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Coupling Reaction of 2-Hydroxyindoline with Arenes by $BF_3 \cdot Et_2O$. A Convenient Synthetic Method of Isolable Diastereomeric Atropisomers

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A simple method for synthesis of 2-aryl-substituted 3,3-dimethylindoline derivatives was established by the reaction of 1-acyl-2-hydroxy-3,3-dimethylindoline with electron-rich arenes in the presence of boron trifluoride-diethyl ether in dioxane. In the reaction with β-naphthol, a pair of isolable diastereomeric atropisomers was isolated. The conformations of both atropisomers were determined by single crystal X-ray analyses. The substitution reaction behavior toward various arenes was accounted for in terms of frontier molecular orbital (FMO) theory.

Keywords 2-hydroxyindoline; electrophilic substitution; arylation; atropisomer; boron trifluoride-diethyl ether; catalysis; 3,3-dimethyl-3*H*-indole; molecular orbital

In the previous papers,[1a] we have communicated a simple method for synthesis of 2-aryl substituted indoline derivatives, based on condensation of 1-acyl-2-hydroxy-3,3-dialkylindoline with various electron-rich aromatic compounds in the presence of boron trifluoride-diethyl ether ($BF_3 \cdot Et_2O$). The reaction proceeded under very mild reaction conditions and provides a very important method for synthesis of isolable diastereomeric atropisomers[1b] arising from restricted rotation about a Csp^3–Csp^2 bond.[2]

These results are discussed here in detail in comparison with previous work[1b] and with additional data that we have obtained.

Results and Discussion

Coupling of 1-(4-Chlorobenzoyl)-2-hydroxy-3,3-dimethylindoline (3) with Various Arenes The electrophile, 1-(4-chlorobenzoyl)-2-hydroxy-3,3-dimethylindoline[3] (**3**) was easily prepared by addition of 4-chlorobenzoyl chloride to 3,3-dimethyl-3*H*-indole (**1**) followed by treatment of the adduct (**2**) with H_2O. Various aromatic compounds (**4**) were allowed to react with **3** using 1.2 eq of $BF_3 \cdot Et_2O$ as a catalyst in dioxane, and coupling products (**5**) were obtained by chromatography on silica gel. The reaction conditions and the compositions of the reaction products are summarized in Table I. As can be seen in Table I, arenes (**4**) bearing electron-donating substituents readily coupled with **3** to give the corresponding coupling products (**5**). On the other hand, the reaction of **3** with toluene (**4c**) or electron-deficient arenes such as 4-nitrophenol (**4d**) did not produce the coupling products but 1-(4-chlorobenzoyl)-2,3-dimethylindole (**6**), which presumably resulted from a Wagner–Meerwein type rearrangement reaction.[4] In the reaction of toluene (**4c**), a small amount of an indole dimer (**7c**) was obtained.

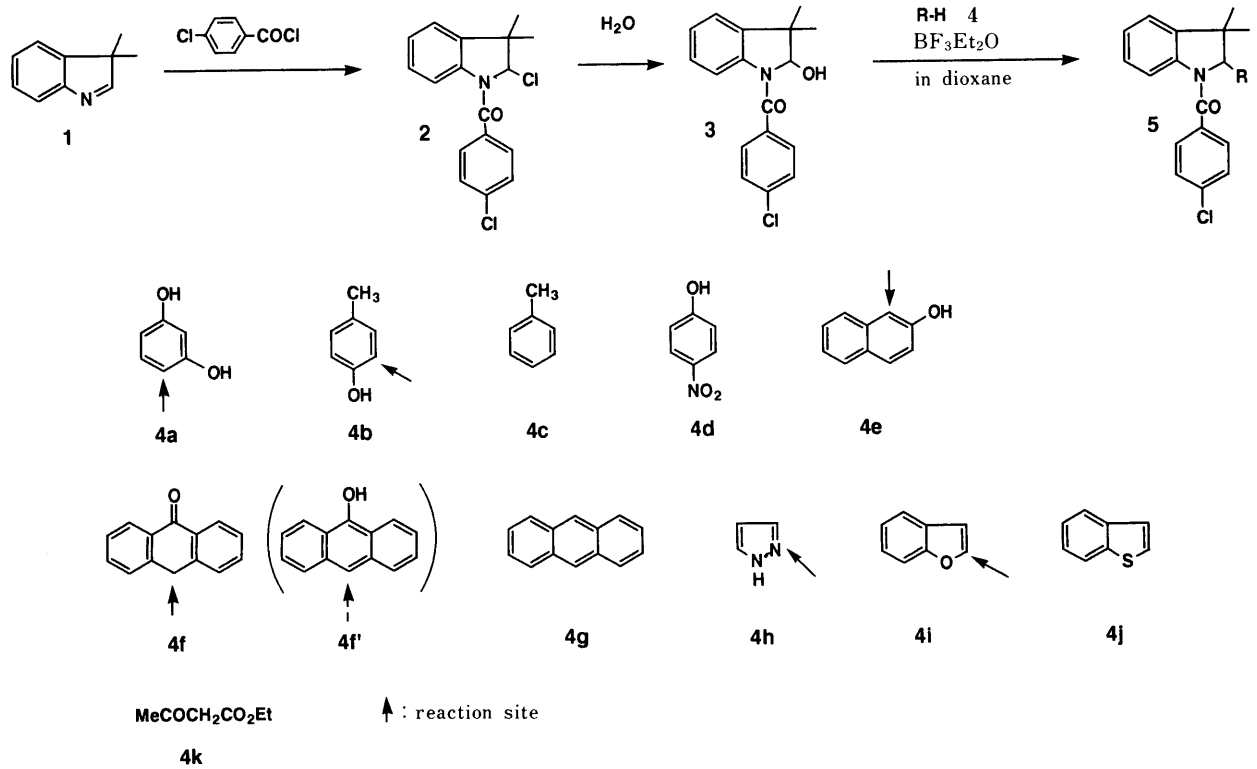


Chart 1

TABLE I. Products Derived from Reaction of 1-(4-Chlorobenzoyl)-2-hydroxy-3,3-dimethylindole (**3**) with Arenes in the Presence of $BF_3 \cdot Et_2O$

Arene, compd No.	Reaction conditions[a]		Product (%)	
	Temp. (°C)	Time (h)	Electrophilic substitution	Wagner–Meerwein rearrangement
Resorcinol, **4a**	40	10	**5a** (100)	
p-Cresole, **4b**	60	72	**5b** (40)	**6** (48)
Toluene, **4c**	55	312	**5c** (2)	**6** (72)
			7c (6)[b]	
p-Nitrophenol, **4d**	Reflux	30		**6** (80)
β-Naphthol, **4e**	50	216	**5e** (29)	**6** (12)
			5e' (45)	
Anthrone, **4f**	40	10	**5f** (77)	**6** (10)
Anthracene, **4g**	Reflux	30		**6** (86)
Pyrazole, **4h**	60	30	**5h** (43)	**6** (35)
Benzofuran, **4i**	70	31	**5i** (42)	**6** (40)
Benzothiophene, **4j**	Reflux	30		**6** (80)
Ethyl acetoacetate, **4k**				**6** (73)

a) In dioxane. *b*) A coupling product of **6** with **3** from the MS data.

The structural determination of the products (**5**) was made on the basis of comparison of the proton-nuclear magnetic resonance (^{1}H-NMR) spectra of **5** with those of structurally similar compounds. The spectral data are summarized in Table II. The 1-(4-chlorobenzoyl)-3,3-dimethylindoline moiety of the coupling products (**5**) showed a common spectral pattern. In the ^{1}H-NMR spectra of **5**, two C_3-methyl proton signals appeared as singlets at 0.80—1.60 ppm and the methine proton at the 2-position appeared as a singlet at 4.70—6.30 ppm. Aromatic protons at the **4**, **5** and **6** positions resonated at 6.90—7.40 ppm. The proton at the 7-position appeared as a broad doublet at 7.70—8.20 ppm, which is deshielded by the amide carbonyl function of the 4-chlorobenzoyl moiety. The aromatic protons on the 4-chlorobenzoyl group of **5** are observed as an AB quartet. The infrared (IR) spectra of **5** exhibited a strong carbonyl absorption band at 1620—1640 cm^{-1}. The mass spectra (MS) of **5** show a characteristic fragmentation

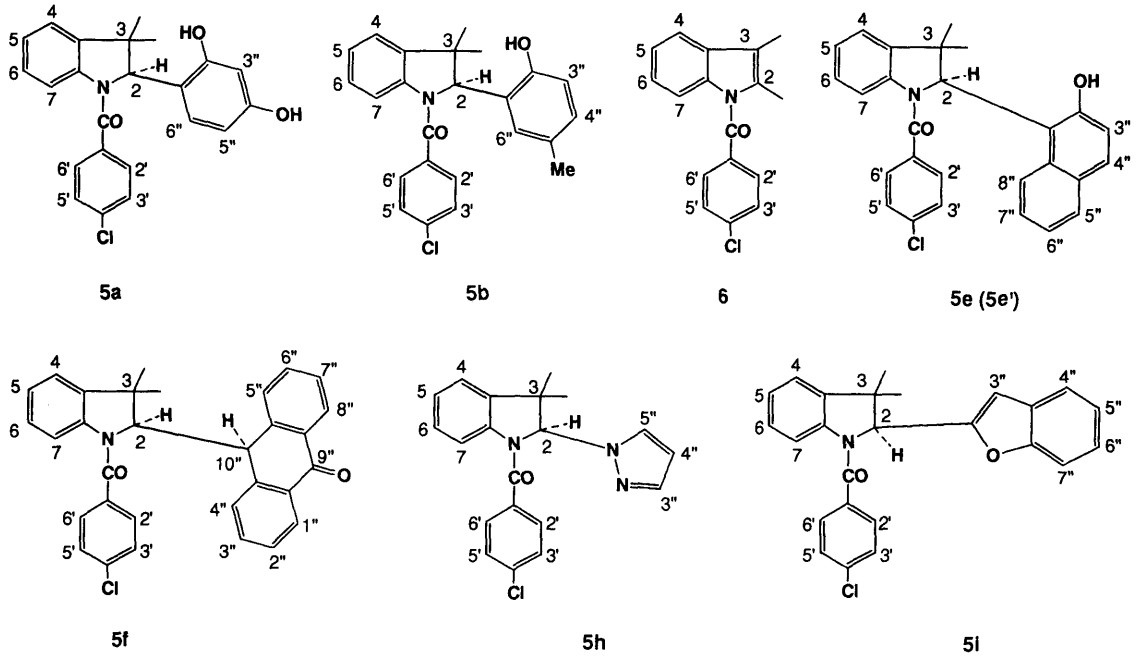


Chart 2

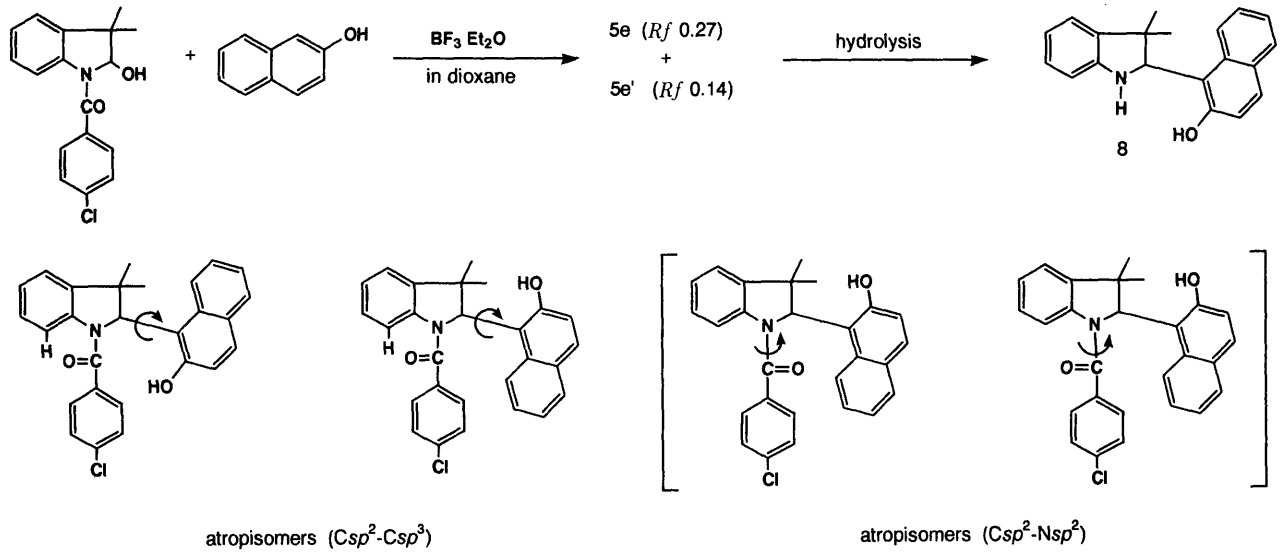


Chart 3

TABLE II. ^{1}H-NMR Spectral Data for the Reaction Products

Compd.	^{1}H-NMR δ (ppm), J (Hz)
5a	1.04 (3H, s, C_3-Me), 1.40 (3H, s, C_3-Me), 3.07 (2H, s, $C_{2''}$-OH, $C_{4''}$-OH), 5.37 (1H, s, $>C_2$-H), 6.19 (1H, dd, J=1.5, 8.2 Hz, $C_{5''}$-H), 6.27 (1H, d, J=1.5 Hz, $C_{3''}$-H), 6.54 (1H, d, J=8.2 Hz, $C_{6''}$-H), 7.04—7.39 (3H, m, C_4-H, C_5-H, C_6-H), 7.22 (2H, d, J=8.8 Hz, $C_{3'}$-H, $C_{5'}$-H), 7.32 (2H, d, J=8.8 Hz, $C_{2'}$-H, $C_{6'}$-H), 8.12 (1H, br d, J=8.5 Hz, C_7-H)
5b	1.31 (3H, s, C_3-Me), 1.36 (3H, s, C_3-Me), 3.87 (3H, s, $C_{5''}$-Me), 4.18 (1H, s, $C_{2''}$-OH), 5.62 (1H, s, C_2-H), 6.90—7.26 (6H, m, C_4-H, C_5-H, C_6-H, $C_{3''}$-H, $C_{4''}$-H, $C_{6''}$-H), 7.39 (2H, d, J=8.7 Hz, $C_{3'}$-H, $C_{5'}$-H), 7.47 (2H, d, J=8.7 Hz, $C_{2'}$-H, $C_{6'}$-H), 7.75 (1H, br d, J=8.7 Hz, C_7-H)
5c	1.31 (6H, s, 2×C_3-Me), 3.76 (2H, s, 2×C_2-H), 6.80—7.90 (4H, m, C_4-H, C_5-H, C_6-H, C_7-H), 7.38 (2H, d, J=8.4, $C_{3'}$-H, $C_{5'}$-H), 7.55 (2H, d, J=8.4, $C_{2'}$-H, $C_{6'}$-H)
6	2.22 (3H, s, C_3-Me), 2.33 (3H, s, C_2-Me), 7.04 (1H, td, J=1.5, 8.2, C_6-H), 7.15 (1H, dd, J=1.5, 8.2 Hz, C_4-H), 7.16 (1H, td, J=1.5, 8.2 Hz, C_5-H), 7.43 (1H, br d, J=8.2 Hz, C_7-H), 7.45 (2H, d, J=8.2 Hz, $C_{3'}$-H, $C_{5'}$-H), 7.63 (2H, d, J=8.2 Hz, $C_{2'}$-H, $C_{6'}$-H)
7c	0.81 (3H, s, C_3-Me), 1.34 (3H, s, C_3-Me), 2.19 (3H, s, $C_{3'}$-Me), 2.35 (3H, s, $C_{2'}$-Me), 4.78 (1H, s, C_2-H), 6.35 (1H, d, J=1.9 Hz, $C_{7'}$-H), 6.62 (1H, dd, J=1.9, 8.8 Hz, C_4-H), 7.10 (1H, td, J=1.9, 8.8 Hz, C_5-H), 6.90—7.60 (4H, m, C_6-H, $C_{7'}$-H, $C_{4'}$-H, $C_{5'}$-H), 7.32 (4H, d, J=8.8 Hz, 2×$C_{3''}$-H, 2×$C_{5''}$-H), 7.48 (4H, d, J=8.8 Hz, 2×$C_{2''}$-H, 2×$C_{6''}$-H)
5e	0.91 (3H, s, C_3-Me), 1.59 (3H, s, C_3-Me), 6.22 (1H, s, C_2-H), 6.68—7.73 (13H, m, Ar), 8.17 (1H, br d, J=8.0 Hz, C_7-H), 9.66 (1H, s, $C_{2''}$-OH)
5e'	0.97 (3H, s, C_3-Me), 1.60 (3H, s, C_3-Me), 5.99 (1H, s, C_2-H), 6.70—7.70 (7H, m, Ar), 6.92 (1H, d, J=8.3 Hz, $C_{3''}$-H), 7.18 (2H, d, J=8.8 Hz, $C_{3'}$-H, $C_{5'}$-H), 7.24 (2H, d, J=8.8 Hz, $C_{2'}$-H, $C_{6'}$-H), 7.56 (1H, d, J=8.3 Hz, $C_{4''}$-H), 8.20 (1H, br d, J=8.0 Hz, C_7-H), 9.62 (1H, s, $C_{2''}$-OH)
5f[a]	1.26 (6H, br s, C_3-Me×2), 5.00—5.70 (2H, br m, C_2-H, $C_{10''}$-H), 6.64—6.84 (2H, m, $C_{4''}$-H, $C_{5''}$-H), 7.16—7.58 (11H, m, C_4-H, C_5-H, C_6-H, $C_{2'}$-H, $C_{3'}$-H, $C_{5'}$-H, $C_{6'}$-H, $C_{2''}$-H, $C_{3''}$-H, $C_{6''}$-H, $C_{7''}$-H), 8.04—8.28 (3H, m, C_7-H, $C_{1''}$-H, $C_{8''}$-H)
5h	0.92 (3H, s, C_3-Me), 1.41 (3H, s, C_3-Me), 5.95 (1H, s, C_2-H), 6.22 (1H, dd, J=1.8, 2.5 Hz, $C_{4''}$-H), 7.05—7.36 (3H, m, C_4-H, C_5-H, C_6-H), 7.10 (1H, d, J=2.5 Hz, $C_{3''}$-H), 7.11 (2H, d, J=8.8 Hz, $C_{3'}$-H, $C_{5'}$-H), 7.31 (2H, d, J=8.8 Hz, $C_{2'}$-H, $C_{6'}$-H), 7.43 (1H, d, J=1.8 Hz, $C_{5''}$-H), 7.83 (1H, br d, J=8.5 Hz, C_7-H)
5i	1.14 (3H, s, C_3-Me), 1.46 (3H, s, C_3-Me), 5.14 (1H, s, C_2-H), 6.35 (1H, s, $C_{2''}$-H), 7.10—7.44 (13H, m, aromatic protons)

a) ^{13}C-NMR (in $CDCl_3$) δ: 20.3, 33.6 (q, Me), 43.6 (s, C_3), 54.3 (d, –CH<), 79.6 (d, NCH<), 167.7 (s, NCO), 184.8 (s, >C=O).

pattern: for example, in the case of **5a**, the m/z 254 peak was due to the fragment formed by elimination of 4-chlorobenzoyl from M^+ (m/z 393 and 395) (3:1). Furthermore, the m/z 239 peak was due to the fragment formed by elimination of the methyl group at the 3-position of the indoline moiety. The m/z 222 peak was due to the fragment formed by elimination of a further methyl group and two hydrogens of OH in resorcinol from m/z 239. The IR spectra and MS of **5** are presented in the experimental section.

Coupling of 3 with β-Naphthol (4e) (Formation of Diastereomeric Atropisomer) β-Naphthol (**4e**) was allowed to react with **3** to give a mixture of the coupling products, as judged from the thin-layer chromatogram (TLC) of the reaction mixture, which showed spots of *Rf* 0.27 (**5e**) and 0.14 (**5e'**). The products could be easily separated by column chromatography on silica gel as crystals, showing the same molecular formula. The formation ratio (**5e**/**5e'**) is 1/1.6. The alkaline hydrolysis of the two products gave the same hydrolyzed product (**8**).

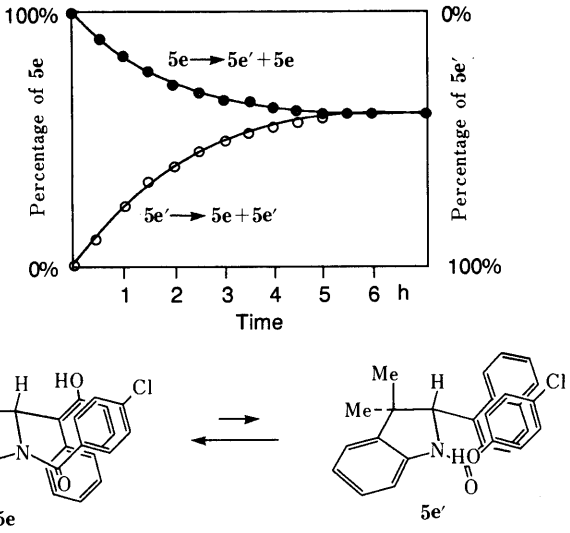


Fig. 1. Equilibrium Reaction of **5e** and **5e'**

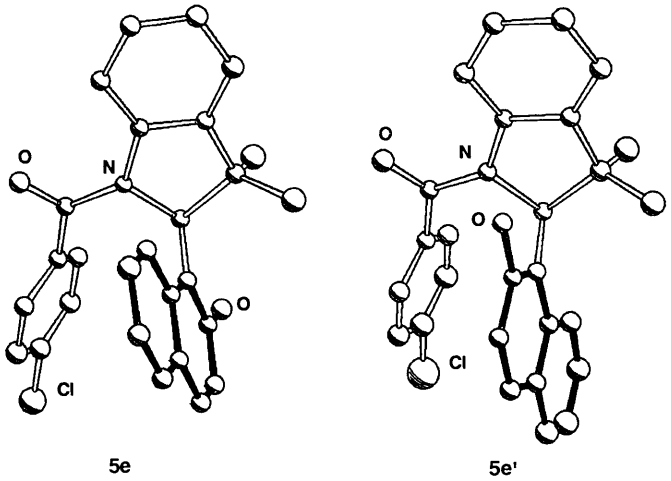


Fig. 2. Computer-Generated Drawings of the X-Ray Structures of **5e** and **5e'**

TABLE III. Kinetic Data for Isomerization of **5e'** to **5e**[a]

Temperature (°C)	$k_{-1}\times10^5$ (s^{-1})[b]	E_a (kcal/mol)
60	1.01	
75	4.39	26±1.5
80	10.2	

a) The equilibrium constant (K) for **5e**↔**5e'** is calculated to be 0.65. b) The average error is ±4%.

Heating **5e** or **5e'** in dioxane at 80 °C for several hours caused transformation into an equilibrium mixture of **5e** and **5e'**. The changes of the composition with isomerization of pure samples are depicted in Fig. 1. The ratio of **5e**/**5e'** at equilibrium was 3/2 in favor of **5e**. These facts strongly suggest that the product is a pair of conformational isomers, **5e** and **5e'**.

The first-order rate constants (k_1 and k_{-1}) for the

interconversion of **5e**↔**5e′** were estimated according to the established method,[5] and from them, the equilibrium constants (K and K') were obtained. The thermodynamically unstable **5e′** is produced preferentially. In the ^{1}H-NMR spectra of **5e** and **5e′**, the C_7-H protons of both the compounds resonate at the same position (8.2 ppm), this being attributable to hydrogen bonding with the amide oxygen. This fact indicates that the compounds are not atropisomers due to restricted rotation about the amide Csp^2–Nsp^2 bond and have almost the same conformation except for the naphthalene moiety. However, definitive evidence for conformational assignments of **5e** and **5e′** could not be obtained from the ^{1}H-NMR spectral data. Therefore, single crystal X-ray analyses were undertaken on **5e** and **5e′**.[6] The conformations of **5e** and **5e′** based on the X-ray analyses are depicted in Fig. 2. The compounds **5e** and **5e′** were found to be a pair of diastereomeric atropisomers due to restricted rotation about the Csp^2–Csp^3 bond, excluding the possibility of atropisomers due to restricted rotation about the amide Csp^2–Nsp^2 bond.

In the previous paper,[1a] possible conformations for **5e** and **5e′** were proposed on the basis of the ^{1}H-NMR analysis of the C_2 methine protons of **5e** and **5e′**. However, the single crystal X-ray analyses[6] indicate that the previous assignments are erroneous and should be interchanged. The X-ray analyses imply that the appearance of the C_2-H proton signal of **5e** at lower field than that of **5e′** is due to the proximity effect of the oxygen atom on the naphthalene ring. Taking the X-ray data into consideration, the ^{1}H-NMR data seem to offer a clue for the structural assignment: comparison of the two crystal conformations reveals that the chemical shift of the protons on the 4-chlorobenzoyl ring of **5e** is more effectively shielded by the ring current effect of the naphthalene moiety than in the case of **5e′**.

Modified Neglect of Diatomic Overlap (MNDO) Calculation of the Atropisomers Crystal structure conformations are known to be affected by intermolecular nonbonded interaction such as hydrogen bonding or van der Waals forces. To obtain information about the conformations free from such interactions, we carried out MNDO[7a] structure optimization on the isomeric compounds. The computer-generated drawings of the optimized structures are depicted in Fig. 3.

The MNDO structure optimization did not reproduce the relative stability between **5e** and **5e′**: the heat of formation (ΔH) of **5e′** is 2.66 kcal/mol more stable than that of **5e**. On the other hand, the calculations based on the crystal coordinates also did not reproduce the relative stability [ΔH(**5e**) − ΔH(**5e′**) = 1.94 kcal/mol].

As for the conformations, the calculations approximately reproduced the structural features of the compounds except for the conformations of the 4-chlorobenzoyl groups and the C_2–C_3 bond lengths. In the crystal structures, the torsion angle of C_7–N_1–C=O for **5e′** is nearly 0°, indicating that the amide possesses an almost planar structure, in which the 4-chlorophenyl group is orthogonal to the amide plane. In the MNDO optimized structures, considerable rotation about the amide C–N bond was observed: the torsion angles of C_7–N_1–C=O for **5e** and **5e′** are 42° and 45°, respectively.

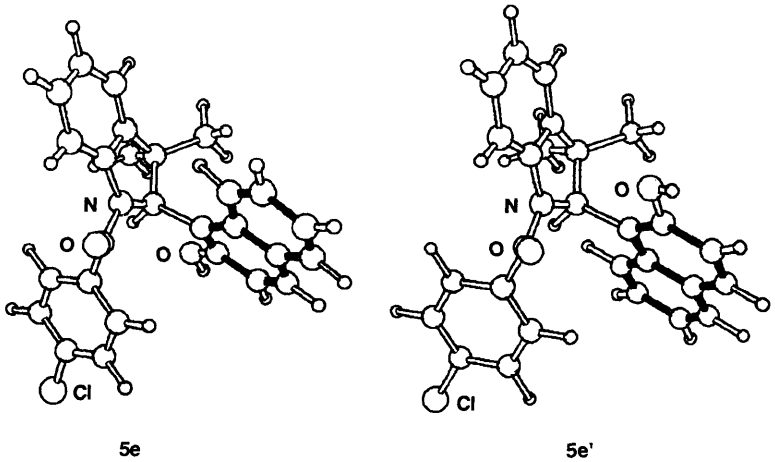
The C_2–C_3 bond lengths (1.601—1.603 Å) were calculated to be considerably longer than those (1.565—1.568 Å) observed in the X-ray analyses.[7b] These results suggest a limitation of applicability of the MNDO method to conformational analysis for constrained compounds. This can probably be attributed to the known tendency of MNDO to overestimate repulsive interactions between atoms.

Coupling of 3 with Anthrone (4f) The reaction behavior of anthrone (**4f**) is of interest. In the reaction, we obtained an unexpected product (**5f**), whose formation could not be accounted for by a simple electrophilic substitution process on **4f**.

Anthrone is known to be in tautomeric equilibrium with the keto-form, 9-hydroxyanthracene (anthranol) (**4f′**), a phenomenon which has been called "transanellar tautomerism." The tautomerism is considered to fall into the category of 1,5-sigmatropic rearrangement.

The frontier molecular orbital (FMO) theory predicts that **4f′** is not a stable aromatic compound and shows high reactivity toward electrophilic substitution because the degree of aromaticity of anthracene is very small (antiaromatic compound).[8a] The MNDO calculations[9] on the ground-state structures of **4f** and **4f′** support this conclusion and suggest that **4f′** will show enhanced reactivity toward electrophiles owing to the high-lying highest occupied molecular orbital (HOMO) (−7.83 eV) with the largest HOMO coefficient localized at the 10 position.

Although the population[10] of anthranol (< 10%) is very



5e **5e′**

Fig. 3. MNDO-Optimized Structures of **5e** and **5e′**

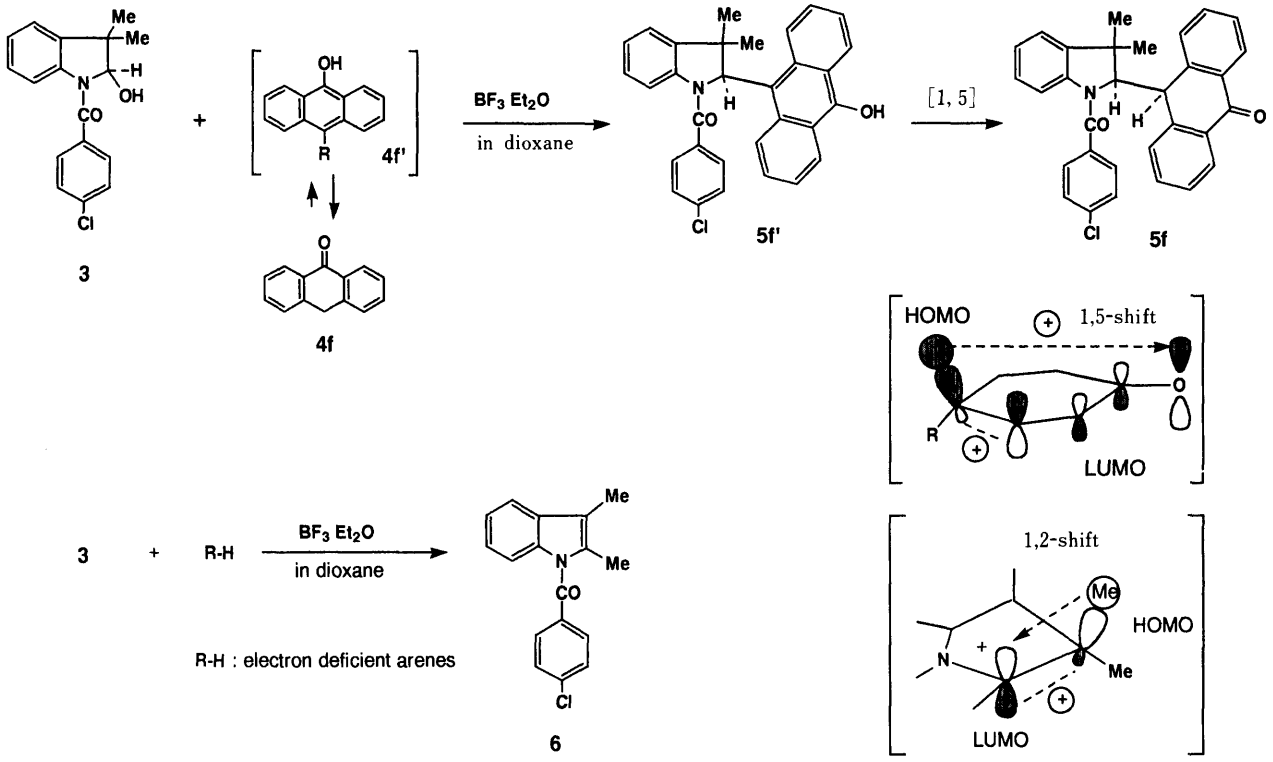


Chart 4

low in the equilibrium mixture, the reaction proceeded under mild reaction conditions. These results indicate that **5f** is presumably derived from the reaction of **3** with the tautomer (**4f'**) of **4f**: **4f'** reacted with **3** to give **5f'**, which also undergoes [1,5]-sigmatropic rearrangement to **5f**. This assumption may be supported by the fact that ethyl acetoacetate (**4k**), having an active methylene, did not show any reactivity toward **3**.

The facile [1,5]-sigmatropic rearrangement in the presence of $BF_3 \cdot Et_2O$ is accounted for by the dissection method[8b] of FMO theory.

The inertness of the parent compound, *i.e.*, anthracene, could not be accounted for by the MNDO calculation data: the calculations indicate that the HOMO energy level (−8.07 eV) of anthracene lies between those of anthranol (**4f'**) (−7.83 eV) and β-naphthol (**4e**) (−8.42 eV) and that the HOMO coefficient of C_{10} is similar to that of **4f'**.

Reactivity of Arenes and Stereochemistry of the Coupling Reaction In general, electron-rich arenes having a high-lying HOMO readily reacted with **3** to give the coupling products, whereas unsubstituted arenes and electron-deficient arenes did not react with **3** to give the Wagner–Meerwein type rearrangement product (**6**). The reactivity of benzofuran (**4i**) is in sharp contrast to that of benzothiophene (**4j**). In the case of **4i**, the corresponding coupling compound was produced, whereas in the case of **4j**, the starting material was recovered. Considering the fact that the HOMO energy levels of furan and thiophene are almost identical[11] the inertness of **4j** is considered to be due to the high degree of aromaticity of the thiophene moiety.[12]

We can find a rough correlation between the magnitudes of the HOMO electron densities and the sites of electrophilic attack, indicating that the frontier orbitals rather than the net charges play an important role in determination of the site selectivity.

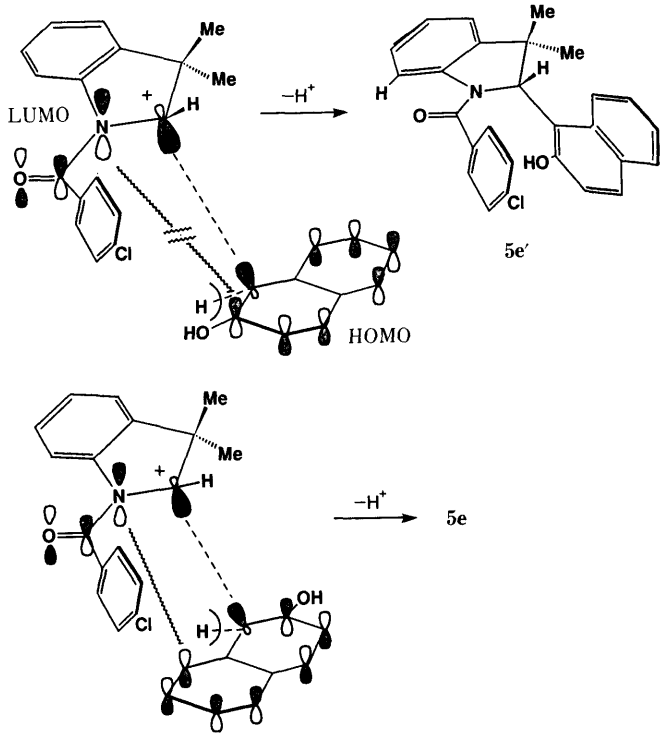


Fig. 4. Transition States for the Reaction of **3** with **4e**

The steric and FMO considerations allow us to explain the formation-reaction behavior of **5e** and **5e'**. As depicted in Fig. 4, in the transition state for **5e'**, the steric repulsions between the naphthyl and *p*-chlorophenyl moieties are not serious in comparison with those in **5e**, wherein the

secondary orbital interaction between p_z orbitals adjacent to the primary interaction is antibonding. Therefore, to avoid such unfavorable interactions, the β-naphthol is considered to approach the indoline cation[13] from a restricted direction (see Fig. 4). From the intermediate, liberation of H^+ leads to the formation of **5e'** without the large conformational change. In the case of **5e**, the steric repulsion is serious but the secondary orbital interaction between the 7 and 8 positions of the naphthalene ring and the amide moiety is bonding, which may be favorable for stabilization of the transition state leading to the formation of **5e**.

Wagner–Meerwein Rearrangement In the electron-deficient arenes or nonactivated arenes such as toluene (**4c**) or anthracene (**4g**), the 1-(4-chlorobenzoyl)-2,3-dimethylindole (**6**) was isolated in high yield. Compound **6** was assumed to be formed *via* thermally allowed 1,2-shift reaction (Wagner–Meerwein type reaction) (see Chart 4). A reaction of this type may be applied to the synthesis of indomethacin-type inflammatory agents.

Conclusion

We have demonstrated that the coupling of 1-acyl-2-hydroxy-3,3-dialkylindoline with arenes under catalysis of $BF_3 \cdot Et_2O$ can provide a convenient method for synthesis of 1-acyl-2-aryl-3,3-dialkylindoline derivatives, and this methodology can be applied to convenient synthesis of diastereometric atropisomers of a new type. We have also characterized a pair of atropisomers by single crystal X-ray analyses.

The details of X-ray analyses of the atropisomers will be published soon in a separate paper.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were taken with a JASCO A-102 spectrometer in Nujol and calibrated with the 3027 and 1601 cm^{-1} absorption bands of polystyrene. The ultraviolet (UV) and visible absorption spectra were recorded on a JASCO UVIDEC-505 spectrophotometer. The ^{1}H-NMR spectra were taken with Hitachi R-600 (60 MHz), JEOL FX-900 (90 MHz), JEOL PS-100 (100 MHz) and JEOL GX-400 (400 MHz) spectrometers. Chemical shifts are expressed in δ using tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, m = multiplet and br = broad. The MS were taken with a JEOL JMS DX-303 spectrometer by direct insertion at 70 eV. Preparative layer chromatography (PLC) was performed on glass plates coated with a 0.1—1.5 mm layer of Silica gel 60 F-254 (Merck). Thin-layer chromatographic analyses were performed with a Shimadzu CS-920 high speed TLC scanner.

Molecular orbital calculations were performed on a FACOM M-780 computer in the Computer Center of Kumamoto University and on a Fujitsu S-4 engineering work station.

Least-squares calculations and molecular graphics were performed on a Fujitsu FM-16β HDII or FMR-60 HD microcomputer.

Materials 3,3-Dimethyl-3*H*-indole (**1**) was prepared according to the reported method.[3a] 1-(4-Chlorobenzoyl)-2-hydroxy-3,3-dimethylindoline (**3**) was prepared by treatment of the corresponding 2-chloro derivative with water.[3b] Arenes were commercially available compounds.

Compound 3 Colorless prisms from benzene, mp 129—130 °C. *Anal.* Calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N; 4.64. Found: C, 67.51; H, 5.24; N, 4.45. HRMS: Found 301.0878, Calcd for $C_{17}H_{16}{}^{35}ClNO_2$ (M^+) 301.0869. ^{1}H-NMR (100 MHz, $CDCl_3$): 1.22 (3H, s, C_3-Me), 1.36 (3H, s, C_3-Me), 4.12 (1H, d, J = 5.7 Hz, OH), 5.35 (1H, d, J = 5.7 Hz, C_2-H), 6.97—7.20 (4H, m, aromatic H), 7.39 (2H, d, J = 8.0 Hz, $C_{3'}$-H, $C_{5'}$-H), 7.55 (2H, d, J = 8.0 Hz, $C_{2'}$-H, $C_{6'}$-H). MS m/z: 303 and 301 (M^+, 1 : 3), 285 and 283 ($M^+ - H_2O$, 1 : 3), 162, 145, 144, 141 and 139 (CO–C_6H_4–Cl, 1 : 3), 130, 115, 113 and 111 (C_6H_4-Cl, 1 : 3), 104, 103. IR ν_{max} cm^{-1}: 3352 (OH), 1631 (>N–C=O), 1590 (aromatic ring). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 227sh (4.15), 261 (4.06), 277sh (4.01), 286 (3.98).

Reaction of 1-(4-Chlorobenzoyl)-2-hydroxy-3,3-dimethyl-indoline (3) with Arenes (General Method) $BF_3 \cdot Et_2O$ (0.189 ml, 1.5 mmol) was added to a solution of the hydroxy compound (**3**) (150.9 mg, 5.0×10^{-1} mmol) and an arene (1.0 mmol) in dioxane (5 ml) and the mixture was stirred under an N_2 atmosphere until the arene (**4**) had disappeared. After cooling, the reaction mixture was diluted with ether and treated with H_2O. The organic layer was separated, washed with Na_2CO_3 solution and dried over anhydrous $MgSO_4$. The ether was evaporated off. The residue was chromatographed on silica gel. The products separated were crystallized from appropriate solvents. The reaction conditions and yield of the products are listed in Table I.

Compound 5a Colorless needles from EtOH, mp 252—254 °C. *Anal.* Calcd for $C_{23}H_{20}ClNO_3$: C, 70.14; H, 5.12; N, 3.56. Found: C, 70.30; H, 5.05; N, 3.49. IR ν_{max} cm^{-1}: 3370 (OH), 3175 (OH), 1620 (>NC=O). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 224 sh (4.38), 274 sh (4.08), 283 (4.10), 292 (4.06). MS m/z: 395 and 393 (M^+, 1 : 3), 254, 238, 237, 236, 222, 123.

Compound 5b Colorless needles from MeOH, mp 231—232 °C. *Anal.* Calcd for $C_{24}H_{22}ClNO_2$: C, 73.56; H, 5.66; N, 3.57. Found: C, 73.39; H, H, 5.60; N, 3.63. IR ν_{max} cm^{-1}: 3447 (OH), 1624 (>NC=O). UV λ_{max}^{EtOH} nm (log ε): 229 (4.01), 254 (3.97), 312 (3.29). MS m/z: 393 and 391 (M^+, 1 : 3), 252, 237, 236, 235, 234, 220.

Compound 5c Colorless solid from EtOH, mp 118—120 °C. IR ν_{max} cm^{-1}: 1643 (>NC=O). UV $\lambda_{max}^{95\%\ EtOH}$ nm: 265, 290. MS m/z: 287 and 285 (M^+, 1 : 3), 272 and 270 ($M^+ - Me$, 1 : 3), 146.

Compound 7c Yellow prisms from EtOH, mp 179.5—180 °C. *Anal.* Calcd for $C_{34}H_{28}Cl_2N_2O_2$: C, 71.96; H, 4.97; N, 4.94. Found: C, 72.26; H, 4.93; N, 4.82. IR ν_{max} cm^{-1}: 1675, 1640 (>NC=O). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 234 (4.56), 271 (4.39). MS m/z: 570, 568 and 566 (M^+, 1 : 4.5 : 6.3), 288, 287, 273, 157, 143.

Compound 5e Colorless plates from MeOH, mp 272—272.5 °C. *Anal.* Calcd for $C_{27}H_{22}ClNO_2$: C, 75.78; H, 5.18; N, 3.27. Found: C, 75.30; H, 5.14; N, 3.16. HRMS: Found 427.1335, Calcd for $C_{27}H_{27}{}^{35}ClNO_2$ (M^+) 427.1339. IR ν_{max} cm^{-1}: 3150 (OH), 1620 (>NC=O). UV λ_{max}^{EtOH} nm (log ε): 232 (4.79), 263 sh (4.20), 270 (4.21), 281 (4.20), 291 (4.15), 324 sh (3.56), 339 (3.56). MS m/z: 288 ($M^+ - COC_6H_4Cl$), 272, 256.

Compound 5'e Colorless prisms from MeOH, mp 210—260 °C. *Anal.* Calcd for $C_{27}H_{22}ClNO_2$: C, 75.78; H, 5.18; N, 3.27. Found: C, 75.61; H, 5.16; N, 3.24. HRMS: Found 427.1316, Calcd for $C_{27}H_{22}{}^{35}ClNO_2$ (M^+) 427.1339. IR ν_{max} cm^{-1}: 3230 (OH), 1624 (>NC=O). UV λ_{max}^{EtOH} nm (log ε): 231 (4.78), 260 sh (4.18), 270 sh (4.18), 282 (4.16), 291 (4.12), 322 (3.59), 337 (3.57). MS m/z: 288 ($M^+ - COC_6H_4Cl$), 272, 256.

Compound 5f Colorless prisms, mp 210—212 °C. *Anal.* Calcd for $C_{31}H_{24}ClNO_2$: C, 77.90; H, 5.06; N, 2.93. Found: C, 77.80; H, 5.10; N, 2.86. IR ν_{max} cm^{-1}: 1666 (C=O), 1642 (>NC=O). MS m/z: 477, 286 and 284 (M^+ – anthrone + 1, 1 : 3), 193, 165, 164, 139. UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 222.0sh (4.46), 268.5 (4.28).

Compound 5h Colorless prisms from EtOH, mp 135—136 °C. *Anal.* Calcd for $C_{20}H_{18}ClN_3O$: C, 68.28; H, 5.16; N, 11.94. Found: C, 68.03; H, 4.95; N, 12.05. IR ν_{max} cm^{-1}: 1668 (>NC=O). UV λ_{max}^{EtOH} nm (log ε): 220 sh (4.21), 252 (3.91), 278sh (3.80), 284 (3.69). MS m/z: 286 and 284 ($M^+ - C_3H_3N_2$, 1 : 3), 80.

Compound 5i Colorless prisms from EtOH, mp 165—170 °C. HRMS: Found 401.11864, Calcd for $C_{25}H_{20}{}^{35}ClNO_2$ (M^+) 401.11825. IR ν_{max} cm^{-1}: 1640 (>NC=O). UV λ_{max}^{EtOH} nm (log ε): 250 (4.22), 278 (3.95), 285 (3.93). MS m/z: 401 and 403 (M^+, 1 : 3), 262, 247, 129.

Compound 6 Yellowish prisms from EtOH, mp 74.5—75.0 °C. *Anal.* Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.98; H, 4.89; N, 4.86. HRMS: Found 283.0762, Calcd for $C_{17}H_{14}{}^{35}ClNO$ (M^+) 283.0762. IR ν_{max} cm^{-1}: 1680 (>NC=O). UV $\lambda_{max}^{95\%\ EtOH}$ nm (log ε): 229 (4.29), 254 (4.26), 312 (3.65).

Hydrolysis of 5e and 5e' (Formation of 8) A solution of **5e** (19 mg) in aqueous ethanol containing KOH [20% KOH (5 ml) + EtOH (10 ml)] was refluxed for 48 h. After cooling, the solution was diluted with water, neutralized with 10% HCl, and then extracted with ether. The organic layer was washed with 10% $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was separated by preparative TLC on silica gel using benzene–ethyl acetate (5 : 1) to give crude **8** (15 mg). The product was recrystallized from *n*-hexane–benzene (2 : 1) to give colorless crystals, mp 223—225 °C. MS m/z: 289 (M^+), 288, 287. HRMS: Found 287.12821. Calcd for $C_{20}H_{17}NO$ ($M^+ - 2$), 287.13101. IR ν_{max} cm^{-1}: 3620 (OH).

Reaction Rates A dioxane solution of **5e** or **5e'** in a test tube was

heated in a thermostated water bath. At appropriate intervals, a small amount of reaction mixture was drawn out by using a capillary tube. The sample was spotted on a silica-gel coated aluminum plate and developed with a benzene–ethyl acetate (10 : 1) solvent system. The chromatogram was dried and analyzed by a TLC scanner using UV detector. The relative amount (**5e**/**5e'**) of the reaction product was determined on the basis of the digital output data. The rate constants were calculated according to the proposed equation.[5)]

The rate law for a first order reversible reaction ($a=b$) is given by $\log [1-(1+1/K)\cdot x/a] = -k_1/2.303\,(1+1/K)t$ where a is the initial concentration of the a-isomer, x the quantity of the b-isomer formed at time t, and K the equilibrium constant $[b]/[a]$. The left side of the equation was calculated from the digital output data of the TLC scanner and the plot against t gave a good straight line, the slope of which afforded the rate constant k_1. This procedure was performed at three temperatures.

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