HETEROCYCLES, Vol 19, No 11, 1982

HINDERED ROTATION IN 2-ARYLINDOLINES. ISOLATION OF DIASTEREOMERIC ATROPISOMERS

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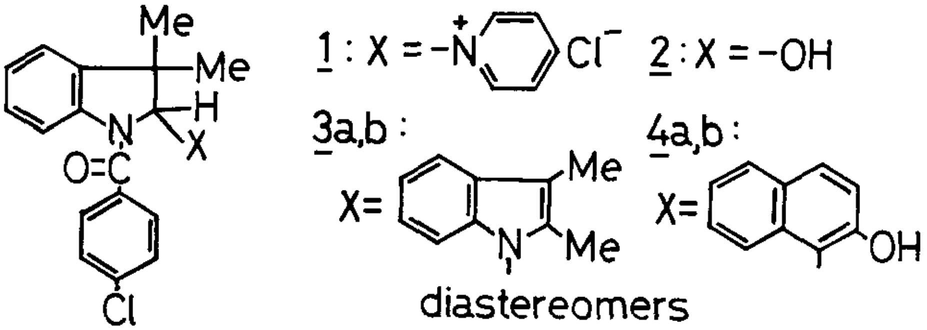
Abstract —— The condensation reaction of 1-(p-chlorobenzoyl)-2-hydroxy-3,3-dimethylindoline with β-naphthol gave a pair of diastereomeric atropisomers due to restricted rotation about an sp^3-sp^2 carbon bond.

During the course of a research on 3H-indole derivatives , two of the authors reported that the pyrolysis of 1-(p-chlorobenzoyl)-3,3-dimethylindolin-2-yl pyridinium chloride (1) afforded two isomeric compounds of molecular formula $C_{27}H_{25}ClN_2O$ which were tentatively assigned as geometrical isomers.[1] Warnhoff and co-workers reexamined the structure of the two compounds and proposed that they are diastereomers 3a and 3b.[2] However, the spectral data could not completely exclude another possibility of the geometrical isomerism resulting from restricted rotation about the amide bond. Thus, we have elucidated the crystal structures[3] of compounds 3a and 3b and confirmed them to be actually atropisomers as suggested by Warnhoff et al.[2] Additional examples of stable atropisomers were provided by extensive works of Ōki[4] on other series of compounds.

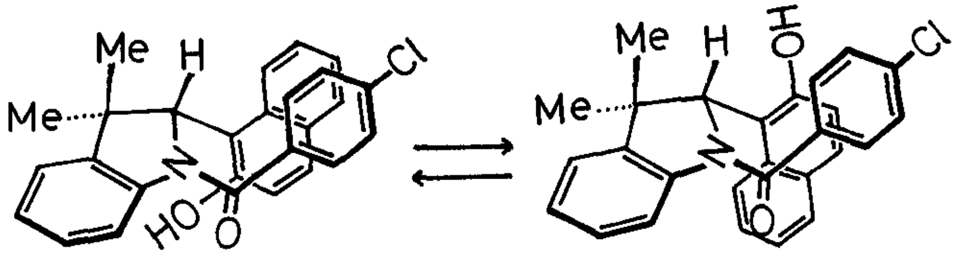
In this situation, further progress is desirable in the field of indoline deriva-



tives where the first success has been recorded.[2,3] In this paper, we wish to communicate another successful isolation of a pair of atropisomeric diastereomers of an indoline derivative whose atropisomerism originates from prevention of rotation about sp^3-sp^2 carbon bond.

Condensation of 1-(p-chlorobenzoyl)-2-hydroxy-3,3-dimethylindoline(2) with β-naphthol using $BF_3 \cdot Et_2O$ as a catalyst in dioxane gave a mixture of two isomeric compounds, 4a and 4b, in a ratio of 1.0:1.6.[5] The isomers were easily separated by chromatography on silica-gel, showing a different R_f value[6] of 0.27 for 4a and 0.14 for 4b. Removal of the bulky group of p-chlorobenzoyl moiety by alkaline hydrolysis of the two compounds gave the same product, racemic 2-(2'-hydroxynaphthyl)-3,3-dimethylindoline, mp 223-225 °C.

Heating of each isomer in dioxane at 80 °C for a few hours resulted in an equilibrium mixture of the two isomers. Figure 1 shows the change in the composition of the isomers by isomerization of pure materials[7] as a function of time upon heating.



4a 4b

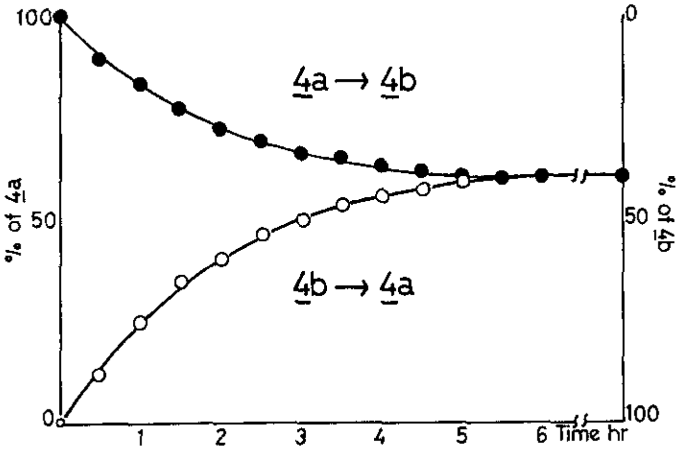


Figure 1. Rate of isomerization, 4a ⇄ 4b in dioxane at 80 °C.

The ratio at eqilibrium was 1.5 in favor of 4a. The first-order rate constants of conversion were obtained from these data: $k_1 = 6.6 \times 10^{-5}$ sec^{-1} for 4a → 4b and $k_{-1} = 1.0 \times 10^{-4}$ sec^{-1} for 4b → 4a. The equilibrium constant K = 0.65 for 4a ⇄ 4b was established by several experiments starting from each of the pure isomers.[8] These facts indicate that the unstable 4b is formed preferentially, suggesting the formation of 4b being kinetically controlled.

The ^1H NMR spectra of these pure isomers are shown in Figure 2. Possible conformations of the two diastereomers are illustrated on the basis of the X-ray results of 3a and 3b. Rotation about the bond linking the naphthyl group to the indoline ring is hindered by steric interactions of the naphthyl moiety with the adjacent substituents, mainly with the 1-acyl moiety. As a result, the singlet for the C_a methine of 4a, which locates in the effective deshielding zone of the naphthalene ring, appears at 6.22 ppm, moderately downfield from the chemical shift of 4b at 5.99 ppm. Compounds 4a and 4b appear to have an almost same conformation except the moiety of naphthyl group. This is deduced from the fact that H_b at ca. 8.2 ppm has suffered a considerable downfield shift in comparison with other aromatic protons, deshielded apparently by the amide carbonyl. Compound 4a exhibited an anisotropic influence

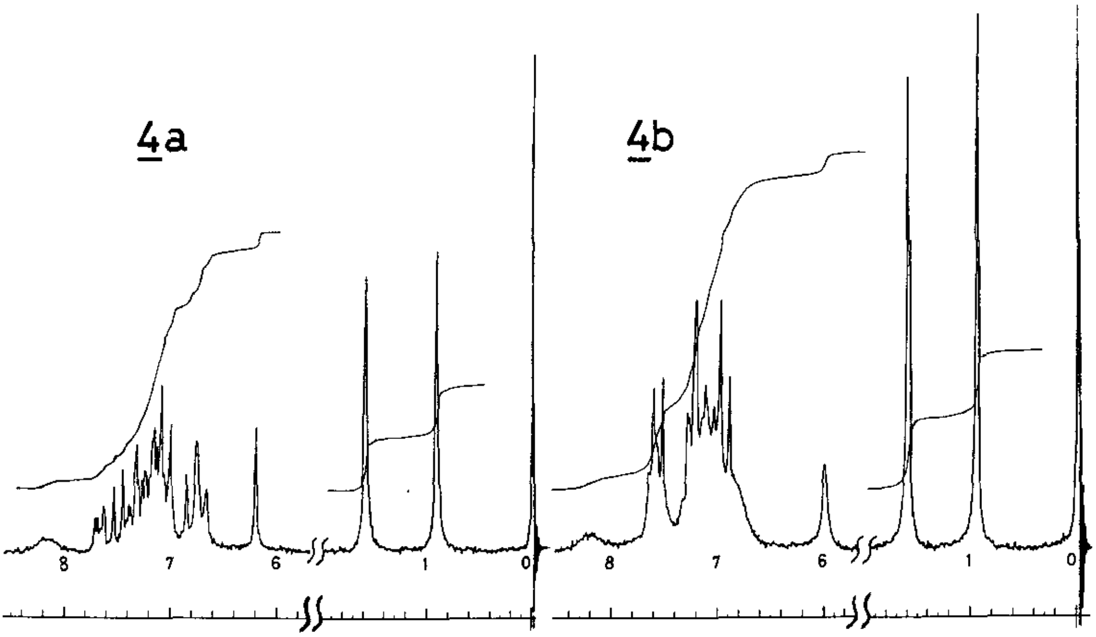


Figure 2. ^1H NMR spectra of 4a and 4b.

of the naphthalene-ring proton signals because of the p-chlorophenyl ring-current effect. These spectral behaviors are similar to those observed in 3a and 3b. These data allow the confident stereochemical assignment of 4a to the stable isomer and 4b to the unstable one.

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5. 4a: yield 29 %; plates; IR ($\nu^{\text{nujol}}_{\text{cm}^{-1}}$) 3150 (OH), 1620 (N-C=O); mp 272.0-272.3 °C. 4b: yield 45 %; prisms; IR ($\nu^{\text{nujol}}_{\text{cm}^{-1}}$) 3230 (OH), 1624 (N-C=O). A sample of 4b begins to liquefy at ca. 210 °C, but a clear melt does not result. It solidifies gradually on heating to isomerize to 4a with the change of prisms to plates and melts completely at 272.5-273.0 °C.

   The phenolic proton signals of 4a and 4b in ^{1}H NMR spectra in $CDCl_3$ appear as a sharp singlet at 9.66 and 9.62 ppm, respectively, slightly downfield in contrast to that of β-naphthol.
6. The values are obtained in benzene-ethyl acetate (10:1) solvent system on silica gel F254 plate containing a fluorescent indicater (Merck).
7. Thin-layer chromatographic analyses were performed with a Shimazu CS-920 High Speed TLC Scanner.
8. The activation energy was obtained by measuring the rate of conversion of 4b to the equilibrium mixture at 60, 75, and 80 °C. The data are as follows: $k_{-1} = 1.01 \times 10^{-5}$ sec^{-1} (60 °C); $k_{-1} = 4.39 \times 10^{-5}$ sec^{-1} (75 °C); $k_{-1} = 1.02 \times 10^{-4}$ sec^{-1} (80°C); $E_a = 26 \pm 2$ kcal/mol.

Received, 6th May, 1982