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Synthesis and Stereoisomerization of Intra- and Intermolecularly Bridged Indigo

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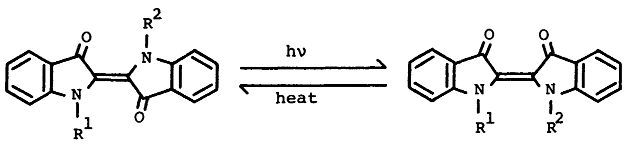
The intramolecularly bridged *N,N'*-azelaoylindigo (**3**) and *N,N'*-sebacoylindigo (**4**) have been synthesized from indigo and the corresponding dichloride. The intermolecularly bridged *N',N''*-sebacoylbis(*N*-acetylindigo) (**5**) has been synthesized from *N*-acetylindigo and sebacoyl dichloride. The relative rates of the cis-to-trans thermal isomerization of **3**, **4**, and **5**, compared with that of *N,N'*-diacetylindigo (**1c**), were as follows: **3**, 0.77; **4**, 3.9; **5**, 1.4; **1c**, 1.0.

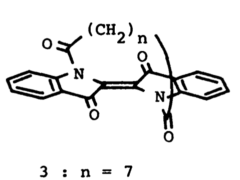
Trichochromes, which were isolated from the red feathers of New Hampshire chickens[1] and human red hair,[2] are low molecular melanin pigments, and are unique in exhibiting photochromism. During the course of an investigation of melanins, we have been interested in indigoid pigments as model compounds of trichochromes.

Indigo (**1a**), an indigoid pigment, exists in trans-form and cannot be isomerized into the corresponding cis-isomer even by irradiation,[3] owing to their photostability caused by a hydrogen-bonding[4] and/or a fast proton transfer in the excited state.[5] Therefore, *N,N'*-dimethyl-(**1b**)[6,7] and *N,N'*-diacetylindigo (**1c**)[3,8] show phototropic behavior, and the stereoisomerization of some *N,N'*-diacylindigo was described in our preceeding report.[9]

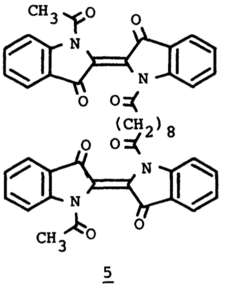


1a : $R^1 = R^2 = H$
1b : $R^1 = R^2 = CH_3$
1c : $R^1 = R^2 = COCH_3$

2 : $R^1 = R^2 = COCO$



3 : n = 7
4 : n = 8



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On the other hand, *N,N'*-oxalylindigo (**2**), which is an intramolecularly bridged indigo, exists only in the cis-form because of its conformational restriction.[8] Insertion of methylene groups between the two carbonyl carbons of the oxalyl group was expected to cause a relaxation of the restriction. Hence, the synthesis of *N,N'*-azelaoylindigo (**3**), *N,N'*-sebacoylindigo (**4**), and *N',N''*-sebacoylbis(*N*-acetylindigo) (**5**) were carried out, and the cis-to-trans thermal isomerization of these intra- and intermolecularly bridged indigos was investigated.

Results and Discussion

Synthesis of Intra- and Intermolecularly Bridged Indigo. By the reported method,[8] *N,N'*-oxalylindigo (**2**) was synthesized from indigo and oxalyl dichloride in nitrobenzene under mild conditions. Attempted synthesis of compound **3** or **4** by this method failed. These compounds were synthesized by the improved method of Posner.[10]

The structure of *N,N'*-azelaoylindigo (**3**) was confirmed by the IR spectrum which showed two characteristic carbonyl bands at 1670 and 1700 cm^{-1}, by the NMR spectrum which showed the peaks of the methylenic protons at δ=1.3—3.7 and peaks of the aromatic protons at δ=7.4—8.5 and by the elemental analysis. The visible spectrum showed that the absorption maximum of **3** was very similar to that of *N,N'*-diacetylindigo (**1c**) which existed in the trans-form rather than that of *N,N'*-oxalylindigo (**2**) which existed in the cis-form. Therefore the configuration of **3** was assumed to be the trans-form. Similarly the structure and configuration of *N,N'*-sebacoylindigo (**4**) was confirmed by its physical properties in Table 1.

The intermolecularly bridged *N', N''*-sebacoylbis(*N*-acetylindigo) (**5**) was synthesized from *N*-acetyl

TABLE 1. PHYSICAL PROPERTIES OF INTRA- AND INTERMOLECULARLY BRIDGED INDIGO

Compound	ν^{KBr}/cm^{-1} (C=O)	δ^{CDCl_3}	λ_{max}^{xylene}/nm (ε)
3	1670, 1700	1.3—3.7 (m, 14H), 7.4—8.5 (m, 8H)	569 (6490)
4	1670, 1700	1.1—3.5 (m, 16H), 7.2—8.3 (m, 8H)	572 (7700)
5	1680, 1690, 1710	0.7—3.0 (m, 16H), 2.5 (s, 6H), 7.1—8.5 (m, 16H)	566 (12500)
2	1660, 1695, 1710		439 (8590)
1c	1680, 1700		562 (6630)

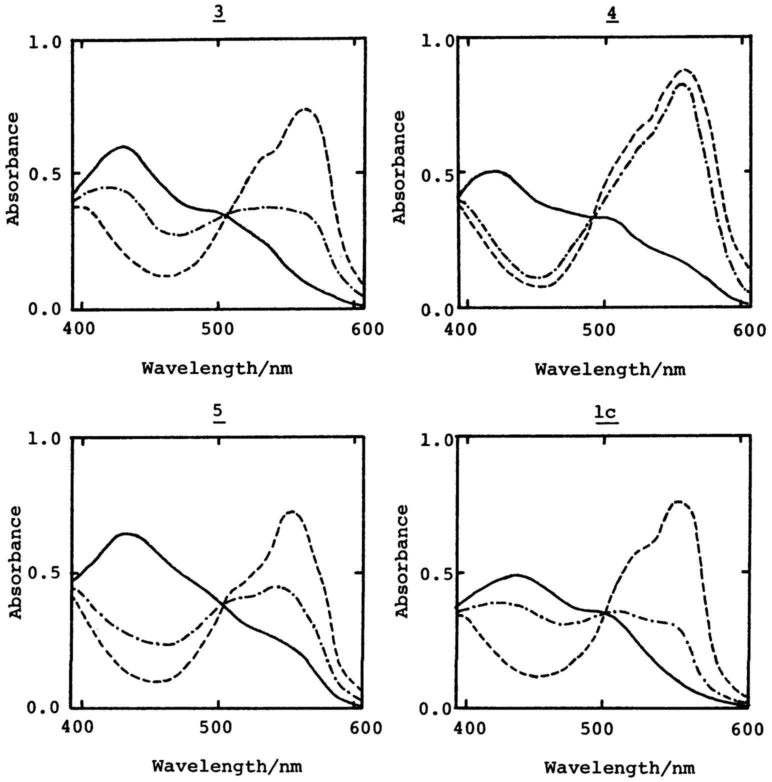

Fig. 1. The cis-to-trans change of the visible spectrum of **3**, **4**, and **5**. Compared with **1c**, after heating at 81.1 °C for 0 min, ——, 1.5 min, —·—·—, 5 min, ----.

Table 2. The cis-to-trans thermal isomerization rate constants (k) and relative rates (k_{rel})

Compound	k/s^{-1} a)	k_{rel} b)
3	1.1×10^{-3}	0.77
4	5.5×10^{-3}	3.9
5	1.8×10^{-3}	1.4
1c	1.4×10^{-3}	1.0

a) Measured in xylene at 81.8 °C. b) Compared with **1c**.

indigo[11] and sebacoyl dichloride.

Thermal cis-to-trans Isomerization of Intra- or Intermolecularly Bridged Indigo. The intramolecularly bridged indigo, **3** or **4**, and the intermolecularly bridged indigo, **5**, were dissolved in xylene and irradiated by a mercury lamp using a filter solution which cuts off the wavelength shorter than 550 nm. The color of the solution changed from red to yellow, accompanied by disappearance of the peak of the trans-form near 570 nm, and appearance of the peak of the cis-form near 440 nm. The change of the visible spectrum was measured as shown in Fig. 1, where the solution was heated, and the thermal cis-to-trans isomerization rates were measured at several wavelengths characteristic to the trans-isomer. The rate constants and the relative rates were calculated and are shown in Table 2.

From Fig. 1 and Table 2, the following facts can be pointed out: i) In the case of intramolecularly bridged indigo, the azelaoyl group neither accelerates nor decelerates the isomerization so much, compared with the acetyl group; ii) The sebacoyl group accelerates the isomerization extremely; iii) In the case of intermolecularly bridged indigo, the bridged sebacoyl substituent neither accelerates nor decelerates the isomerization.

It is of interest that a great difference between the isomerization rate of the two intramolecularly bridged indigo, **3** and **4**, was observed. This can be explained by the instability of **4** in the cis-form because of the strain caused by the highly populated methylene chain.

Also, in the intermolecularly bridged indigo **5**, the bridged substituent did not change the stability because there is no steric restriction.

Experimental

Melting points were measured by Micro Melting Point Apparatus (Yanagimoto Seisakusho) and uncorrected. The IR spectra were recorded on JASCO IRA-1 IR Spectrophotometer. The ^{1}H-NMR spectra were determined with Hitachi R-24 NMR Spectrometer. The visible spectra were recorded on a Shimadzu UV-365 UV-VIS-NIR Recording Spectrophotometer.

N,N′-*Diacetylindigo (1c).* Prepared by the method of Blanc and Ross.[12]

N,N′-*Oxalylindigo (2).* Prepared by the method of Wyman and Zenhäusern.[8]

N,N′-*Azelaoylindigo (3).* Indigo (262 mg) and azelaoyl dichloride (0.6 ml) were dissolved in an anhydrous pyridine (100 ml) and the mixture was heated in a sealed tube at 200 °C for 1 h. The reaction mixture was poured into hydrochloric acid (100 ml and water 300 ml) and extracted with dichloromethane. The organic layer was evaporated and purified first with benzene–ethyl acetate (10:1) on silica-gel column chromatography, and then with hexane–dichloromethane-acetonitrile (7:2:1) on silica gel (20×20 cm). The product was recrystallized from benzene-hexane to give purple plates. Yield 10%. Mp 228—230 °C. Found: C, 72.74; H, 5.61; N, 6.40%. Calcd for $C_{25}H_{22}N_2O_4$: C, 72.44; H, 5.35; N, 6.75%.

N,N′*-Sebacoylindigo (4).* Prepared from indigo (262 mg) and sebacoyl dichloride (0.8 ml). Yield 19%. Mp 262—264 °C. Found: C, 72.56; H, 5.68; N, 6.41%. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.64; N, 6.53%.

N*-Acetylindigo.* Prepared by the method previously reported.[11]

N′,N″*-Sebacoylbis(*N*-acetylindigo) (5).* A solution of *N*-acetylindigo (246 mg) was heated under reflux with stirring in an anhydrous pyridine (15 ml) and sebacoyl dichloride (193 mg) for 10 min. The reaction mixture was treated in the same manner in **3**. Yield 3%. Mp 120—121 °C. Found: C, 72.05; H, 5.10; N, 6.58%. Calcd for $C_{46}H_{38}N_4O_8$: C, 71.30; H, 4.94; N, 7.23%. It was difficult to remove the solvent from the specimen; calculation was taken into account of the solvent for $C_{46}H_{38}N_4O_8 \cdot 0.5\ C_6H_6$: C, 72.31; H, 5.08; N, 6.88%.

Thermal cis-to-trans Isomerization. The compound, **3**, **4**, **5**, or **1c** was dissolved in distilled xylene, the concentration being in the order of 10^{-4} mol/l. The solution was sealed in several ampoules, and was irradiated by a mercury lamp using a filter solution which cuts off the wavelength shorter than 550 nm until the solution reached a photostationary state, and kept in the dark at 81.8 °C. After 1.5 and 5 min., the solution was quenched in a dry ice-methanol mixture at −78 °C. The change of the visible spectrum in thermal cis-to-trans isomerization was recorded between 350 and 650 nm, by JASCO UVIDEC-1 UV and VIS Absorption Spectrometer. Furthermore, the increase of absorption at 560, 570, and 580 nm was recorded by the improved spectrophotometer (JASCO UVIDEC-100 III) and the rate constants were calculated.

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