SYNTHESIS AND SPECTROSCOPIC PROPERTIES OF 9-SUBSTITUTED BENZ[g]INDOLES

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Abstract- Photolysis of 1,1'-(1,8-naphthylene)-di-1H-1,2,3-triazoles in methanol has given new benz[g]indoles with a triazole ring at 9-position. Similar photolysis of 1-(8-dimethylamino-1-naphthyl)-1H-1,2,3-triazoles also gives new benz[g]indoles with a dimethylamino group at 9-position. The spectral properties of these compounds were studied in comparison with those of corresponding benz[g]indoles obtained from the similar photolysis of 1-(1-naphthyl)-1H-1,2,3-triazoles. Since the substituent at 9-position and the pyrrole moiety exist in close proximity in peri- position of the naphthalene ring, unique properties such as the strong intramolecular hydrogen bonding and the restricted rotation of C(sp2)-N(sp3) single bond were observed in the 9-substituted benz[g]indoles .

Owing to the substituents existing in close proximity, 1,8-disubstituted naphthalenes exhibit unique properties in both structure and reactivity. A typical example of such "proximity effects" is an unusual high basicity in 1,8-bis(dimethylamino)naphthalenes, in which the strong N---H---N hydrogen bonds are formed very easily.[1]

In connection with the study about the structure and reactivity of 1,8-disubstituted naphthalenes, we have synthesized new 1,8-diheteroaromatic naphthalenes, 1,1'-(1,8-naphthylene)-di-1H-1,2,3-triazoles (1), and investigated their spectral properties comparing with those of the corresponding 1-(1-naphthyl)-1H-1,2,3-triazoles (2).[2] According to the X-Ray diffraction study of 1, the naphthalene ring is distorted due to the repulsion between the two triazole rings.[3] The photoreaction of 1 has also been studied, and proved to give the new heteroaromatic system compounds, indolo[6,7-g]indoles(3).[4] By comparing with the spectrum of corresponding benz[g]indoles(4), which are generated by the photolysis of 2, an interesting intramolecular hydrogen bonding was observed in 3.

In this note, we report on the preparation of 9-substituted benz[g]indoles (5 and 6) by the similar photolyses of 1,8-disubstituted naphthalenes with the triazole ring and on the results of the spectroscopic analyses of these compounds.

RESULTS AND DISCUSSION

Photoreaction of tetraethyl 1,1'-(1,8-naphthylene)-di-1H-1,2,3-triazole-4,5-dicarboxylate (1a) in methanol was followed by HPLC using ODS column and methanol/water as an eluent.   As a result, 15 min of irradiation of 1a afforded indolo[6,7-g]indole derivatives (3a), which was produced by the elimination of nitrogen molecules from the two triazole rings as reported before.[4]   Irradiation of 1a for 2 min, however, gave intermediate products, diethyl 9-(1H-1,2,3-triazol-4,5-diethoxycarbonyl-1-yl)-benz[g]indole-2,3-dicarboxylate (5a), with 3a and the starting material.   Similar photoreactions took place in the isopropyl ester analogue (1b), and 5b was obtained after 2 min irradiation as well as the indolo[6,7-g]indole derivative (3b).   In the case of 2, similar reactions were observed on photolyses and 1H-benz[g]indoles (4) were formed almost quantitatively after 15 min irradiation. Several spectroscopic data showed that diethyl 9-dimethylaminobenz[g]indole-2,3-dicarboxylate (6a) was formed by the photoreaction from 7a. The amount of 6a became maximum after 60 min irradiation.   The longer irradiation caused further photolyses, and the amount of 6a gradually decreased.   Yield of 6a, 12%, is notably low compared with that of 3a and 4a, 70% and 95%, respectively.   The rates of the photolysis of 1a were slower than that of diethyl 1-(1-naphthyl)-1H-1,2,3-triazole-4,5-dicarboxylate (2a), and much slower rate was observed in the case of diethyl 1-(8-dimethylamino-1-naphthyl)-1H-1,2,3-triazole-4,5-dicarboxylate (7a).   It took 2 min, 10 min, and 90 min for 2a, 1a, and 7a, respectively, to disappear completely in the photolysis.   In photolysis of isopropoxycarbonyl derivative (7b) in methanol, 6b was formed similar slow rate and low yield (16 %).   The lower reactivity of 7 was caused probably by the proximity of the adjacent dimethylamino group, which inhibits the cyclization.

Spectroscopic data for 5a, 5b, 6a, and 6b are listed in Table 1 together with those for corresponding 4a and 4b.

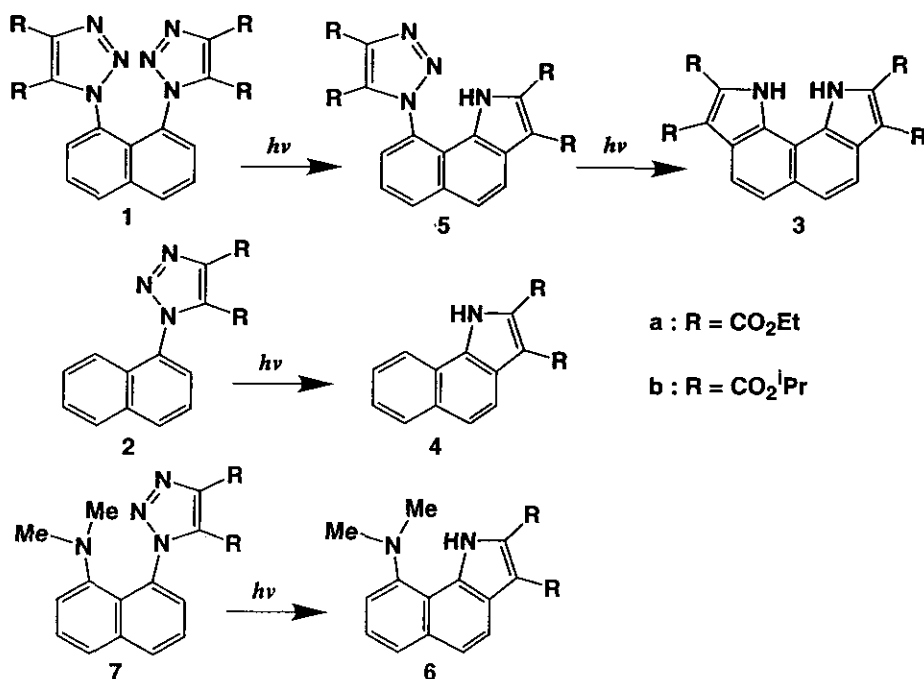**Table 1.** Spectroscopic data of benz[g]indoles.

Compd	^{1}HNMR(CDCl$_3$) δ/ppm from TMS	IR(KBr) ν/cm^{-1}	UV(MeOH) λ/nm	MS m/z(rel. intensity, %)
4a	1.43(t, J=7.1 Hz, CH$_3$), 1.47(t, J=7.1 Hz, CH$_3$), 4.44-4.52(m, CH$_2$), 7.50-7.61(m, Ar), 7.91(d, J=7.5 Hz, Ar), 7.99(d, J=8.9 Hz, Ar), 8.23(d, J=7.9 Hz, Ar), 10.52(s, NH),	3448, 2984, 1732, 1697,	349, 335, 275, 249, 207	311(M+,76), 265(96), 193(100), 165(16), 164(14), 138(10)
4b	1.43(d, J=6.2 Hz, CH$_3$), 1.50(d, J=6.2 Hz, CH$_3$), 5.34-5.42(m, CH), 7.49-7.59(m, Ar), 7.90(d, J=7.5 Hz, Ar), 7.94(d, J=9.0 Hz, Ar), 8.24(d, J=7.7 Hz, Ar), 10.57(s, NH)	3449, 2980, 1734, 1700	349, 335, 274, 249, 207	339(M+, 70), 297(12), 279(20), 237(100), 193(40), 164(12)
5a	0.83(t, J=7.1 Hz, CH$_3$), 1.40(t, J=7.1 Hz, CH$_3$), 1.44(t, J=7.1 Hz, CH$_3$), 1.48(t, J=7.1 Hz, CH$_3$), 4.07(q, J=7.1 Hz, CH$_2$), 4.36(q, J=7.1 Hz, CH$_2$), 4.45-4.56(m, CH$_2$), 7.54(d, J=7.5 Hz, Ar), 7.64(dd, J=8.1, 7.5 Hz, Ar), 7.76(d, J=9.0 Hz, Ar), 8.19(d, J=8.1 Hz, Ar), 8.21(br, NH), 8.24(d, J=9.0 Hz, Ar)	3446, 2985, 1746, 1709	352, 335, 278, 253, 210	522(M+, 22), 448(60), 421(28), 376(100), 258(50)
5b	0.78(br, CH$_3$), 1.37(d, J=6.2 Hz, CH$_3$), 1.45(d, J=6.2 Hz, CH3), 4.88(m, CH), 5.22(m, CH), 5.34-5.42(m, CH), 7.52(d, J=7.4 Hz, Ar), 7.63(dd, J=8.3, 7.4 Hz, Ar), 7.75(d, J=9.1 Hz, Ar), 8.19(d, J=8.3 Hz, Ar), 8.22(br, NH), 8.23(d, J=9.1 Hz, Ar)	3448, 2983, 1744	351, 335, 278, 253, 209	578(M+, 36), 404(30), 388(40), 362(100), 320(72), 276(54)
6a	1.46(t, J=7.1 Hz, CH$_3$), 1.48(t, J=7.1 Hz, CH$_3$), 2.90(s, CH$_3$), 4.45-4.51(m, CH$_2$), 7.43(d, J=7.7 Hz, Ar), 7.48(dd, J=7.9, 7.7 Hz, Ar), 7.60(d, J=8.8 Hz, Ar), 7.71(d, J=7.9 Hz, Ar), 8.05(d, J=8.8 Hz, Ar), 11.81(s, NH)	3381, 2984, 1729, 1699	353, 340, 274, 249, 206	354(M+, 66), 308(24), 293(15), 279(100), 265(16), 208(35)
6b	1.44(d, J=6.3 Hz, CH$_3$), 1.47(d, J=6.2 Hz, CH$_3$), 2.89(s, CH$_3$), 5.30-5.41(m, CH$_2$), 7.42(d, J=7.7 Hz, Ar), 7.48(dd, J=7.9, 7.7 Hz, Ar), 7.59(d, J=8.9 Hz, Ar), 7.70(d, J=7.9 Hz, Ar), 8.01(d, J=8.9 Hz, Ar), 11.77(s, NH)	3383, 2983, 1728, 1699	352, 276, 250, 204	382(M+, 52), 322(36), 280(100), 236(24), 205(10), 196(18)

In the ^{1}H NMR spectra of **5a**, the N-H signal was observed at *ca.* 2.3 ppm up-field compared with that of **4a**. The reason of this extremely up-field shift of NH signal in **5a** is due to an anisotropic effect of the triazole ring as previously described.[4] Probably, the triazole ring in **5a** is perpendicular to the benz[*g*]indole ring because of steric repulsion between the triazole ring and the pyrrole moiety. Then, the triazole ring in **5a** faces toward the NH hydrogen in short distance, which makes the large up-field shift as described above. The methyl signal of 0.83 ppm in **5a** was assigned to ethoxycarbonyl group at 5-position of the triazole ring. The signal appeared in very up-field compared with the other three methyl signals of **5a**. The anisotropic effect of the benz[*g*]indole ring influences the shift as the hydrogen locates above the plane of the benz[*g*]indole ring. Contrary to the case of **5a**, the NH signal of 11.81 ppm in **6a** appeared at significantly low field compared with that of **4a** (10.52 ppm). The reason of such lower field shift is considered to be the intramolecular hydrogen bonding between the lone pair of the nitrogen in the dimethylamino group and the NH hydrogen in the pyrrole moiety in **6a**. In the IR spectra, the N-H stretching frequencies of **4a** and **5a** were nearly equal, 3348 cm^{-1} and 3346 cm^{-1}, respectively. While in the case of **6a**, the frequency was remarkably high as 3381 cm^{-1}. This indicates the existence of the strong intramolecular hydrogen bonding in **6a** in accordance with the result of NMR.

The longest wavelength bands of **5a** and **6a** showed slightly red shift compared with that of **4a** in the UV spectrum. Pronounced differences, however, could not be seen for the UV spectra among them. The similar spectroscopic trend as described above is also obtained in the compounds with isopropoxy carbonyl group such as **5b** and **6b**. The ^{1}H NMR spectra for the methyl region in **5b** at several temperatures are shown in Figure 1. The signal of 0.78 ppm, which was assigned to the methyl proton of the isopropyl group at the 5-position of the triazole ring, showed large broadening at room temperature. The signal became sharp doublet peaks as a usual signal of the isopropyl group. When the temperature decreased, it turned into two doublet signals at lower temperatures. These phenomena indicate that the hydrogens of two methyl groups in the 5-isopropoxycarbonyl group reveal magnetically non-equivalent at considerably low temperature. Such non-equivalence can be explained by the molecular asymmetry of **5b**. The restricted rotation around the C-N bond between the triazole and benz[*g*]indole rings produce the molecular asymmetry at the low temperature.
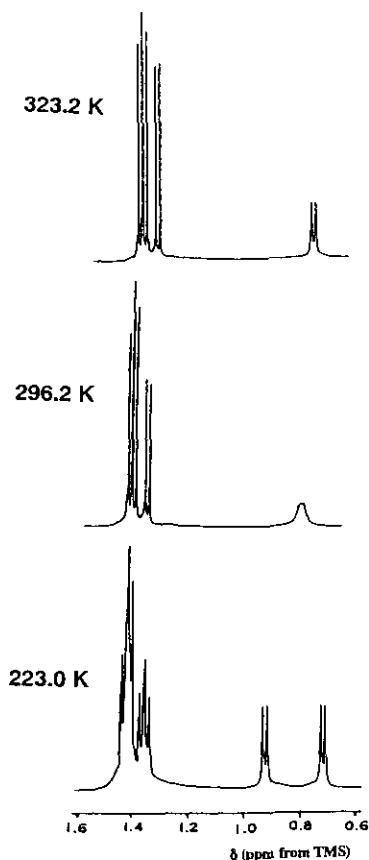

Figure 1.   Temperature-dependent ^{1}H NMR spectra of the methyl region in **5b**.

This non-equivalence of the methyl signal is also observed in the ^{13}C NMR spectrum ($\Delta\delta$ =42.6 Hz at 203 K) of **5b**.   The activation parameters about the rotation of the C-N bond described above are determined by the complete line-shape analysis of the temperature dependent NMR signals of the methyl proton in the isopropyl group of 5-position in **5b** as follows:

$\Delta H^{\ddagger}$ =10.8$\pm$0.6 kcal/mol, $\Delta S^{\ddagger}$ =-7.8$\pm$1.1 e.u., $\Delta G^{\ddagger}$ =13.1$\pm$0.8 kcal/mol at 298 K in acetone-d_6.

In order to compare the rotational barriers, similar analyses were performed for diisopropyl 1-(1-naphthyl)-1H-1,2,3-triazole-4,5-dicarboxylate (**2b**), which has only one bonded triazole ring.   The following activated parameters were obtained for the temperature dependent NMR signals of the methyl proton in the isopropyl group of 5-position in **2b**:

$\Delta H^{\ddagger}$=8.1$\pm$0.6 kcal/mol, $\Delta S^{\ddagger}$ =-9.9$\pm$1.1 e.u. $\Delta G^{\ddagger}$ =10.3$\pm$0.8 kcal/mol at 217 K in acetone-d_6.

These differences in the activation parameters between **5b** and **2b** are caused by the neighboring rigid pyrrole ring, which restricts the rotation of the triazole ring in **5b**.

In order to know similar dynamic behaviour of **6a** and **6b**, their ^1H NMR spectra were measured at the low temperature as 173 K.   However, no significant changes could be seen in the spectra.   The signal of the dimethylamino group showed one sharp singlet peak and was not yet split even at this low temperature. The followings are supposed to be the reasons of these results:

(1) The rotational barrier is very low for the C-N bond between the dimethylamino group and the benz[g]indole ring.

(2) Though the rotation is restricted, the difference between the chemical shifts for the two N-methyl groups is very small.

Usually, a rotational barrier is low about the C-N bond between a dimethylamino group and an aromatic ring, but if there exist bulky substituents in close proximity, the barrier becomes relatively high.   For example, the two N-methyl hydrogens are already non-equivalent at room temperature in **7a** and the activation energy ($\Delta G^{\ddagger}$) for the rotation about the dimethylamino group is 17.5 kcal/mol at 371 K,[5] while in N,N-dimethylaniline, the activation energy is 5.1 kcal/mol at 133 K.[6]

In **6b**, the neighboring pyrrole ring as in the case of **5b** may hinder the rotation of the dimethylamino group.
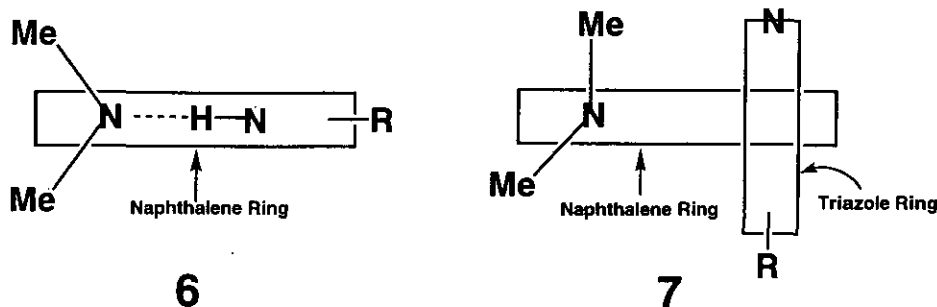

Figure 2. Conformation of the dimethylamino group in 6 and 7.

On the other hand, the existence of intramolecular hydrogen bonding in **6** is expected between the lone pair of the dimethylamino group and NH hydrogen in the pyrrole ring as described before in the IR discussions. In this case, the conformation of the dimethylamino group in **6** is shown in Figure 2, which is different from that in **7a** obtained by X-Ray diffraction study.[7] The magnetic environments of the two methyl groups have nearly the same conformation in **6**. Even if the rotation of the dimethylamino group is restricted, the differences of the chemical shifts may be too small to be detected in NMR spectra.

As described above, novel 9-substituted benz[*g*]indoles (**5**, **6**) are synthesized by the photolysis of the naphthyltriazoles, and their spectroscopic properties are investigated. As a result, interesting phenomena, especially the existence of the intramolecular hydrogen bonding and the restricted rotation about the 9-substituents, were found because of the functional groups in close proximity in peri-position of the naphthalene ring.

EXPERIMENTAL

All melting points were determined on a Mettler FP61 instrument and were uncorrected. ^{1}H NMR spectra recorded on a JEOL GX-400 spectrometer at 399.65 MHz using TMS as an internal standard. IR spectra were measured with JASCO 5MP spectrometer. UV spectra were measured with Shimadzu MPS-2000 spectrophotometer. MS spectra were measured with a JEOL JMS-01SG-2 spectrometer at 75 eV of ionization energy. Elemental analyses were performed on a Yanaco MT-3 CHN micro analyzer.

Diethyl 1*H*-benz[*g*]indole-2,3-dicarboxylate (**4a**) and diisopropyl 1*H*-benz[*g*]indole-2,3-dicarboxylate (**4b**) were prepared as previously reported.[4]

Photolyses of Naphthyltriazoles.

A solution of **1** (0.22 mmol) in 400 mL of methanol under nitrogen atmosphere was irradiated with a Ushio 450 W high-pressure mercury lamp through a quart well at 30-35 °C for 2 min. Then, the solvent was evaporated, and the reaction residue was chromatographed over silica gel (ether and hexane as an eluent) to give **5** together with starting material (**1**) and indoloindole derivative (**3**).

Diethyl 9-(4,5-diethoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-1*H*-benz[*g*]indole-2,3-dicarboxylate (**5a**): colorless needles, mp 93-94°C, 25 %. *Anal.* Calcd for $C_{26}H_{26}N_4O_8$: C, 59.77; H, 5.02; N, 10.72. Found: C, 59.65; H, 4.97; N, 10.65.

Diisopropyl 9-(4,5-diisopropoxycarbonyl-1*H*-1,2,3-triazol-1-yl)-1*H*-benz[*g*]indole-2,3-dicarboxylate (**5b**): colorless needles, mp 67-68°C, 30 %. *Anal.* Calcd for $C_{30}H_{34}N_4O_8$: C, 62.27; H, 5.92; N, 9.68. Found: C, 62.33; H, 5.95; N, 9.59.

A solution of **7** (0.26 mmol) in 400 mL of methanol was irradiated at 30-35 °C for 30 min using above apparatus under nitrogen atmosphere. The irradiated solution was evaporated and the residue was subjected to silica gel chromatography (ether and hexane as an eluent) to give **6**.

Diethyl 9-dimethylamino-1*H*-benz[*g*]indole-2,3-dicarboxylate (**6a**): colorless needles, mp 58-59°C, 12%. *Anal.* Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.71; H, 6.28; N, 7.85.

Diisopropyl 9-dimethylamino-1*H*-benz[*g*]indole-2,3-dicarboxylaye (**6b**): colorless needles, mp 52-53°C,

16%.   *Anal.*   Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.00; H, 6.77; N, 7.37.

Dynamic NMR Amalyses

Calculation for the complete line shape analysis of ^{1}H NMR spectra was carried out with a FACOM M-380 computer using the computer program EXNMR0,[8] which is based on well established theoretical models.[9] Theoretical spectra were calculated to get a best fit with the observed spectra by varying the exchange rate constants.   The activation parameters were obtained using the Eyring equation.[10]

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