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In this study, novel substituted quinoxaline 1,4-dioxides were synthesized from novel substituted benzofuroxan. 4,5(6,7)-Dimethylbenzofuroxan **3** was prepared by the thermal decomposition of 2,3-dimethyl-6-nitrophenylazide **2**. Novel quinoxaline 1,4-dioxides derivatives were obtained using compound **3** and the enolic form of 1,3-diketones **4** catalyzed by silica gel or molecular sieves. These reactions gave isomeric quinoxaline 1,4-dioxides **5** and **6**. These reactions of compound **3** may involve tautomers 4,5-dimethylbenzofuroxan **3a**, 6,7-dimethylbenzofuroxan **3b** on the surface of a solid catalyst.

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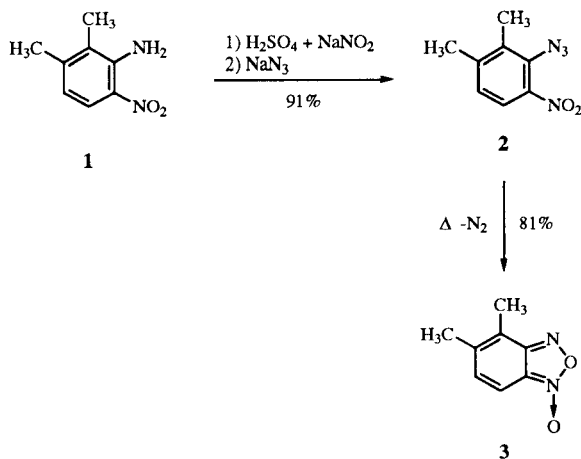
Benzofuroxan has been shown to have numerous pharmacological and industrial applications [1a-c]. The reactions of benzofuroxan with 1,3-diketones in basic medium provide the corresponding quinoxaline 1,4-dioxide derivatives [2]. Quinoxaline 1,4-dioxide derivatives have antibacterial and growth promoting activity. Some compounds are remarkably effective and currently used as animal feed additives. As a part of benzofuroxan chemistry, reactions of benzofuroxans with the corresponding quinoxaline 1,4-dioxides catalyzed by silica gel [3] or molecular sieves have been reported [4,5] and photo reactions of benzofuroxan using a high or low pressure mercury lamp have been examined [6]. This paper presents the synthesis of novel substituted quinoxaline dioxides from novel benzofuroxan derivatives with the enolic form of 1,3-diketones catalyzed by silica gel or molecular sieves.

The main synthetic routes of benzofuroxans were previously shown to be oxidation of *o*-quinone dioximes, decomposition of *o*-nitroaryl azides and oxidation of *o*-nitroanilines [1a-c]. The synthesis of 4,6-dimethylbenzofuroxan, 4,7-dimethylbenzofuroxan and 5,6-dimethylbenzofuroxan is discussed in previous articles [1a], but 4,5(6,7)-dimethylbenzofuroxan **3** has not been

reported. On this study, compound **3** was synthesized in good yield from 2,3-dimethyl-6-nitroaniline **1**. 2,3-Dimethyl-6-nitroaniline sulfate was diazotized by sodium nitrite. The diazo compound was converted to 2,3-dimethyl-6-nitrophenylazide **2** by sodium azide. The thermal decomposition of the azide in diethylene glycol gave the corresponding compound **3** (see Scheme I).

The method for synthesizing quinoxaline 1,4-dioxides derivatives was as follows: A solution of compound **3** and carbonyl compound in dichloromethane was evaporated in the presence of silica gel or molecular sieves. Both reagents were adsorbed on the silica gel or molecular sieves followed by standing at 110°. The reaction mixture was chromatographed on silica gel to give the corresponding isomeric quinoxaline 1,4-dioxides derivatives **5** and **6**. Assignments of product structures were based on the position of the carbonyl absorption band in the ir spectrum and ¹H nmr data. For example, compounds **5c** and **6c** showed

Scheme I



Scheme II

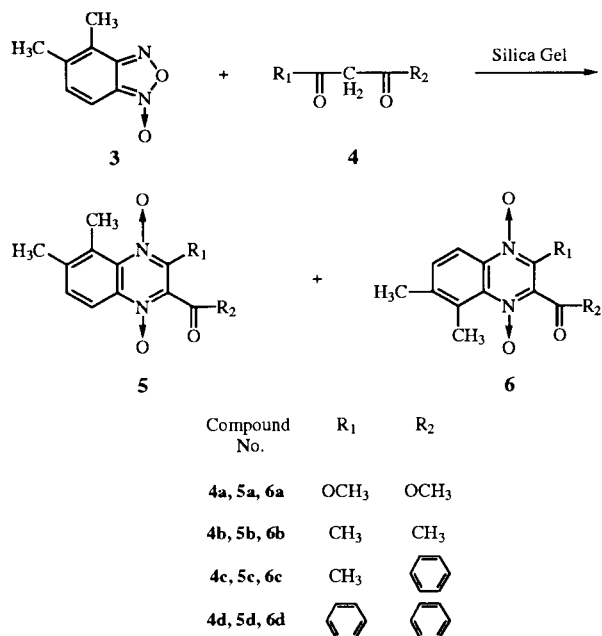


Table 1

Compound No.	Yield		5 + 6 (%)	Enol Content of 4 (%) (in Ethanol) [8]
	5	6		
a	—	—	0 [a]	0
b	17	10	27	84
c	18	15	33	94
d	23 [b]	12 [b]	35	90-100

[a] Recovery of compound **3** was 99%. [b] We couldn't separate compound **5d** and **6d**. These yields based on nmr data.

strong ir bands, the former at 1678 and the latter at 1681 cm^{-1} . These bands appeared to correspond to the benzoyl substituent, not the acetyl substituent. The ^1H nmr spectra showed a doublet at δ 7.63 for the proton at C7 of compound **5c** and δ 7.68 for the proton at C6 of compound **6c**. The proton at C6 of compound **6c** may possibly have incurred the polar effect of the carbonyl group. The products were characterized by comparison of ir and ^1H nmr spectra with those of other quinoxaline 1,4-dioxides [7].

Various 1,3-diketones **4a-d** in reaction with compound **3** were examined (see Table 1). Compound **4a** failed to react with compound **3** and unreacted **3** was almost recovered. By comparing yields of quinoxaline derivatives with enol content of the carbonyl compounds, it was found that the greater the enol content of carbonyl compound, the higher was the reactivity with compound **3**. The enol form of carbonyl compounds was found essential to the formation of quinoxaline dioxide derivatives.

A comparison of the reactivity of compound **3** with benzoylacetone was made with that of other dimethylbenzofuroxans. Table 2 shows the reaction of 5,6-dimethylbenzofuroxan **9** to proceed in good yield. However, compound **3** did not react very smoothly and 4,7-dimethylbenzofuroxan

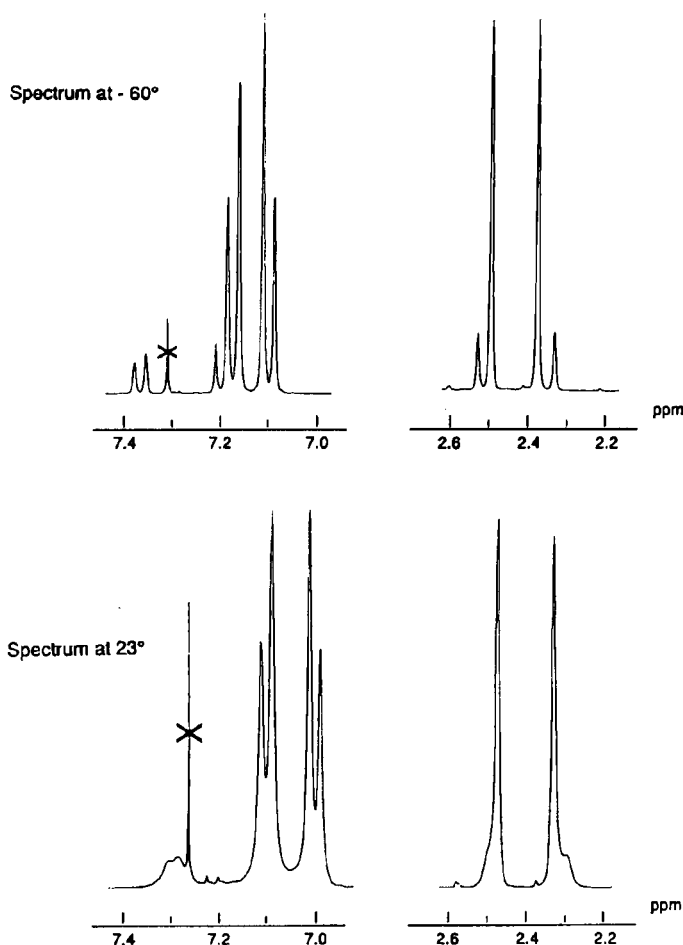


Figure 1. Low and Room Temperature nmr Spectra of Compound 3.

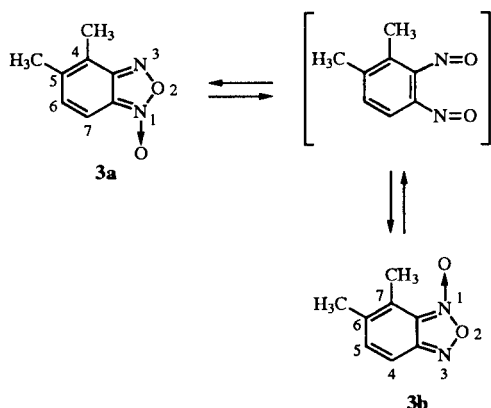
10 was recovered almost unchanged in the reaction with benzoylacetone. In these reactions, hyperconjugation of the

Table 2

3, 9, 10	4c	5, 6, 7, 8	
Compound No. and R	Product No. and R	Yield (%)	Reaction time (hours)
9 R1 = R4 = H R2 = R3 = CH ₃	7 R1 = R4 = H R2 = R3 = CH ₃	88	2
10 R1 = R4 = CH ₃ R2 = R3 = H	8 R1 = R4 = CH ₃ R2 = R3 = H	0 [a]	24
3 R1 = R2 = CH ₃ R3 = R4 = H	5c R1 = R2 = CH ₃ R3 = R4 = H	2 [b]	2
	6c R1 = R2 = H R3 = R4 = CH ₃	26 [b]	24

[a] Recovery of compound **10** was 92%. [b] Yields were compound **5c** + **6c**.

Scheme III



4-methyl group with the *N*-oxide group may possibly lessen the electron affinity of 1-nitrogen atoms. In addition, the reaction of compound **10** with the carbonyl compound may possibly be affected by steric hindrance between the 7-methyl group and *N*-oxide group.

The tautomerism of benzofuroxans was studied [1a-c]. It is that benzofuroxan rapidly rearranges between the two asymmetrical bicyclic structures through the ring opened dinitroso form in solution. Boulton reported 4,6-dimethylbenzofuroxan undergoes rearrangement to 5,7-dimethylbenzofuroxan [9]. Possibly, 4,5-dimethyl isomer **3a** readily undergoes rearrangement to 6,7-dimethyl isomer **3b** in solution (see Scheme III).

In Figure 1, ^1H nmr spectra of compound **3** are shown at low and room temperature, the low temperature spectra correspond to 4,5-dimethylbenzofuroxan and 6,7-dimethylbenzofuroxan, and those at room temperature to rapid equilibrating mixture of the two equivalent unsymmetrical forms.

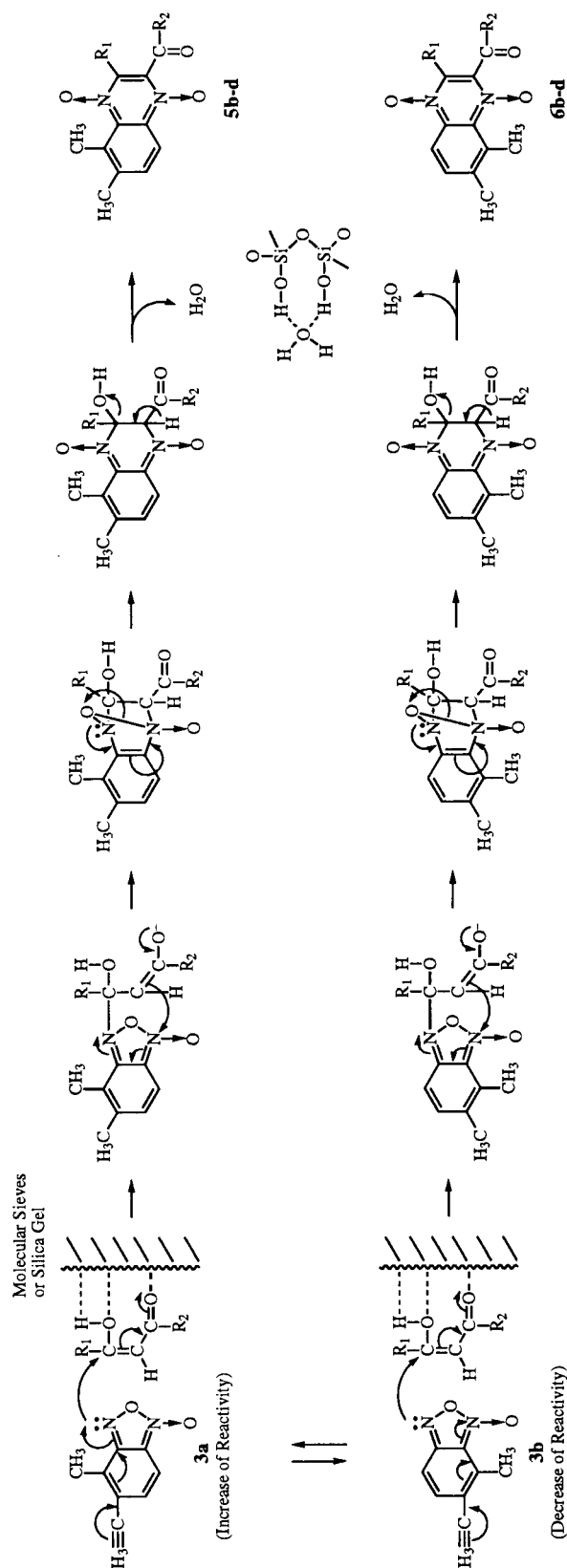
These reactions of compound **3** may involve tautomers **3a**, **3b** on the surface of a solid catalyst. Thus, with 1,3-diketones **4b-d**, the reactions may lead to the formation of isomeric quinoxaline 1,4-dioxides derivatives. Table I shows the yields of type-6 quinoxaline 1,4-dioxides to be less than those of type-5 quinoxaline 1,4-dioxides. The hyperconjugation of 6-methyl group of **3b** with *N*-oxide group may possibly lessen the electron affinity of 1-nitrogen atoms. The reaction mechanism may thus be considered to be the following:

The present reactions will be studied in greater detail in the future.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. The ir spectra were recorded on a Jasco FT IR-300 spectrometer. The ^1H and ^{13}C nmr spectra were recorded on a JEOL JNM-GSX 400 FT NMR and JNM-EX 400 FT NMR System with TMS as the internal

Scheme IV



standard. The mass spectra were recorded on a Hitachi M-2000 spectrometer with an electron beam energy of 70 eV. Microanalyses were performed at microanalytical laboratory of the Center for Instrumental Analysis in College of Science & Technology, Nihon University.

2,3-Dimethyl-6-nitrophenylazide **2**.

A solution of 2,3-dimethyl-6-nitroaniline **1** (3.32 g, 0.02 mole) in glacial acetic acid (30 ml) and concentrated sulfuric acid (16 ml) was cooled until the temperature of solution was 0–5° and treated with sodium nitrite (1.73 g, 0.025 mole) in water (3 ml). To the resulting solution of the diazonium ion was added sodium azide (3.0 g, 0.045 mole) in water (8.4 ml) and maintained at 0–5°. Stirring was then continued for 0.5 hour at room temperature. The reaction mixture was then diluted with water (50 ml). The precipitate was collected, washed with water and dried overnight. It was then added to a silica gel (Wakogel C-200, Wako Pure Chemical Industries) column and product 2,3-dimethyl-6-nitrophenylazide **2** was eluted with *n*-hexane/dichloromethane (9:1). There was obtained 3.50 g (yield 91%) of **2**. Recrystallization from *n*-hexane afforded white prisms. Compound **2** had mp 67–68°; ir (potassium bromide): ν 2140, 1584, 1512, 1343 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.11 (d, 1H, H-4, $J_{4,5}$ = 8 Hz), 7.75 (d, 1H, H-5, $J_{4,5}$ = 8 Hz); hrms: (m/z) 192.0636. Calcd. for $\text{C}_8\text{H}_8\text{N}_4\text{O}_2$: M, 192.0646.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_4\text{O}_2$: C, 49.99; H, 4.20; N, 29.16. Found: C, 50.04; H, 4.18; N, 29.36.

4,5(6,7)-Dimethylbenzofuroxan **3**.

Compound **2** (3.46 g, 0.018 mole) was dissolved in diethylene glycol (10 ml) and heated at 150° for 2 hours and then this reaction mixture was poured onto crushed ice. The crude product was collected, washed with water, dried over night. It was then added to a silica gel column and product 4,5-dimethylbenzofuroxan **3** was eluted with *n*-hexane/dichloromethane (9:1). There was obtained 2.40 g (yield 81%) of **3**. Recrystallization from *n*-hexane afforded light yellow needles. Compound **3** had mp 86–88°; ir (potassium bromide): ν 1614, 1587, 1538, 1486, 1380 cm^{-1} ; ^1H nmr (deuteriochloroform): at –60°, δ 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 7.10 (d, 1H, J = 9 Hz), 7.17 (d, 1H, J = 9 Hz), 7.20 (d, 1H, J = 9 Hz), 7.37 (d, 1H, J = 9 Hz), at 23°, δ 2.33 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 7.01 (d, 1H, J = 9 Hz), 7.10 (d, 1H, J = 9 Hz); hrms: (m/z) 164.0581. Calcd. for $\text{C}_8\text{H}_8\text{N}_2\text{O}_2$: M, 164.0585.

Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_2\text{O}_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.67; H, 4.88; N, 17.15.

2-Acetyl-3,5,6-trimethylquinoxaline 1,4-Dioxides **5b** and 2-Acetyl-3,7,8-trimethylquinoxaline 1,4-Dioxides **6b**.

To a solution of **3** (164.0 mg, 0.001 mole) and acetylacetone **4b** (110 mg, 0.0011 mole) in dichloromethane (10 ml) was added silica gel (Wakogel C-200, Wako Pure Chemical Industries, 30 g) and the mixture was evaporated in an evaporator at 30°. The silica gel containing the adsorbed reagents was allowed to stand for 24 hours, at 110°. It was then added to a silica gel column and products 2-acetyl-3,5,6-trimethylquinoxaline 1,4-dioxides **5b** and 2-acetyl-3,7,8-trimethylquinoxaline 1,4-dioxides **6b** were eluted with dichloromethane/methanol (98:2). They were purified by preparative tlc (Merck silica gel plate 60 F₂₅₄ Art. 5717) with dichloromethane/methanol (97:3), yield **5b** 42 mg (17%), **6b** 25 mg (10%).

Recrystallization of **5b** from methanol afforded light yellow needles. Compound **5b** had mp 136–138°; ir (potassium bromide): ν 1704 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.03 (s, 3H, CH_3), 7.62 (d, 1H, H-7, $J_{7,8}$ = 9 Hz), 8.36 (d, 1H, H-8, $J_{7,8}$ = 9 Hz); hrms: (m/z) 246.0995. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$: M, 246.1003.

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.59; H, 5.81; N, 11.30.

Recrystallization of **6b** from methanol afforded light yellow needles. Compound **6b** had mp 146–148°; ir (potassium bromide): ν 1720 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.49 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 7.65 (d, 1H, H-6, $J_{5,6}$ = 9 Hz), 8.44 (d, 1H, H-5, $J_{5,6}$ = 9 Hz); hrms: (m/z) 246.0994. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$: M, 246.1003.

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.43; H, 5.79; N, 11.26.

2-Benzoyl-3,5,6-trimethylquinoxaline 1,4-Dioxides **5c** and 2-Benzoyl-3,7,8-trimethylquinoxaline 1,4-Dioxides **6c**.

To a solution of **3** (164 mg, 0.001 mole) and benzoylacetone **4c** (178 mg, 0.0011 mole) in dichloromethane (10 ml) was added silica gel (30 g) and the mixture was evaporated in an evaporator at 30°. The silica gel containing the adsorbed reagents was allowed to stand for 24 hours, at 110°. It was then added to a silica gel column and products 2-benzoyl-3,5,6-trimethylquinoxaline 1,4-dioxides **5c** and 2-benzoyl-3,7,8-trimethylquinoxaline 1,4-dioxides **6c** were eluted with dichloromethane/methanol (98:2). They were purified by preparative tlc with dichloromethane/acetonitrile (98:2), yield **5c** 55 mg (18%), **6c** 46 mg (15%).

Recrystallization of **5c** from methanol afforded light yellow needles. Compound **5c** had mp 221–223°; ir (potassium bromide): ν 1678 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.41 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 7.52–7.58 (m, 2H, arom), 7.63 (d, 1H, H-7, $J_{7,8}$ = 9 Hz), 7.64–7.68 (m, 1H, arom), 7.89–7.90 (m, 2H, arom), 8.37 (d, 1H, H-8, $J_{7,8}$ = 9 Hz); hrms: (m/z) 308.1149. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$: M, 308.1159.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.34; H, 5.24; N, 9.14.

Recrystallization of **6c** from methanol afforded light yellow needles. Compound **6c** had mp 229–230°; ir (potassium bromide): ν 1681 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 7.50–7.54 (m, 2H, arom), 7.65–7.69 (m, 1H, arom), 7.68 (d, 1H, H-6, $J_{5,6}$ = 9 Hz), 7.89–7.90 (m, 2H, arom), 8.51 (d, 1H, H-5, $J_{5,6}$ = 9 Hz); hrms: (m/z) 308.1155. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$: M, 308.1159.

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.30; H, 5.20; N, 9.07.

2-Phenyl-3-benzoyl-5,6-dimethylquinoxaline 1,4-Dioxides **5d** and 2-Phenyl-3-benzoyl-7,8-dimethylquinoxaline 1,4-Dioxides **6d**.

To a solution of **3** (164 mg, 0.001 mole) and dibenzoylmethane **4d** (246 mg, 0.0011 mole) in dichloromethane (10 ml) was added silica gel (30 g) and the mixture was evaporated in an evaporator at 30°. The silica gel containing the adsorbed reagents was allowed to stand for 2 hours, at 110°. It was then added to a silica gel column and products 2-phenyl-3-benzoyl-5,6-dimethylquinoxaline 1,4-dioxides **5d** and 2-phenyl-3-benzoyl-7,8-dimethylquinoxaline 1,4-dioxides **6d** were eluted with dichloromethane/methanol (99:1), yield **5d** 23%, **6d** 12%. We

could not separate **5d** and **6d**. These yields based on nmr data, the integration of methyl protons was used to determine the isomeric ratio of **5d**:**6d** in a mixture. A mixture of **5d** and **6d** had mp 218-222°; ir (potassium bromide): ν 1684 (C=O) cm^{-1} ; ^1H nmr (deuteriochloroform): δ 2.55 (s, 3H, CH_3), 3.01 (s, 3H, CH_3), 7.13-7.80 (m, 10H, arom), 7.64 (d, 1H, H-7, $J_{7,8} = 9$ Hz), 8.55 (d, 1H, H-8, $J_{7,8} = 9$ Hz) for **5d**, and 2.57 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 7.13-7.80 (m, 10H, arom), 7.69 (d, 1H, H-6, $J_{5,6} = 9$ Hz), 8.44 (d, 1H, H-5, $J_{5,6} = 9$ Hz) for **6d**; hrms: (m/z) 370.1267. Calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$: M, 370.1315.

Anal. Calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_3$: C, 74.58; H, 4.90; N, 7.56. Found: C, 74.37; H, 4.73; N, 7.37.

Reactions of Other Dimethylbenzofuroxans with Compound **4c** on Molecular Sieves 3A.

General Procedure.

2-Benzoyl-3,6,7-trimethylquinoxaline 1,4-Dioxides **7**.

To a solution of 5,6-dimethylbenzofuroxan **9** (164 mg, 0.001 mole) and **4c** (178 mg, 0.0011 mole) in dichloromethane (10 ml) was added molecular sieves (3A powder, Nacalai Tesque Inc., 5 g) and the mixture was evaporated in an evaporator at 30°. The molecular sieves containing the adsorbed reagents was allowed to stand for 2 or 24 hours, at 90°. It was then added to a silica gel column and 2-benzoyl-3,6,7-trimethylquinoxaline 1,4-dioxides **7** was eluted with dichloromethane/methanol (98:2). It was

purified by preparative tlc with dichloromethane/methanol (98:2), yield **7** 269 mg (88%). Product **7** was characterized by comparison of mp and ir spectrum with authentic sample prepared according to our previous article [5].

REFERENCES AND NOTES

- * To whom correspondence should be addressed.
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