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The Stereoisomerization of *N,N′*-Diacyl Derivatives of Indigo

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The *cis*-isomers of *N,N′*-diacylindigo (*e.g.*, *cis-N,N′*-diacetyl-, distearoyl-, dibenzoyl-, and bis(3,5-dinitrobenzoyl)-indigo) were found to separate out in a crystalline form from a solution of the corresponding *trans*-isomer upon irradiation. The kinetics of the *cis*-to-*trans* isomerization of these four *cis-N,N′*-diacylindigos was studied, the relative rates being 7.9, 11.0, 1.0, and 5.1 respectively. Several amines were found to accelerate the *cis*-to-*trans* isomerization in the order of: $Et_2NH>PrNH_2>Et_3N>i\text{-}Pr_2NH$ in the case of *cis-N,N′*-diacetylindigo and in the order of: $Et_2NH>i\text{-}Pr_2NH>PrNH_2>Et_3N$ in the case of *cis-N,N′*-dibenzoylindigo.

Photochemical and thermal isomerizations are of interest in the field of natural products, including retinal,[1] bilirubin,[2] phytochrome,[3] and trichochrome.[4] During the course of an investigation of melanins, we have interested indigoid pigments as model compounds of trichochromes.

Indigo is a *trans* compound: attempts to convert it photochemically to the corresponding *cis*-isomer have been unsuccessful.[5] This photostability was first explained by hydrogen-bonding,[6] and the explanation was substantiated by the observation that the *N,N′*-diacetyl-[5,7] and *N,N′*-dimethylindigo[8,9] show phototropic behavior. Wyman[10] later suggested the contribution of a fast proton transfer in the excited state, and also reported the existence of a photochemical equilibrium between *cis*- and *trans*-thioindigo in an inert solvent. Recently, the preparation and spectroscopic properties of a basic chromophore of thioindigo have been reported.[11]

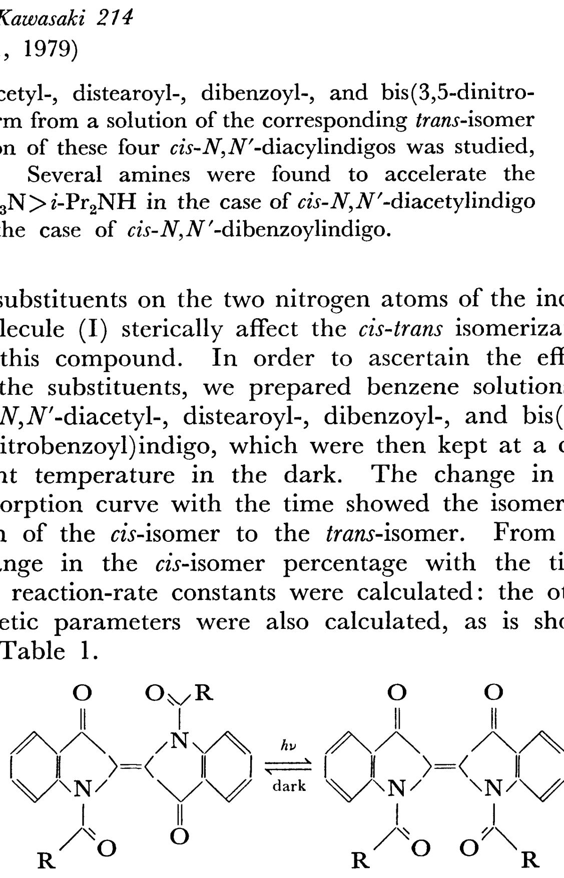
As far as indigo derivatives are concerned, the separation of the *cis*-isomer has been unsuccessful, while the isomerization of *cis-N,N′*-diacylindigo has not yet been examined. This paper will be concerned with the isolation of *cis*-isomers of *N,N′*-diacylindigo and with a kinetic study of the *cis*-to-*trans* isomerization in the dark as well as the effect of amines on the *cis*-to-*trans* isomerization of *N,N′*-diacylindigo.

Results and Discussion

Isolation of cis-N,N′-*Diacylindigo.* We found that *cis-N,N′*-diacetyl-, distearoyl-, dibenzoyl-, and bis(3,5-dinitrobenzoyl)indigo separated in crystalline form from a solution of the corresponding *trans*-isomer on irradiation. The yield of the *cis*-isomer was almost quantitative after repeated irradiation and concentration.

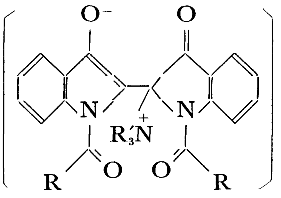
The structure of each *cis*-isomer was confirmed by elemental analyses and UV and IR spectra. The IR spectra show two carbonyl bands characteristic of the *cis*-isomer.[11] The UV spectrum of *cis-N,N′*-diacetylindigo was almost superimposable with the calculated spectrum.[12] All four *cis-N,N′*-diacylindigos changed quantitatively into the corresponding *trans*-isomers when dissolved in a solvent.

The cis-*to*-trans *Isomerization of* cis-N,N′-*Diacylindigo.* It is generally accepted that the size and the structure of substituents on the two nitrogen atoms of the indigo molecule (I) sterically affect the *cis-trans* isomerization of this compound. In order to ascertain the effects of the substituents, we prepared benzene solutions of *cis-N,N′*-diacetyl-, distearoyl-, dibenzoyl-, and bis(3,5-dinitrobenzoyl)indigo, which were then kept at a constant temperature in the dark. The change in the absorption curve with the time showed the isomerization of the *cis*-isomer to the *trans*-isomer. From the change in the *cis*-isomer percentage with the time, the reaction-rate constants were calculated: the other kinetic parameters were also calculated, as is shown in Table 1.



I II

a. $R=CH_3$ b. $R=CH_3(CH_2)_{16}$ c. $R=C_6H_5$
d. $R=3,5\text{-}(NO_2)_2C_6H_3$



III

The relative rate shows that alkyl substituents correspond to a faster rate than do the aryl substituents. The value of the activation free energy is almost 20 kcal/mol, while the activation energy is between 19 and 23 kcal/mol. The value of the activation energy is far less than that of stilbene, 42.8 kcal/mol,[13] or methyl cinnamate, 41.6 kcal/mol.[14] Substituents on stilbene decrease the activation energy.[15] These facts reveal that *cis-N,N′*-diacylindigos are less stable than *cis*-stilbene or *cis*-cinnamate because the structure of the latter can be planar.

Effects of Amines on the cis-*to*-trans *Isomerization of* cis-N,N′-*Diacylindigo.* We found that amines accelerate the *cis*-to-*trans* (IIa to Ia) isomerization of *cis-N,N′*-diacetylindigo. In order to clarify the rela-

TABLE 1. KINETIC DATA FOR *cis*-TO-*trans* ISOMERIZATION OF *cis-N,N'*-DIACYLINDIGOS (IIa—d)

II	$k^{a)}$ / s^{-1}	Rel. rate	ΔG^{*} a) / kcal/mol	E_a / kcal/mol	ΔH^{*} / kcal/mol
a	4.92×10^{-4}	7.9	23.5	19.5	18.8
b	6.84×10^{-4}	11.0	23.3	19.9	19.2
c	6.21×10^{-5}	1.0	24.5	23.1	22.4
d	3.14×10^{-4}	5.1	23.8	19.4	18.8

a) At 45.2 °C.

TABLE 2. RELATIVE RATES OF *cis*-TO-*trans* ISOMERIZATION OF *cis-N,N'*-DIACETYL- AND DIBENZOYLINDIGO IN THE PRESENCE OF AMINES

Amine$^{a)}$	Diacetylindigo$^{b)}$	Dibenzoylindigo$^{c)}$
Et_3N	3.7	1.0
i-Pr_2NH	3.4	1.7
Et_2NH	18.2	6.1
$PrNH_2$	14.7	1.5
$PhNH_2$	1.1	1.0
None	1.0	1.0

a) Equimolar amount of amines. b) At 25.0 °C. c) At 50.0 °C.

tion between the effectiveness and the amount of amines for the *cis*-to-*trans* isomerization, the rate was measured in the presence of an equimolar amount of triethylamine under various concentrations. The reaction was found to be pseudo-first-order for the indigo, and the amine concentration was constant during the reaction. These facts reveal that the amine acts as a catalyst.

Also, the observed reaction rate constant was proportional to the concentration of triethylamine. This suggests that equimolar amounts of the indigo and the amine make up the reaction intermediate (III).

Furthermore, the effects of several kinds of amines were compared in the case of *cis-N,N'*-diacetylindigo (IIa) as well as in the case of *cis-N,N'*-dibenzoylindigo (IIc). Their relative rates are summarized in Table 2. It can be concluded that the order of acceleration by these amines is roughly in accord with the basicity of the amines except when steric hindrance plays an important role, as in the case of diisopropylamine or triethylamine.

Experimental

trans-*N,N'-Diacetylindigo (Ia).* Ia was prepared by the modified method reported by Blanc and Ross[12] and was recrystallized from benzene: mp 256—257 °C. IR (KBr): 1690, 1680, 1595 cm^{-1}. UV (C_6H_6) max: 562 nm (ε 7000).

trans-*N,N'-Distearoylindigo (Ib).* A mixture of indigo (1.0 g) and stearoyl chloride (11.6 g) in pyridine (10 ml) was refluxed for 20 min to give Ib, which was then recrystallized from petroleum ether: 28% yield: mp 101—102 °C. IR (KBr): 1690, 1670, 1600 cm^{-1}. UV (C_6H_6) max: 567 nm (ε 7100). Found: C, 78.28; H, 9.65; N, 3.43%. Calcd for $C_{52}H_{78}N_2O_4$: C, 78.54; H, 9.88; N, 3.52%.

trans-*N,N'-Dibenzoylindigo (Ic).* Ic was prepared by the modified method reported by Posner.[12b] Mp 256—257 °C. IR (KBr): 1700, 1660, 1590 cm^{-1}. UV (C_6H_6) max: 574 nm (ε 7700).

trans-*Bis(3,5-dinitrobenzoyl)indigo (Id).* Id was prepared from indigo (1.0 g) and 3,5-dinitrobenzoyl chloride (8.89 g) and was recrystallized from hexane–chloroform. 50% yield. Mp 249—252 °C. IR (KBr): 1700, 1680, 1620, 1600, 1550, 1345 cm^{-1}. UV (C_6H_6) max: 552 nm (ε 6200). Found: C, 55.38; H, 2.14; N, 12.23%. Calcd for $C_{30}H_{14}N_6O_{12}$: C, 55.39; H, 2.16; N, 12.92%.

General Method for the Isolation of cis-*N,N'-Diacylindigo.* The *trans*-isomer was dissolved in a slightly soluble solvent, such as benzene, petroleum ether, or hexane, and was then irradiated with visible light, the wave length being more than 550 nm, the light source being a mercury lamp (100 W), and the filter solution being cobalt sulfate 60 g+potassium chromate 3.24 g+sodium carbonate 12 g/750 ml water, for an appropriate period. This afforded precipitates of the corresponding *cis*-isomer.

cis-*N,N'-Diacetylindigo (IIa).* Ia was dissolved in benzene by heating, and then an equivalent volume of hexane was added (5×10^{-4} mol/l). The solution was irradiated with visible light for 5 h. Crimson needles; mp 244—246 °C. IR (KBr): 1720, 1690, 1590 cm^{-1}. UV (C_6H_6) max: 438 nm (ε 4500). Found: C, 69.29; H, 3.95; N, 7.99%. Calcd for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.08%.

cis-*N,N'-Distearoylindigo (IIb).* Ib was dissolved in petroleum ether by heating, and an approximately saturated solution was irradiated by visible light for 30 min. Orange needles; mp 101—103 °C. IR (KBr): 1720, 1700, 1600 cm^{-1}. UV (C_6H_6) max: 435 nm (ε 3900). Found: C, 78.58; H, 9.92; N, 3.48%. Calcd for $C_{52}H_{78}N_2O_4$: C, 78.54; H, 9.88; N, 3.52%.

cis-*N,N'-Dibenzoylindigo (IIc).* Ic was dissolved in benzene by heating, and then petroleum ether was added to the mixture. After cooling, precipitates were filtered off, and the filtrate was irradiated with visible light for 10 h: mp 245—247 °C. IR (KBr): 1725, 1675, 1595 cm^{-1}. UV (C_6H_6) max: 460 nm (ε 3900). Found: C, 76.01; H, 3.71; N, 5.82%. Calcd for $C_{30}H_{18}N_2O_4$: C, 76.58; H, 3.85; N, 5.95%.

cis-*N,N'-Bis(3,5-dinitrobenzoyl)indigo (IId).* Id was dissolved in benzene by heating (4×10^{-4} mol/l), and then the solution was irradiated with visible light for 4 h to afford orange needles; mp 205—210 °C. IR (KBr): 1730, 1680, 1620, 1600, 1540, 1340 cm^{-1}. UV (C_6H_6) max: 436 nm (ε 2800). Found: C, 55.93; H, 2.18; N, 12.48%. Calcd for $C_{30}H_{14}N_6O_{12}$: C, 55.39; H, 2.16; N, 12.92%.

Kinetics for the cis-*to*-trans *Isomerization of* N,N'-*Diacylindigo.* The *cis*-isomer was dissolved in benzene, the concentration being in the order of 10^{-4} mol/l. The sample solution was sealed in several ampoules, each aliquot being 3 ml. Each ampoule was wrapped in aluminum foil and kept in a thermostat. After an appropriate time, each ampoule was pulled out from the thermostat and the *cis*-isomer percentage was measured from the change in the visible absorption curve of each ampoule solution. From the change in the *cis*-isomer percentage with the time pseudo-first-order rate constant, k, was calculated at 45.2 °C, from which the activation free energy, ΔG^{*}, was subsequently calculated. The activation enthalpy, ΔH^{*}, was derived from the activation energy, E_a, which was itself calculated from the rate constants at different temperatures, 45.2 °C and 54.6 °C.

Acceleration Effect of Amines on the cis-*to*-trans *Isomerization of* cis-*N,N'-Diacetylindigo.* *Concentration of Amines*: A benzene solution (5 ml) of *cis*-*N*,*N′*-diacetylindigo (IIa) with a concentration of 6.54×10^{-4}, 7.52×10^{-4}, 8.18×10^{-4}, and 1.02×10^{-3} mol/l, and a benzene solution of triethylamine with an equivalent mol/l concentration were prepared. Each indigo solution was mixed with 5 ml of a triethylamine solution of the corresponding concentration. Then the absorbance at 562 nm was scanned by the recorder at time intervals of 15 min. For each concentration, the rate constants were found to be 3.85×10^{-5}, 4.90×10^{-5}, 5.74×10^{-5}, and $7.74\times10^{-5}/\text{s}^{-1}$.

Acceleration Effect and Structure of Amines. The relation between the acceleration effect and the structures of the amines was examined by measuring the reaction rate of the *cis*-to-*trans* isomerization of *cis*-*N*,*N′*-diacetylindigo or *cis*-*N*,*N′*-dibenzoylindigo in a benzene solution to which an equimolar amount of each amine had been added.

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