethylamine followed by cyclization into a 3,4-dihydroisoquinoline (Bischler–Napieralski cyclization)⁴ are important reactions in the syntheses of isoquinoline alkaloids.⁵ The best known reactivity of dopamine is its vulnerability to oxidation. **DA** is easily autoxidized in neutral or alkaline solution to furnish a black polymer called melanin via a series of intermediates such as semiquinone and quinone.⁶ On the other hand, **DA** is stable to oxidation under acidic conditions. In fact, since dopamine is difficult to isolate as the free amine under air, it is distributed commercially as a salt with hydrochloric acid (**DA•HCl**) or hydrobromic acid (**DA•HBr**). Enzymatic or non-enzymatic oxidation of catechols giving rise to melanin or tanned materials is ubiquitous in the animal, plant and fungi kingdoms.⁷ Also, oxidative polymerization of phenolic compounds leading to dark-colored humic substances is an important reaction in soil.⁸

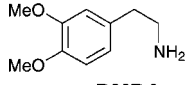
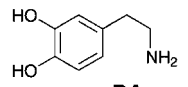
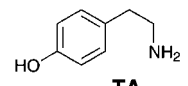
In the course of our study on the photochemistry of two-component crystals,⁹ we were interested in the oxidation of catecholamines. We have found that dopamine (**DA**) and its analogs, homoveratrylamine (O,O'-dimethyldopamine, **DMDA**) and tyramine (**TA**), are able to form a 1 : 1 crystalline molecular complex with suitable electron acceptors such as 3,5-dinitrobenzoic acid (**dnba**), 3-nitrobenzoic acid and picric acid (**pic**). Thermal analysis of the crystalline complexes **DA•dnba** and **DA•pic** by differential scanning calorimetry (DSC) has revealed a large exothermic peak near the melting-points and black materials have resulted. As will be described in this paper, we investigated these thermal reactions in some detail, because the chemical structures of all the black–brown materials (melanin, humus, etc.) that were formed from oxidation of catechols^{6–8} are as yet unknown.

RESULTS AND DISCUSSION

All the crystalline molecular complexes listed in Table 1 were obtained by cocrystallization of the amine and the acceptor from suitable solvents (all the cocrystals shown in Table 1 were photoinert in the solid state under similar irradiation conditions to those described previously.⁹) Their melting-points are summarized in Table 2. X-ray crystallographic analyses of cocrystals **DA•dnba**,¹⁰ **DMDA•dnba**,¹¹ **DMDA•pic** (S. Ohba and Y. Ito, unpublished result), and **TA•pic**¹² have already been carried out

*Correspondence to: Y. Ito, Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501, Japan.
E-mail: yito@sbchem.kyoto-u.ac.jp

Table 1. Formation of crystalline molecular complexes of catecholamines (B) with electron acceptors (A)

B	A	
	dnba	pic
	1 : 1	1 : 1
DMDA		
	1 : 1	1 : 1 (+2H ₂ O)
DA		
	1 : 1	1 : 1
TA		

and their amine component was found to exist as the ammonium salt like that in dopamine hydrochloride, **DA·HCl**.¹³ The **DA** molecule in the **DA·dnba** cocrystal was stable to autoxidation for an indefinite time, as in **DA·HCl**.

Heating cocrystals of **DA·dnba** or **DA·pic** on a hot-plate resulted in the sudden decomposition of the crystal when the plate temperature reached near the melting-point of the sample, giving a black pigment along with a small amount of 3-amino-5-nitrobenzoic acid (**1**) or picramic acid (**2**) [reactions (1) and (2) in Scheme 1]. These thermal

Table 2. Solvents for cocrystallization and melting-points of cocrystals

Cocrystal	Cocrystallization solvent	M.p. (°C)
DA·dnba	EtOH–H ₂ O	221–229 (decomp.)
DA·pic	MeOH–H ₂ O	209–216 (decomp.) ^a
DMDA·dnba	EtOH–MeOH	195–199
DMDA·pic	EtOH	172–175 ^b
TA·dnba	EtOH–H ₂ O	226–234
TA·pic	MeOH–H ₂ O	205–207
PA·dnba ^c	MeOH	166–172
BA·dnba ^c	EtOH–MeOH	186–190
DHBA·dnba ^c	MeOH–H ₂ O	191–193 (decomp.)

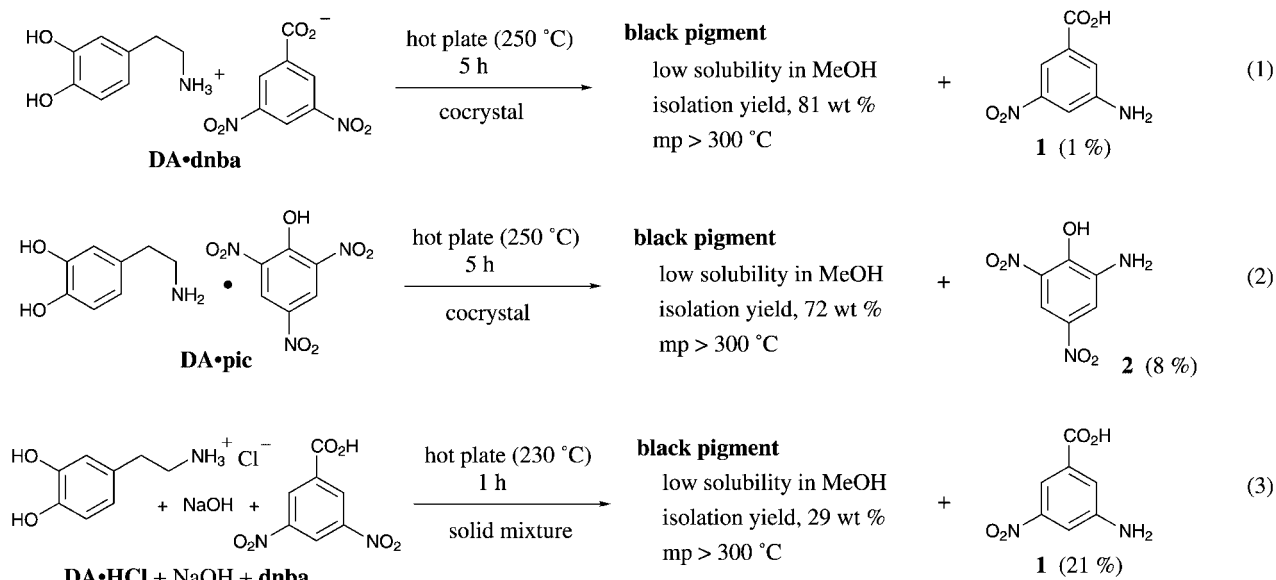
^a Lit.¹⁷ m.p. 189–190 °C (decomp.).

^b Lit.¹⁸ m.p. 164–166 °C.

^c **PA**, β -phenylethylamine; **BA**, benzylamine; **DHBA**, 3,4-dihydroxybenzylamine.

reactions were followed by DSC. As can be seen from Figs 1(a) and 2(a), both **DA·dnba** and **DA·pic**, upon heating, first showed an endothermic peak due to melting. This was suddenly replaced by a large exothermic peak, indicating the occurrence of certain violent chemical reactions. In contrast, cocrystals of **DMDA·dnba** or **DMDA·pic** showed only an endotherm due to melting [Figs 1(b) and 2(b), respectively]. It should be noted that **DA·HCl** [lit.¹⁴ m.p., 241 °C (decomp.)] also showed only an endothermic peak at the melting-point [Fig. 1(c)], suggesting no accompanying drastic reactions.

A typical experiment for the thermal reaction of **DA·dnba** is as follows. Cocrystals of **DA·dnba** were crushed in an agate mortar and 222 mg were heated on a hot-plate (250 °C). The sample turned brown–black with melting and concomitant bubbling, and after 10 min the whole mass changed into a black solid. Heating was continued for additional 4.8 h. The reaction mixture was washed with hot MeOH several times (10 ml $\times$ 9) to give

**Scheme 1.** Pyrolysis of **DA·dnba**, **DA·pic**, and a 1:1:1 mixture of **DA·HCl**, NaOH and **dnba**

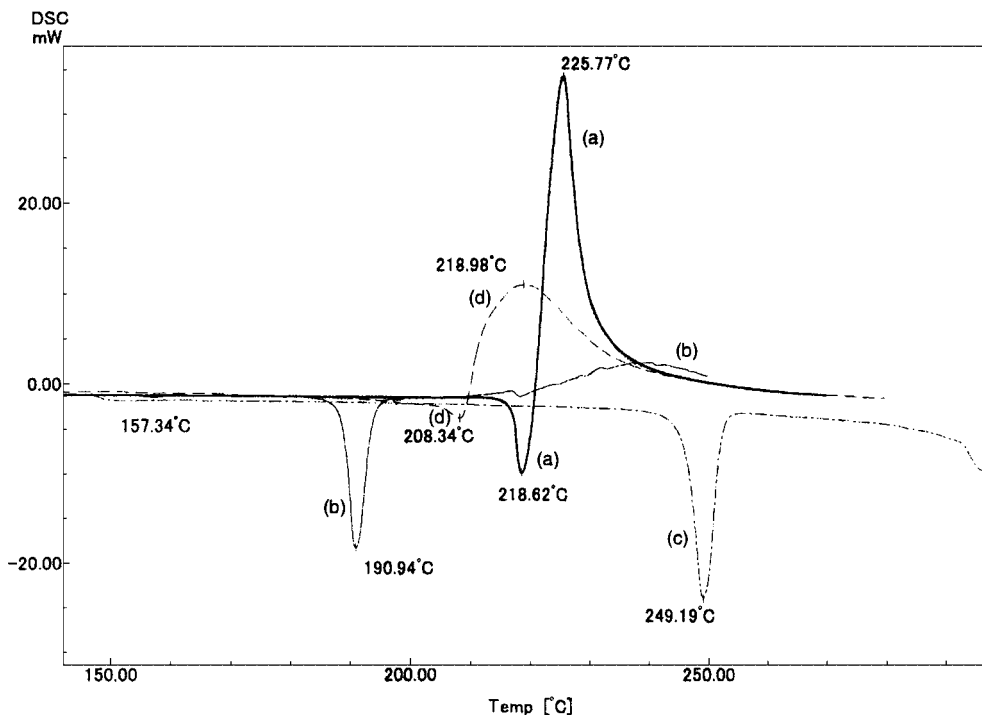


Figure 1. DSC traces for (a) **DA•dnba**, (b) **DMDA•dnba**, (c) **DA•HCl** and (d) a 1 : 1 : 1 mixture of **DA•HCl**, NaOH and **dnba**

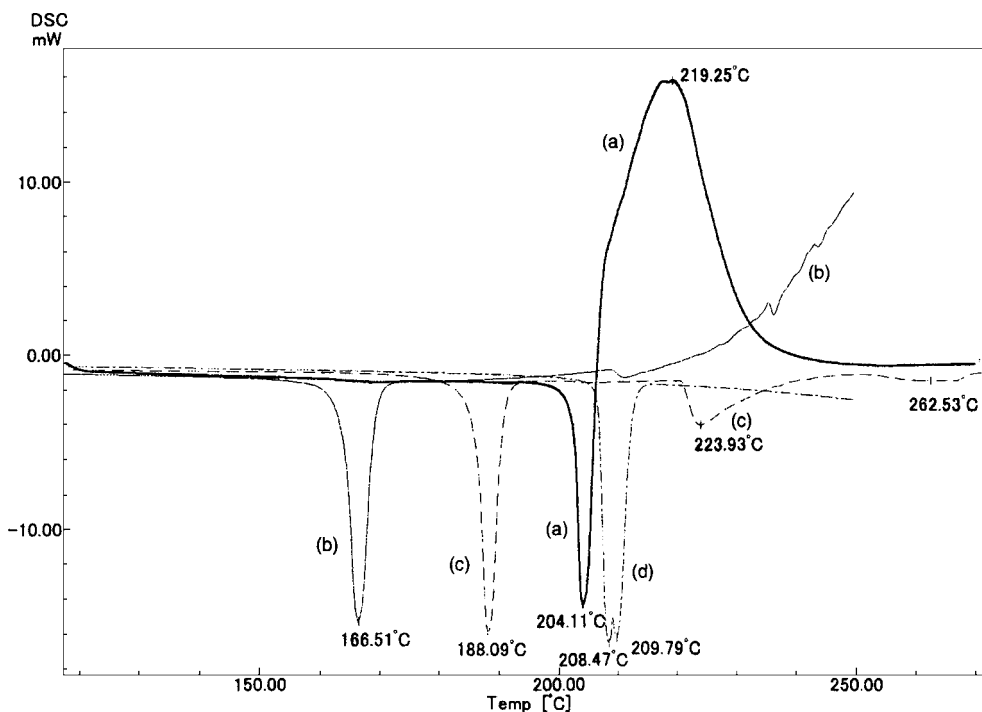


Figure 2. DSC traces for (a) **DA•pic**, (b) **DMDA•pic**, (c) **PA•dnba** and (d) **dnba**

a black residue (180 mg, 81 wt%). From the MeOH washing, 3-amino-5-nitrobenzoic acid (**1**) was obtained in a small quantity (1 mg, ~1%). In a separate pyrolysis experiment employing an equimolar mixture of **DA•HCl**, NaOH, and **dnba** [reaction (3) in Scheme 1], **1** was produced in a much higher yield (21%) and was isolated by PTLC, followed by HPLC (see below).

In order to obtain some structural information, the black residue was subjected to measurements by powder x-ray diffraction (PXD), IR (in KBr), ^1H NMR (in D_2O containing 5% NaOD), UV/Vis (in 1 M NaOH), FAB-MS (in 1 M NaOH or DMF) and elemental analysis. The PXD pattern [Fig. 3(A)] and the IR spectrum [Fig. 3(B)] are broad, but the IR absorption attributable to the nitro group

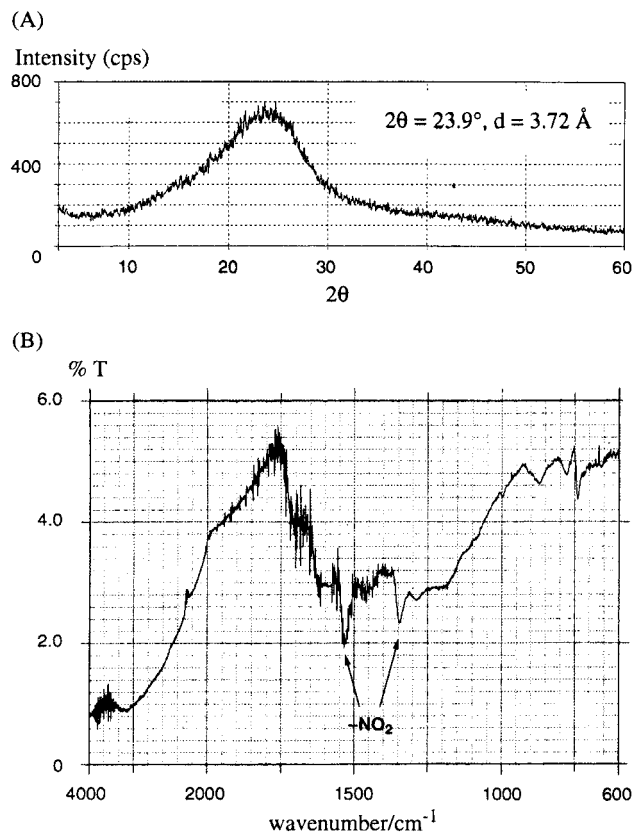


Figure 3. (A) Powder x-ray diffraction pattern and (B) IR spectrum (in a KBr disc) for the black pigment

is clearly visible at 1530 and 1345 cm^{-1} . The ^1H NMR (not shown) and UV/Vis (not shown) spectra are also very broad. However, because of the low solubility in the

solvent used, the ^1H NMR, UV/Vis and FAB-MS (not shown) spectra do not reflect the property of the entire sample. The broad nature of the PXD, IR and ^1H NMR spectra and the low solubility in all kinds of solvents suggest that the black material is polymeric.

The analytical data for the black solid [H, 2.74; C, 57.88; N, 13.23; (O, 26.15)%] is in fair agreement with the empirical formula $\text{C}_{15}\text{H}_9\text{N}_3\text{O}_5$: H, 2.92; C, 57.88; N, 13.50; O, 25.70%. The black solid that was obtained from a different pyrolysis experiment afforded nearly the same analytical data, confirming its reproducibility. The empirical formula $\text{C}_{15}\text{H}_9\text{N}_3\text{O}_5$ suggests that three molecules of H_2O are eliminated from the thermal decomposition of one molecule of **DA•dnba**. The black pigment obtained from **DA•pic** [reaction (2) in Scheme 1] was analyzed as C 53.09, H 2.16, N 15.59%. These analytical data can be approximated by the elemental composition $\text{C}_{14}\text{H}_{6.5}\text{N}_{3.5}\text{O}_6$, which requires C 52.59, H 2.05, N 15.33%, i.e. by (dopamine)₁(picric acid)₁-3 H_2O -0.5 NH_3 .

For comparison with the pyrolysis of cocrystal **DA•dnba**, pyrolysis of an equimolar mixture of **DA•HCl**, NaOH and **dnba** was carried out (reaction 3 in Scheme 1). A black solid (m.p. $>300^\circ\text{C}$), whose IR spectrum was very similar to that shown in Fig. 3(B), was obtained. However, the yield of the black solid was much lower (29 vs 81 wt%) and the elemental analysis was considerably different (H, 3.37; C, 56.71; N, 10.96% vs H, 2.74; C, 57.88; N, 13.23%). Furthermore, the yield of **1** was much higher (21% vs 1%), and the peak width of the DSC exotherm was much broader [Fig. 1(d) vs Fig. 1(a)]. Considering this difference in the DSC patterns, the crystal structure of the cocrystal **DA•dnba** may possibly

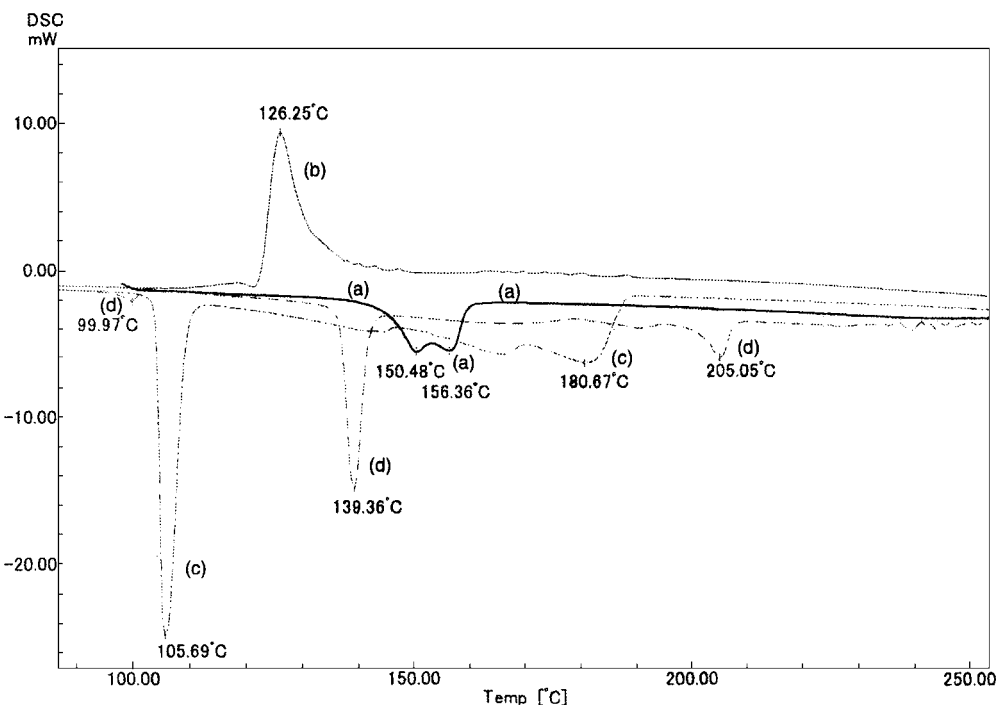
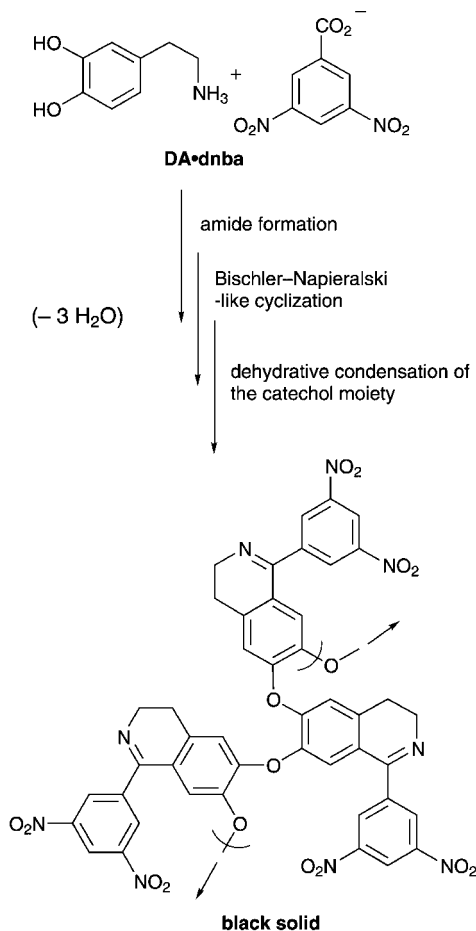


Figure 4. DSC traces for (a) a 1 : 1 mixture of **DA•HCl** and NaOH, (b) a 1 : 1 : 1 mixture of **DA•HCl**, NaOH and **dnbn**, (c) catechol and (d) a 1 : 1 mixture of catechol and **dnba**



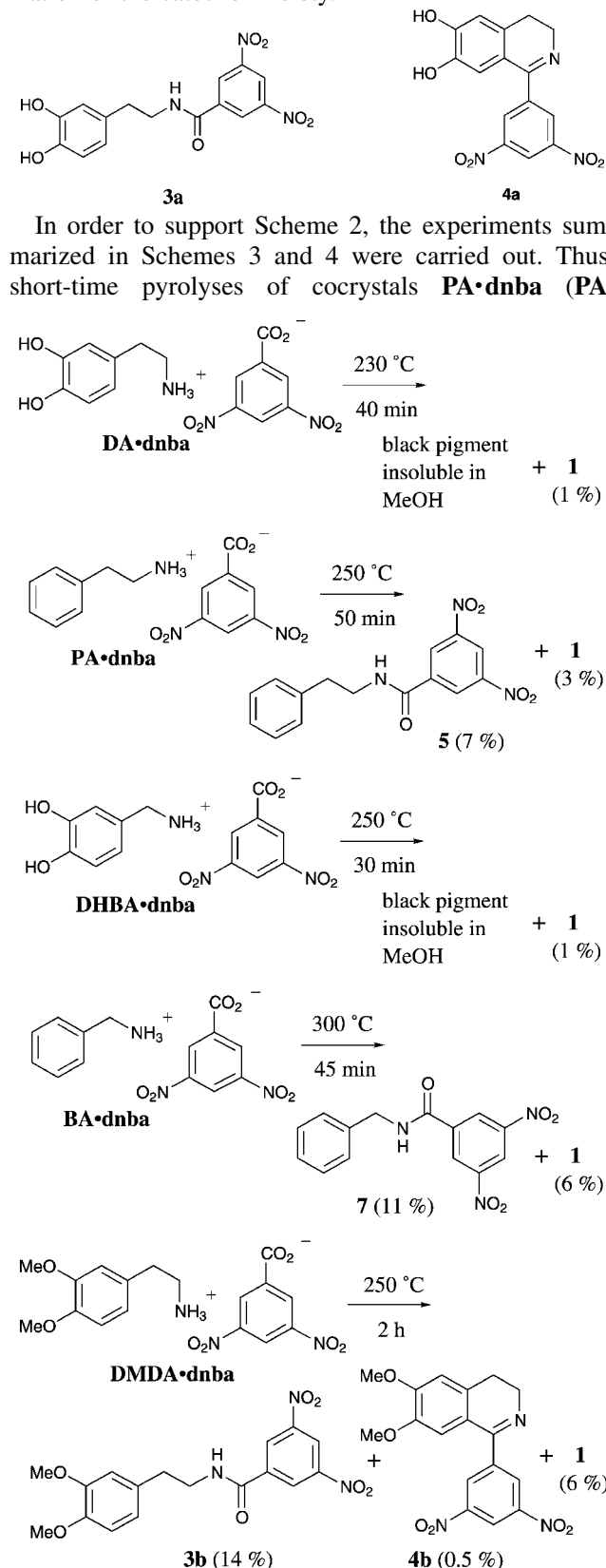
Scheme 2. A tentative scheme showing the formation of one possible structure for the black pigment that was produced from pyrolysis of cocrystal **DA•dnba**

be more or less favorable for the exothermic thermal reaction to occur (see below).

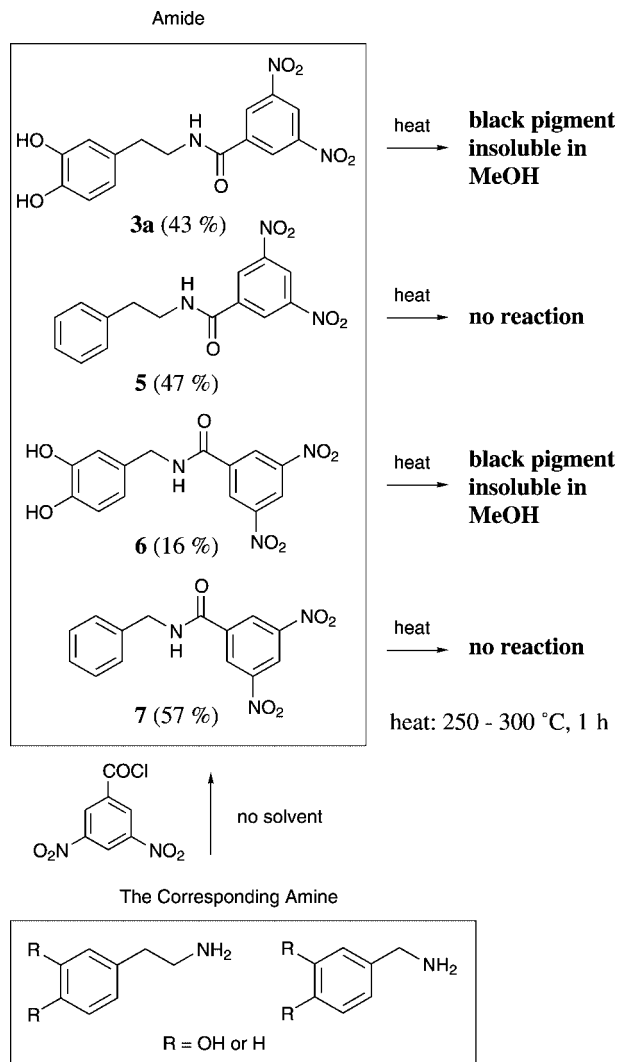
Thermal analyses of a 1:1 mixture of **DA•HCl** and NaOH, a 1:1:1 mixture of **DA•HCl**, NaOH and 3,5-dinitrobenzonitrile (**dnbn**), catechol, and a 1:1 mixture of catechol and **dnba** (Fig. 4) were also performed. Only a 1:1:1 mixture of **DA•HCl**, NaOH and **dnbn** exhibited an exotherm [Fig. 4(b)]. Therefore, it seems in view of the above thermal analyses (Figs 1, 2 and 4) that both a catechol moiety and an amino group of **DA** in addition to a strong electron acceptor such as **dnba**, **pic** and **dnbn** are required for the appearance of an exothermic peak. Compounds **3a**, **DHBA•dnba** and **6** showed an exothermic DSC peak, whereas **5**, **BA•dnba**, and **7** displayed only an endothermic peak. We are planning further thermochemical studies, including thermogravimetry.

As mentioned earlier, the elemental analysis of the black solid suggests that three molecules of H₂O are eliminated from the thermal decomposition of one molecule of **DA•dnba**. Although it may be too early to do so, Scheme 2 is presented as a tentative mechanism for the formation of the black solid. The mechanism involves the competing occurrence of three dehydration steps: amide formation (e.g. **DA•dnba** → **3a**), a Bischler-Napieralski-

like cyclization (e.g. **3a** → **4a**) and dehydrative polymerization of the catechol moiety.



Scheme 3. Short-time pyrolysis of **DA•dnba** and other related cocrystals **PA•dnba**, **DHBA•dnba**, **BA•dnba** and **DMDA•dnba**

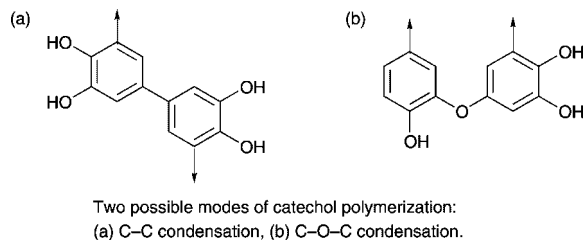


Scheme 4. Preparation and short-time pyrolysis of the relevant amides **3a**, **5**, **6** and **7**

β -phenylethylamine), **BA**•**dnba** (**BA**: benzylamine), and **DMDA**•**dnba** furnished the amides **5**, **7** and **3b** in reasonable yields (7, 11 and 14%, respectively), while similar short-time pyrolyses of cocrystals **DA**•**dnba** and **DHBA**•**dnba** (**DHBA**: 3,4-dihydroxybenzylamine) did not afford detectable amounts of the corresponding amides **3a** and **6** (Scheme 3). In the latter cases, only black solids were obtained. The unsuccessful detection of **3a** and **6** is probably due to their rapid thermal decomposition, because they contain a reactive catechol system in the molecule. In fact, the amides **3a** and **6** were prepared by an alternative method using 3,5-dinitrobenzoyl chloride and the amine, and these amides were found to be easily converted to black materials by short-time pyrolysis (Scheme 4). As a result, the amide formation upon pyrolysis of **DA**•**dnba** appears to be a true event. In addition, these pyrolysis data indicate that a catechol moiety is necessary for the production of a black pigment, since all the compounds having this moiety (**DA**•**dnba**, **DHBA**•**dnba**, **3a** and **6**) produced one (see Schemes 3 and 4).

We have no very strong evidence for the formation of the dihydroisoquinoline ring. However, pyrolysis of **DMDA**•**dnba** formed a 3,4-dihydroisoquinoline (**4b**), albeit in a trace quantity (0.5%, Scheme 3). Furthermore, the FAB mass spectra of the black solid, which were measured under several different conditions, always displayed a peak at m/z 329. These findings are consistent with the formation of the ring structure for 1-(3,5-dinitrophenyl)-6,7-dihydroxy-3,4-dihydroisoquinoline (**4a**) (m/z 329) upon pyrolysis of **DA**•**dnba**. It is known that the Bishler–Napieralski cyclization is promoted by substituting electron-releasing groups (e.g. OMe) on the β -phenethyl aryl ring.⁴

As stated above, production of 3-amino-5-nitrobenzoic acid (**1**) is a very minor reaction in the pyrolysis of **DA**•**dnba** (Scheme 1). Indeed, regardless of the pyrolysis time (~ 0.1 –5 h at a hot-plate temperature of 250 °C), the yield of **1** was constantly low ($\sim 1\%$). Interestingly, reduction of nitro-aromatics into amino-aromatics by the reaction with phenols or humic monomers and polymerization of catechols leading to humic substances are important reactions in the environment or in soil.^{8,15} Two possible modes for the catechol polymerization were considered to occur [see structures (a) and (b)]. Both modes are oxidative polymerization and are different from the dehydrative polymerization mode assumed in Scheme 2. It is likely that in the case of the pyrolysis of an equimolar mixture of **DA**•**HCl**, NaOH and **dnba**, the oxidative polymerization had substantially taken place, since the yield of **1** was much higher (21%). In the production of **1**, the nitro group of **dnba** was presumably reduced by the catechol and amino groups of **DA**.



X-ray crystallographic analyses of cocrystals **DA**•**dnba**,¹⁰ **DMDA**•**dnba**,¹¹ **PA**•**dnba** (S. Arimoto and Y. Ito, unpublished result), and **DA**•**HCl**¹³ have already been carried out. [Incidentally, we would like to mention that the solid-state conformation of the β -phenylethylamine component is *gauche perpendicular* for **DA**•**dnba**, **DMDA**•**dnba**, **DMDA**•**pic** (S. Ohba and Y. Ito, unpublished result), and **TA**•**pic**,¹² whereas it is *anti perpendicular* for **DA**•**HCl**¹³ and **PA**•**dnba**. At the binding site of dopamine receptors D₁ and D₂, **DA** is assumed to take a *trans coplanar* conformation,¹⁶ which is different from that observed in the crystal]. The shortest intermolecular distance between the ammonium nitrogen and the neighboring carboxylate carbon is 3.38 Å for **DA**•**dnba**, 3.50 Å for **DMDA**•**dnba**, and 3.51 Å for **PA**•**dnba**. The shortest intermolecular distance between the catechol oxygen is

Table 3. Analytical data for cocrystals^a

	Calc (%)			Found (%)		
	C	H	N	C	H	N
DA•dnba	49.32	4.14	11.50	49.23	4.06	11.47
DA•pic ^b	40.20	4.34	13.39	40.46	4.15	13.69
DMDA•dnba	51.91	4.87	10.68	51.67	4.81	10.69
DMDA•pic	46.83	4.42	13.65	47.07	4.47	13.35
TA•dnba	51.58	4.33	12.03	51.54	4.26	12.08
TA•pic	45.91	3.85	15.30	45.85	3.78	15.33
PA•dnba	54.05	4.54	12.61	54.09	4.67	12.61
BA•dnba	52.67	4.10	13.16	52.77	4.26	13.14
DHBA•dnba ^b	46.79	3.90	11.69	47.09	3.94	11.31

^a All the cocrystals, except **DA•pic** and **DHBA•dnba**, gave satisfactory C, H and N analyses (within $\pm 0.3\%$) as (amine)₁(nitro compound)₁.

^b Cocrystals **DA•pic** and **DHBA•dnba** contained water in the crystal: (**DA**)₁(**pic**)₁(H₂O)₂ and (**DHBA**)₁(**dnba**)₁(H₂O)_{0.45}.

4.65 Å for **DA•dnba** and 4.83 Å for **DA•HCl**. The fact that both intermolecular atomic distances are shortest for **DA•dnba** is compatible with the present result that **DA•dnba** has the highest thermal reactivity among these four cocrystals, since only **DA•dnba** displayed an exothermic DSC peak (Figs 1 and 2). Because of melting or disruption of the crystal structure, however, it is not clear to what extent the crystal structure controls the thermal reactivity of these crystals.

CONCLUSIONS

The cocrystal between dopamine and 3,5-dinitrobenzoic acid **DA•dnba** underwent a violent thermal reaction, giving a black solid. From inspection of the DSC patterns for **DA•dnba** and other compounds (Figs 1, 2 and 4), it was indicated that both a catechol moiety and an amino group of **DA** in addition to a strong electron acceptor such as **dnba**, picric acid (**pic**) and 3,5-dinitrobenzonitrile (**dnbn**) are required for appearance of an exothermic peak. Probably, the black solid was formed mainly from multiple dehydration reactions. Evidently, further studies such as thermogravimetric analysis and more structural elucidation of the black solid are needed to establish the mechanisms of the present thermal reactions of dopamine with electron acceptors.

EXPERIMENTAL

General procedures

DSC traces were recorded on a Shimadzu DSC-60 calorimeter at a scanning rate of 10 °C min⁻¹. DSC experiments were performed under a nitrogen atmosphere. IR, ¹H NMR, MS and UV/Vis spectra were measured with Shimadzu FTIR-8100A, JEOL EX-270J, JEOL JMS-HX 110A and Shimadzu UV-2400PC spectrometers, respectively. Powder x-ray diffraction (PXD) patterns were obtained with a MAC Science MX Labo

diffractometer using Cu K α radiation (1.5406 Å). For pyrolysis, the sample was placed in a 100 ml Erlenmeyer flask equipped with a water-cooled condenser and heated on a Barnstead hot-plate (Thermolyne Type 1900).

Materials

All the compounds used for preparation of cocrystals were purchased commercially. 3-Amino-5-nitrobenzoic acid (**1**) and picramic acid (**2**) were also commercially available.

Cocrystallization⁹

The solvents for cocrystallization, the melting-points of cocrystals and their analytical data are summarized in Tables 2 and 3. ¹H NMR spectra (in DMSO-*d*₆) of all the cocrystals were essentially a simple sum of the spectra of their components, confirming that the molar ratio of the corresponding amine and the nitro compound was 1 : 1 in the cocrystal. The IR spectra (in KBr) of the cocrystals were definitely different from the superposition of the spectra of the components. For example, the IR frequency for the CO₂H group of **dnba** at 1703 cm⁻¹ is missing in all the **dnba** cocrystals.

DA•dnba. A hot solution containing 1.188 g (5.03 mmol) of dopamine hydrobromide (**DA•HBr**) in EtOH (10 ml) was mixed with a hot solution containing 1.087 g (5.02 mmol) of 3,5-dinitrobenzoic acid (**dnba**) in EtOH (6 ml), then 5.0 ml of 1 M NaOH solution were added. The mixture was filtered and the filtrate was left for 2 days at room temperature. Orange prisms appeared and these were collected by filtration and *in vacuo* at room temperature. Yield, 1.36 g (60%); m.p. 221–229 °C (decomp.).

DA•pic. A hot solution containing 964 mg (4.98 mmol) of dopamine hydrochloride (**DA•HCl**) in water (10 ml)

was mixed with a hot solution containing 1.342 g (4.98 mmol) of picric acid (**pic**) in MeOH (27 ml). The mixture was filtered and the filtrate was left overnight at room temperature. Tiny yellow crystals appeared and these were collected by filtration and dried *in vacuo* at room temperature. Yield, 1.82 g (79%); m.p. 209–216 °C (decomp.) [lit.¹⁷ m.p. 189–190 °C (decomp.)].

DMDA•dnba. A hot solution containing 881 mg (4.15 mmol) of **dnba** in EtOH (20 ml) was mixed with a hot solution containing 752 mg (4.15 mmol) of homoveratrylamine (O,O'-dimethyldopamine, **DMDA**) in MeOH (25 ml). The mixture was filtered and the filtrate was left overnight at room temperature. Yellow plates appeared and these were collected by filtration and dried *in vacuo* at room temperature. Yield, 1.42 g (87%); m.p. 195–199 °C.

Other cocrystals were similarly prepared.

Pyrolysis

Pyrolysis of DA•dnba. A typical procedure is described in the text. When necessary, the yield of **1** was estimated from ¹H NMR analysis (in DMSO-*d*₆) of the pyrolysis mixture by adding nitromethane as the integration standard.

Pyrolysis of DA•pic. Cocrystals of **DA•pic** (218 mg) were heated on a hot-plate (250 °C) for 5 h. During this pyrolysis, the sample turned into a black solid and a substantial amount of an orange–yellow solid (ca 10 mg) was sublimed. The black reaction mixture was washed with hot MeOH several times to give a black residue (145 mg, 72 wt%, m.p. > 300 °C), with elemental analysis H, 2.13; C, 53.13; N, 15.62; (O, 29.12)%. From the ¹H NMR analysis (in DMSO-*d*₆), the orange–yellow sublimate was found to consist mainly of picramic acid (**2**) (8% yield), which was identified by direct comparison with a commercial sample.

Pyrolysis of an equimolar mixture of DA•HCl, NaOH and dnba. **DA•HCl** (103 mg, 0.53 mmol), NaOH (21 mg, 0.53 mmol) and **dnba** (115 mg, 0.53 mmol) were mixed in an agate mortar with a pestle for 10 min. The thermochemical behavior of this mixture was examined by DSC [Fig. 1(d)]. Then, pyrolysis was carried out on a hot-plate (230 °C) for 1 h. This pyrolysis mixture was washed with MeOH several times to give a black residue [58 mg (29%), m.p. > 300 °C], which was subjected to measurements of IR, ¹H NMR and UV/Vis spectra and to elemental analysis. The IR, ¹H NMR, and UV/Vis spectra were similar to those of the black sample obtained from pyrolysis of **DA•dnba**. The MeOH washing was subjected to preparative TLC on silica gel (1 : 1 MeOH–benzene), followed by preparative HPLC on Asahipak GS-320

(MeOH), to afford 21 mg (21%) of 3-amino-5-nitrobenzoic acid (**1**), whose ¹H NMR, IR and mass spectra were the same as those of a commercial sample.

Short-time pyrolyses of cocrystals DA•dnba, PA•dnba, DHBA•dnba, BA•dnba and DMDA•dnba. These pyrolyses were performed at 230–300 °C (hot-plate temperature) for 0.5–2 h. The results are summarized in Scheme 3. The reaction products were analyzed by ¹H NMR and HPLC. Amides **5**, **7** and **3b** and dihydroisoquinoline **4b** were detected from the pyrolysis mixture of the corresponding cocrystals, while the reduction product **1** was detected in all cases. Insoluble black pigments were formed from **DA•dnba** and **DHBA•dnba** and partly from **DMDA•dnba**. The conversions were high for **DA•dnba** and **DHBA•dnba**. For **PA•dnba**, **BA•dnba** and **DMDA•dnba**, the conversions were <50%.

Short-time pyrolyses of amides. The pyrolyses of the amides **3a**, **5**, **6** and **7** were carried out under conditions similar to those for the short-time pyrolyses of cocrystals described above. The results are summarized in Scheme 4. Amides containing a catechol moiety, **3a** and **6**, decomposed to give insoluble black pigments, whereas amides bearing no catechol moiety, **5** and **7**, gave with negligible reactions.

Preparation of amides and dihydroisoquinolines

Preparation of 3b, 5 and 7. All the amides produced upon pyrolysis above were prepared by alternative methods under solvent-free conditions.¹⁹ Thus, in order to obtain **3b**, **5** and **7**, the corresponding amine (5 mmol) and 3,5-dinitrobenzoyl chloride (2.5 mmol) were mixed in a porcelain mill with a pestle for 30 min. The reaction mixture was separated by column chromatography and/or by recrystallization with a suitable solvent, affording the amide of interest.

3b:²⁰ isolated by column chromatography (silica gel, 9 : 1 CHCl₃–acetone) followed by recrystallization with CHCl₃, yield 92%, m.p. 195–196 °C; ¹H NMR (DMSO-*d*₆), δ 9.23 (1 H, t, *J* = 7 Hz, NH), 9.02 (2 H, s, aromatic for the **dnba** moiety), 8.93 (1 H, s, aromatic for the **dnba** moiety), 6.85 (1 H, d, *J* = 8.5 Hz, aromatic), 6.84 (1 H, s, aromatic), 6.75 (1 H, d, *J* = 8.5 Hz, aromatic), 3.73 (3 H, s, CH₃O), 3.70 (3 H, s, CH₃O), 3.54 (2 H, q, *J* = 7 Hz, CH₂NH), 2.82 (2 H, t, *J* = 7 Hz, CH₂); IR (KBr), 1669 (C=O), 1542 (NO₂) cm⁻¹; MS (FAB, NBA) *m/z* (relative intensity, %) 376 [100, (M+ H)⁺], 375 (72, M⁺); HRMS, calculated for C₁₇H₁₇N₃O₇ 375.1067, found 375.1064. **5:** recrystallized with CHCl₃–acetone, yield 47%, m.p. 139–140 °C (lit.²¹ m.p. 150 °C). **7:** recrystallized with benzene, yield 57%, m.p. 202–203 °C (lit.²¹ m.p. 201 °C).

Preparation of 3a. Immediately after quick mixing of **DA·HCl**, 504 mg (2.61 mmol), with NaOH, 103 mg (2.61 mmol), in a porcelain mill, 301 mg (1.31 mmol) of 3,5-dinitrobenzoyl chloride were added. This mixture was further ground with a pestle for 30 min. The resultant mixture was dissolved in acetone (40 ml) and the insoluble residue was removed by filtration. To the filtrate was added benzene on a water-bath, until a milky precipitate appeared. After standing for 4 days at room temperature, *N*-[2-(3,4-dihydroxyphenyl)ethyl]-3,5-dinitrobenzamide (**3a**) was obtained as yellow crystals: yield 197 mg (43%), m.p. 256–260 °C (decomp.); ¹H NMR (DMSO-*d*₆), δ 9.23 (1 H, t, *J* = 7 Hz, NH), 9.11 (2 H, s, aromatic for the **dnba** moiety), 8.93 (1 H, s, aromatic for the **dnba** moiety), 8.75 (1 H, s, OH), 8.63 (1 H, s, OH), 6.63 (1 H, d, *J* = 8.5 Hz, aromatic), 6.59 (1 H, s, aromatic), 6.47 (1 H, d, *J* = 8.5 Hz, aromatic), 3.47 (2 H, q, *J* = 7 Hz, CH₂NH), 2.70 (2 H, t, *J* = 7 Hz, CH₂); IR (KBr), 3277, 3191, 1648 (C=O), 1540 (NO₂) cm⁻¹; MS (FAB, NBA), *m/z* (relative intensity, %) 348 [100, (M+H)⁺], 347 (43, M⁺); HRMS, calculated for C₁₅H₁₃N₃O₇ 347.0753, found 347.0754.

Preparation of 6. Likewise, *N*-(3,4-dihydroxybenzyl)-3,5-dinitrobenzamide (**6**) was prepared from 3,4-dihydroxybenzylamine hydrobromide, NaOH and 3,5-dinitrobenzoyl chloride by mixing in a porcelain mill: yield 16%, m.p. 235–248 °C (decomp.) (crystallized from MeOH–H₂O); ¹H NMR (DMSO-*d*₆), δ 9.60 (1 H, t, *J* = 7 Hz, NH), 9.09 (2 H, s, aromatic for the **dnba** moiety), 8.95 (1 H, s, aromatic for the **dnba** moiety), 8.87 (1 H, s, OH), 8.77 (1 H, s, OH), 6.73 (1 H, d, *J* = 8 Hz, aromatic), 6.67 (1 H, s, aromatic), 6.59 (1 H, d, *J* = 8 Hz, aromatic), 4.37 (2 H, d, *J* = 7 Hz, CH₂); IR (KBr), 3389, 3087, 1648 (C=O), 1546 (NO₂) cm⁻¹; HRMS, calculated for C₁₄H₁₁N₃O₇ 333.0597, found 333.0598.

Preparation of 4b. 6,7-Dimethoxy-1-(3,5-dinitrophenyl)-3,4-dihydroisoquinoline (**4b**) was prepared from dehydrative cyclization of amide **3b** in refluxing benzene in the presence of POCl₃ (Bischler–Napieralski reaction):²⁰ m.p. 154.5–155 °C (crystallized from MeOH); ¹H NMR (CDCl₃), δ 9.11 (1 H, s, aromatic for the **dnba** moiety), 8.86 (2 H, s, aromatic for the **dnba** moiety), 6.85

(1 H, s, aromatic), 6.63 (1 H, s, aromatic), 3.98 (3 H, s, CH₃O), 3.90 (2 H, t, *J* = 7.5 Hz, CH₂N), 3.75 (3 H, s, CH₃O), 2.77 (2 H, t, *J* = 7.5 Hz, CH₂). Preparation of 6,7-dihydroxy-1-(3,5-dinitrophenyl)-3,4-dihydroisoquinoline (**4a**) was unsuccessful.

REFERENCES

- Roth RH, Tarazi FI, Baldessarini RJ. In *Encyclopedia of Neuroscience*, vol. 1, Adelman G, Smith BH (eds). Elsevier: Amsterdam, 1999; 557–561, 561–565.
- (a) Pufulete M. *Chem. Br.* 1997; 31–35; (b) Martin C. *Chem. Br.* 1998; 40–42.
- Whaley WM, Govindachari TR. *Org. React. (N.Y.)* 1951; **6**: 151–190.
- Whaley WM, Govindachari TR. *Org. React. (N.Y.)* 1951; **6**: 74–150.
- Bentley KW. *The Isoquinoline Alkaloids*. Harwood Academic Publishers: Amsterdam, 1998; chap. 2.
- (a) Protá G, d'Ischia M, Napolitano A. In *The Pigmentary System*, Nordlund JJ, Boissy RE, Hearing VJ, King RA, Ortonne JP (eds). Oxford University Press: New York, 1998; chap. 24; (b) Herlinger E, Jameson RF, Linert W. *J. Chem. Soc., Perkin Trans. 2* 1995; 259–263.
- (a) Riley PA. *Int. J. Biochem. Cell Biol.* 1997; **29**: 1235–1239; (b) Waite JH. *Comp. Biochem. Physiol.* 1990; **97B**: 19–29.
- Sánchez-Cortés S, Francioso O, García-Ramos JV, Ciavatta C, Gessa C. *Colloids Surf. A* 2001; **176**: 177–184, and references cited therein.
- (a) Ito Y. *Synthesis* 1998; 1–32; (b) Ito Y. In *Organic Molecular Photochemistry*, Ramamurthy V, Schanze KS (eds). Marcel Dekker: New York, 1999; 1–70; (c) Ito Y, Hosomi H, Ohba S. *Tetrahedron* 2000; **56**: 6833–6844. (d) Ito Y, Fujita H. *Chem. Lett.* 2000; 288–289.
- Ohba S, Ito Y. *Acta Crystallogr., Sect. E* 2002; **58**: o586–o587.
- Ohba S, Ito Y. *Acta Crystallogr., Sect. E* 2002; **58**: o588–o589.
- Ohba S, Ito Y. *Acta Crystallogr., Sect. E* 2002; **58**: o584–o585.
- Giesecke J. *Acta Crystallogr., Sect. B* 1980; **36**: 178–181.
- The Merck Index* (12th edn). Merck: Rahway, NJ, 1996; 578.
- (a) Wang CJ, Thiele S, Bollag JM. *Arch. Environ. Contam. Toxicol.* 2002; **42**: 1–8; (b) Bruns-Nagel D, Knicker H, Drzyzga O, Bütehorn U, Steinbach K, Gemsa D, von Löw E. *Environ. Sci. Technol.* 2000; **34**: 1549–1556.
- (a) Aliste MP, Cassels BK. *J. Chem. Soc., Perkin Trans. 2* 2001; 906–915; (b) Wilcox RE, Tseng T, Brusniack MYK, Ginsburg B, Pearlman RS, Teeter M, DuRand C, Starr S, Neve KA. *J. Med. Chem.* 1998; **41**: 4385–4399; (c) Mottola DM, Laiter S, Watts VJ, Tropsha A, Wyrick SD, Nichols DE, Mailman R. *J. Med. Chem.* 1996; **39**: 285–296.
- Hahn G, Stiehl K. *Chem. Ber.* 1936; **69**: 2627–2654.
- Ahl A, Reichstein T. *Helv. Chim. Acta* 1944; **27**: 366–381.
- Ito Y, Horie S, Shindo Y. *Org. Lett.* 2001; **3**: 2411–2413.
- Jansen ABA, Hollywood J, Wilson AB. *Chem. Abstr.* 1974; **83**: 58672a.
- Berger J, Sørensen DA. *Acta Chem. Scand.* 1966; **20**: 2002–2004.