Rotational Isomerism in Fluorene Derivatives. XIII.[1] Conformational Equilibria of 9-(2-Methylaminophenyl)-fluorene and the Effect of Acid on It

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(Received March 18, 1988)

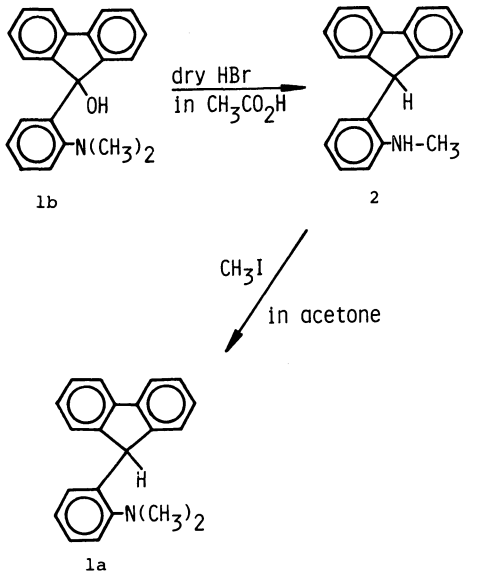
The compound 9-(2-methylaminophenyl)fluorene (**2**) was obtained by treatment of 9-(2-dimethylaminophenyl)-9-fluorenol (**1b**) with dry hydrogen bromide in acetic acid. The conformational equilibrium (*ap*⇄*sp*) of **2** was investigated on the basis of dynamic ^{1}H NMR spectra in $CDCl_3$. The stabilization of the *ap*-form could be ascribed to an N–H···π interaction between the methylamino group and the fluorene ring. The effect of trifluoroacetic acid on the equilibrium of **2** is also discussed.

Recently, we have investigated the conformational equilibria of 9-substituted 9-(2-dimethylaminophenyl)-fluorenes (**1**) on the basis of D NMR spectra. We also discussed the effect of trifluoroacetic acid on 9-(2-dimethylaminophenyl)fluorene (**1a**). In that case, we recognized the presence of N–H···π interaction in the *ap*-trifluoroacetate.[2] In the present paper, we wish to report on the preparation of 9-(2-methylaminophenyl)-fluorene (**2**) and on the conformational equilibrium of **2**, which essentially has an N–H group in the molecule. We also discuss the effect of trifluoroacetic acid on the equilibrium of **2**.

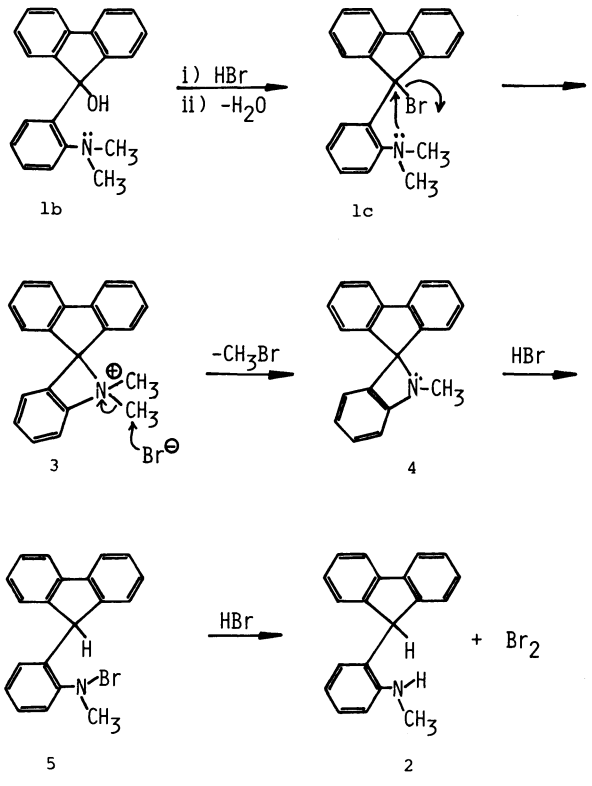
Results and Discussion

Preparation of 9-(2-Methylaminophenyl)fluorene (2). The reaction of 9-fluorenone with 2-dimethylaminophenylmagnesium bromide in dry ether-benzene gave 9-(2-dimethylaminophenyl)-9-fluorenol[2] (**1b**). Bubbling hydrogen bromide into a solution of **1b** in acetic acid unexpectedly afforded **2** in satisfactory yield (75%). In this case, the expected product, 9-bromo-9-(2-dimethylaminophenyl)fluorene (**1c**), was not obtained at all. The structure of **2** could be confirmed by elementary analysis and from its ^{1}H NMR and IR spectra. Furthermore, **2** could be converted into **1a** by treatment with methyl iodide in acetone at room temperature for a week, followed by treatment with aqueous sodium hydroxide.

It is interesting to form **2** by the reaction of **1b** with hydrogen bromide. The following mechanism has been suggested to account for the formation of **2** from **1b** with the aid of hydrogen bromide (Scheme 2). Actually, we confirmed the production of bromine by the usual test using iodo-starch paper. Elimination of methyl bromide from the four membered ring ammonium salt (**3**) to give four membered ring amine (**4**) is inferred from analogy with the von Braun



Scheme 1.



Scheme 2.

reaction,[3] in which a tertiary amine eliminates alkyl bromide to give a disubstituted cyanamide by means of cyanogen bromide. An *N*-bromoamine derivative (**5**) should be derived from **4** with hydrogen bromide owing to the release of the unstable four membered ring system.

On the other hand, the reaction of 9-(4-dimethylaminophenyl)-9-fluorenol (**6**) with hydrogen bromide in acetic acid and subsequent treatment of sodium hydroxide produced **6** instead of 9-(4-methylaminophenyl)fluorene (**7**). The result supported the above reaction mechanism which includes the four membered ring system.

Conformational Equilibria of 2 in Chloroform. Usually, in 9-(2-substituted phenyl)fluorene derivatives, two rotamers (*ap* and *sp*) were identified by their NMR spectra because of their high barriers to rotation about the C(9)–C(Ar) bond. The conformational equilibria *ap*⇄*sp* of these compounds are mainly controlled by intramolecular steric effects, nonbonding intramolecular interaction (attraction or repulsion), and solvent effects. The isomerization of **2** by rotation about the C(9)–C(Ar) bond is shown in Fig. 1.

As shown in Table 1, the two CH_3 signals were observed at δ 2.22 and 2.98 as broad singlets at room temperature, respectively. The dynamic NMR spectra of the methyl protons at various temperatures from 60 to −30 °C are shown in Fig. 2. The signal for the methyl group appeared as a sharp singlet at 60 °C, and this signal gradually split into two broad singlets with lowering of the temperature. Finally, the methyl signal showed one singlet (δ 3.00) and one doublet (δ 2.20, J=5 Hz) (1:2.1) at −30 °C. The former corresponded to the methyl proton of the *sp*-form; the latter corresponded to that of the *ap*-form. Two amino protons (N–H) were observed as a broad singlet at δ 4.36 (*sp*-form) and a broad quartet at δ 2.42 (*ap*-form) at −30 °C.

Since the amino protons easily exchange with one another, if the rate of the exchange is faster than the time scale of NMR, no coupling of the amino proton with the vicinal proton should occur. Therefore, in the case of the *sp*-form of **2**, both the methyl and amino protons are observed as singlets. For the other *ap*-form, the methyl and amino protons couple with one another; that is, the rate of the exchange of the amino proton is found to be slower than the NMR time scale.

Iwamura et al.[4] already proposed the presence of the N–H···π internal hydrogen bonding in the *ap*-form of 9-(2-aminophenyl)fluorene (**8**) to stabilize this form (the ratio; *ap*/*sp*=4/1 at −51 °C). Similarly,for compound **2**, we can show that N–H···π interaction exists between the methylamino group and the fluorene ring. This stabilizes the *ap*-form (*ap*/*sp*=2.1/1 at −30 °C) (Fig. 3). Thus, the methyl signal of **2**-*ap*

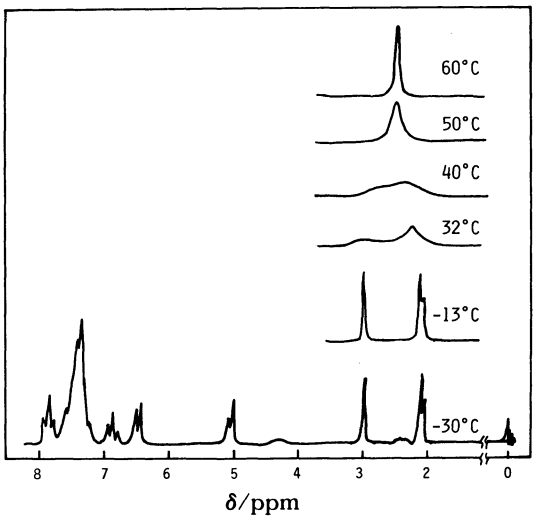


Fig. 2. Temperature-dependent spectra of **2** in $CDCl_3$.

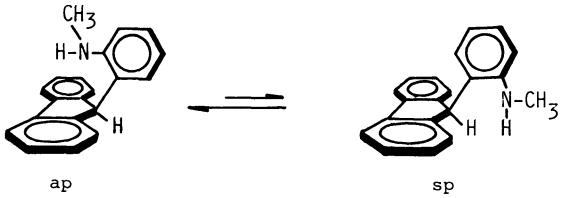


Fig. 1. Isomerization process between *ap* and *sp* form of 9-(2-methylaminophenyl)fluorene **2**.

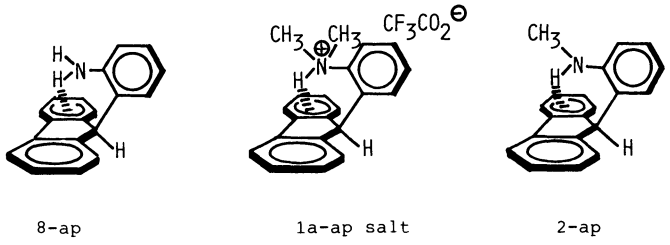


Fig. 3. N–H···π interaction in **8**-*ap*, **1a**-*ap* salt, and **2**-*ap*.

Table 1. ^{1}H NMR Data of **2** in $CDCl_3$

Temp/°C	δ/ppm				
	$NHCH_3$	$NHCH_3$	9-H	6′-H	Aromatics
25	2.22br.s 2.98br.s	—	5.02br.s	—	6.02—7.70m
−30	2.20d[a] 3.00s	2.42br.q 4.36br.s	4.98s 5.02s	— 6.48d[b]	6.08—7.90m

a) J=5 Hz. b) J=7 Hz.

should be observed as a doublet.

The IR spectrum of **2** in 0.1 mol l^{-1} solution of carbon tetrachloride exhibited an N-H streching frequency at 3435 cm^{-1}. This value did not alter on dilution with the solvent down to 0.02 mol l^{-1} concentration. According to this phenomenon, we can not detect the presence of the N-H···π hydrogen bonding in **2**, because intermolecular hydrogen bonding due to an N-H group is usually not influenced with respect to variation of its concentration.[5] The reference compound **7**, which was obtained from the reaction of 9-(4-dimethylaminophenyl)-fluorene (**9**) with cyanogen bromide, showed corresponding absorption at the same 3435 cm^{-1} in 0.05 mol l^{-1} solution of carbon tetrachloride.

Iwamura et al. observed the frequencies of the N-H stretching in **8** and 9-(4-aminophenyl)fluorene (**10**), and proposed that the low frequency shift of the symmetric NH vibration in **8** relative to the para isomer **10** indicates the presence of N-H···π hydrogen bonding in **8**.[4] However, Ōki et al. have recently examined the N-H streching frequencies of 9-(2-amino-1-naphthyl)fluorene (*ap*- and *sp*-) (**11**) and 9-(2-methylamino-1-naphthyl)fluorene (*ap*- and *sp*-) (**12**). They have confirmed that the N-H···π interactions in **11**-*ap* and **12**-*ap* have little affected on the N-H stretching frequencies because the frequencies are almost the same in both the *ap*- and *sp*-rotamers.[6] Thus, unfortunately, the N-H···π interaction in **2**-*ap* had not been confirmed from its IR spectral behavior because **2** and **7** give the same N-H stretching frequencies.

DNMR spectra of **2** were measured in $CDCl_3$ containing D_2O. The *ap*-methyl signal was observed as a singlet peak because the vicinal N-H proton exchanges rapidly with D^+ (Fig. 4). By line-shape analyses of the methyl signal in the DNMR spectra,[7] the activation free energies ($\Delta G^{\ddagger}$) of internal rotation (*ap*⇄*sp*) of **2** in $CDCl_3$-D_2O were obtained as 15.5 and 15.9 kcal mol^{-1} for the *sp*→*ap* and *ap*→*sp* processes, respectively. As compared with the $\Delta G^{\ddagger}$ values in **1a** ($\Delta G^{\ddagger}_{sp\to ap}$=15.5, $\Delta G^{\ddagger}_{ap\to sp}$=13.8 kcal mol^{-1}; 1 cal=4.184 J), it turned out that the ground state of **2**-*d*-*ap* is considerably stabilized.

Variation of Conformational Equilibria of 2 by Adding Trifluoroacetic Acid in the Chloroform Solution. As shown above, it is recognized that compound **2** maintains an equilibrium *ap*/*sp*=2.1/1 in chloroform at −10 °C. When trifluoroacetic acid was added dropwise to the solution of **2** in chlorofrm, the ^1H NMR signal of the methylamino group gradually changed in an interesting manner as shown in Fig. 5.

Compound **2** reacts with trifluoroacetic acid and gives a salt ammonium trifluoroacetate. In the process shown in Fig. 5, we can explain the variation of the methyl signal on adding trifluoroacetic acid as follows. (1) In the case of [CF_3COOH]≲[**2**]: By protonation of the methylamino group, the *sp*-methyl signal (singlet) gradually develops with shift to lower field, while the *ap*-methyl signal (doublet) changes into a singlet and gradually sinks with shift to higher

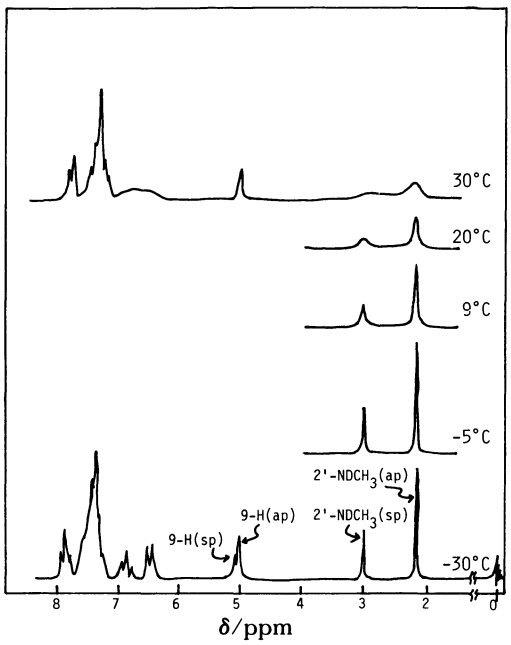


Fig. 4. Temperature-dependent spectra of **2** in $CDCl_3$-D_2O.

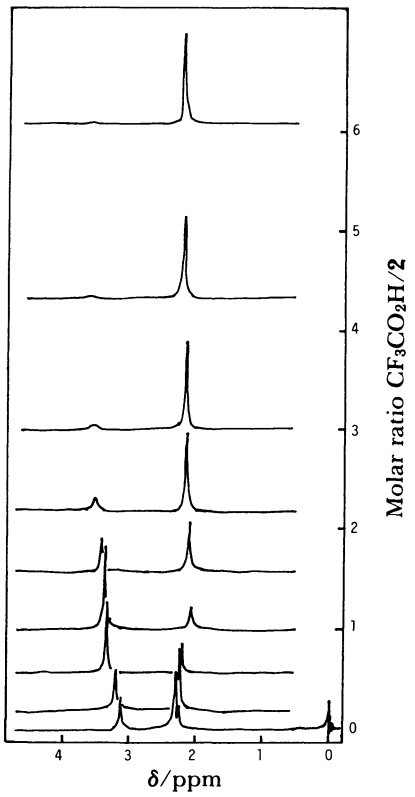


Fig. 5. ^1H NMR spectra of **2** and **2**-CF_3CO_2H salt at −10 °C.

field. That is, in the resulting ammonium trifluoroacetate the *sp*-form is more stable than the *ap*-form, contrary to the case of the free amine **2**. It is presumed that the trifluoroacetate ion acts as a medium to reduce the distance between the methylammonium group and the 9-proton (Fig. 6). This suggested bridging effect of the trifluoroacetate ion will make the *ap*⇄*sp* equilibrium incline predominantly to the *sp*-form. (2) In the case of [CF_3COOH]> [**2**]: The *sp* signal gradually shrinks with convergence to about δ 3.6, and the *ap* signal gradually enhances with convergence to about δ 2.2. That is, when excess equivalent of the acid is added, the trifluoroacetate ion associates with excess trifluoroacetic acid and loses its bridging effect between the methylammonium group and the 9-proton. In fact, with addition of methanol (or dimethylsulfoxide) to the solution of **2** in excess amount of acid, the *ap* signal, which had considerably developed, almost disappeared. In this case, the acid is associated with added methanol and its concentration is essentially diluted. Thus, it can be postulated that by increasing the concentration of the acid, the N–H···π interaction between the methylammonium group and the fluorene ring in the *ap*-salt predominates over the bridging effect of the trifluoroacetate ion in the *sp*-salt. In this way the *ap*-salt may be stabilized. Furthermore, in the case of [CF_3COOH]⩾[**2**], the *sp* signal almost disappears and the sharp *ap* signal (about δ 2.2) is observed. Accordingly, the N–H···π interaction makes the equilibria *ap*⇄*sp* incline to the *ap*-form, exclusively. However in any case, both the *ap*- and *sp*-methyl signals are probably observed together as weighted average of those of **2** and **2**-salt.

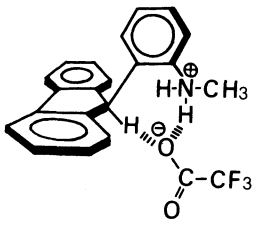


Fig. 6. A bridging effect of trifluoroacetate ion in **2**-*sp*-salt.

In this system, we can recognize a conformational equilibrium of **2** owing to the restricted rotation about the C(9)–C(Ar) bond, and both acid–base equilibria owing to the protonation of each conformer of **2** with trifluoroacetic acid, and additionally a conformational equilibrium exists between the two **2**-salts. Thus, at least the four equilibria described above participate in this system. The first and last equilibria can be determined by the relative stability of the two rotamers (*ap*- and *sp*-) in **2** and **2**-salt, respectively. Also the acid–base equilibria are governed by the concentration

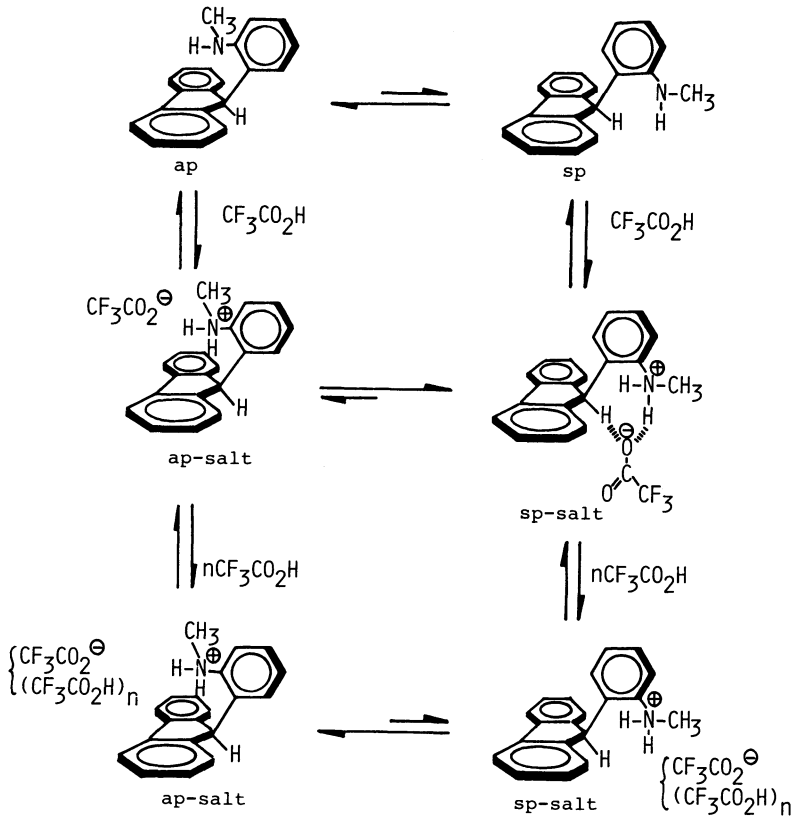


Fig. 7. Isomerization processes for **2** (*ap* and *sp*) and their trifluoroacetate salts.

of trifluoroacetic acid because the quantity of **2** is held constant. However, we consider that the stability of the rotamer may be independent of the rate of proton exchange between the acid and base.

We now show the above-mentioned interconversion for the conformers of the free amine **2** and its salt in Fig. 7.

Experimental

^{1}H NMR spectra were recorded on a JEOL-MH-100 spectrometer with a JEOL model JES-VT-3 variable temperature controller. The chemical shifts are expressed in ppm, with tetramethylsilane as an internal standard. Dynamic NMR spectra were analized by using a modified version of the computer program DNMR 3. The IR spectra were measured on a JASCO IRA-1 spectrometer solutions in carbon tetrachloride. Melting points are uncorrected.

9-(2-Methylaminophenyl)fluorene (2). To a solution of 9-(2-dimethylaminophenyl)-9-fluorenol (**1b**) (0.2 g, 0.7 mmol) in acetic acid (5 ml) was bubbled hydrogen bromide gas generated for 1 h. The mixture was concentrated, alkalized by sodium hydroxide solution, and extracted with benzene. The benzene solution was dried with magnesium sulfate, and concentrated in vacuo to obtain the residue which was recrystallized from acetone to give **2** as colorless needles; yield: 0.14 g (75%); mp 121—122 °C. IR (CCl_4): 3420 cm^{-1} (NH). Found: C, 88.38; H, 6.13; N, 5.05%. Calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.32; N, 5.16%.

^{1}H NMR data of **2** in $CDCl_3$ at 25 and −30 °C were shown in Table 1.

9-(4-Dimethylaminophenyl)-9-fluorenol (6). A solution of fluorenone (1.8 g, 0.01 mol) in dry THF was added to the Grignard reagent prepared from magnesium turnings (0.4 g, 0.017 mol) and *p*-bromo-*N*,*N*-dimethylaniline (3 g, 0.015 mol). The mixture was refluxed for 1 h. After cooling, the solution was poured into dil. hydrochloric acid, alkalized by sodium hydroxide solution and extracted with benzene. The benzene solution was dried with magnesium sulfate, distilled off in vacuo, leaving a residue which was recrystallized from benzene to give **6** as colorless prisms; yield 2.0 g (66%); mp 157—158 °C. ^{1}H NMR ($CDCl_3$) δ=2.52 (1H, s, OH), 2.89 (6H, s, $2CH_3$), 6.68 (2H, d, J=8 Hz, 3′,5′-H), 7.16—7.73 (11H, m, 2′,6′-H and fluorenyl protons). Found: C, 83.99; H, 6.18; N, 4.41%. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.36; N, 4.65%.

9-(4-Dimethylaminophenyl)fluorene (9). Hydriodic acid (57%, 6.0 g, 50 mmol) was added to a solution of **6** (1.2 g, 4 mmol) in acetic acid (30 ml), and refluxed for 1.5 h. The reaction mixture was concentrated in vacuo to obtain a residue which was treated by sodium bisulfite, alkalized by sodium hydroxide solution, and extracted with benzene. The benzene solution was dried with magnesium sulfate and evaporated in vacuo to give **9** yield: 0.8 g (70%); colorless needles; mp 155—156 °C (from benzene–hexane (1:2)). ^{1}H NMR ($CDCl_3$) δ=2.92 (6H, s, $2CH_3$), 5.02 (1H, s, 9-H), 6.72 (2H, d, J=8 Hz, 3′, 5′-H), 7.06 (2H, d, J=8 Hz, 2′, 6′-H), 7.28—7.96 (8H, m, fluorenyl protons). Found: C, 88.72; H, 6.56; N, 4.68%. Calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91%.

9-(4-Methylaminophenyl)fluorene (7). A solution of **9** (0.3 g, 1.05 mmol) and cyanogen bromide (0.3 g, 3.2 mmol) in acetone(5 ml) was refluxed for 16 h, and concentrated at atmospheric pressure to obtain a residue, which was extracted with dry ether. The ether filtrate was extracted with 15% hydrochloric acid solution and washed with water. The ether solution was dried with magnesium sulfate and concentrated in vacuo. The crude product (9[4-(*N*-cyano-*N*-methylamino)phenyl]fluorene (0.2 g)) was refluxed continuously in 20% hydrochloric acid solution for 6 h. The reaction mixture was alkalized by sodium hydroxide solution, extracted with benzene, dried with magnesium sulfate. The solution was evaporated in vacuo, leaving a residue which was column-chromatographed on alumina using benzene as an eluent to give **7**; yield: 0.06 g (22%); colorless needles; mp 126—127 °C. IR (CCl_4): 3420 cm^{-1} (NH). ^{1}H NMR ($CDCl_3$) δ=2.83 (3H, s, CH_3), 3.52 (1H, br. s, NH), 5.06 (1H, s, 9-H), 6.60 (2H, d, J=8 Hz, 3′,5′-H), 7.02 (2H, d, J=8 Hz, 2′,6′-H), 7.20—8.0 (8H, m, fluorenyl protons). Found: C, 88.40; H, 6.29; N, 5.07%. Calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.32; N, 5.16%.

***N*-Methylation of 2.** To a solution of **2** (0.22 g, 0.8 mmol) was added methyl iodide (0.22 g, 1.6 mmol) and the mixture was allowed to stand for a week at room temperature. The reaction mixture was concentrated, alkalized by sodium hydroxide solution, and extracted with benzene. The benzene solution was dried with magnesium sulfate and the solvent distilled off in vacuo to give **1a**; yield: 0.14 g (60%); colorless crystals; mp 121—122 °C (from methanol–benzene). ^{1}H NMR ($CDCl_3$) δ=2.86 (6H, br.s, $2CH_3$), 5.86 (1H, br. s, 9-H), 6.34 (1H, d, 6′-H), 6.92—7.70 (11H, m, aromatic protons).

The authors wish to thank Professor Masashi Tashiro, Institute of Advanced Material Study, Kyushu University, for the elemental analyses, and are grateful for the financial support of this work by Research Grant-in-Aid from the Ministry of Education, Science and Culture (No. 60470023).

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