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SYNTHESIS OF 6-BROMO-4-METHYLBENZOFUROXAN

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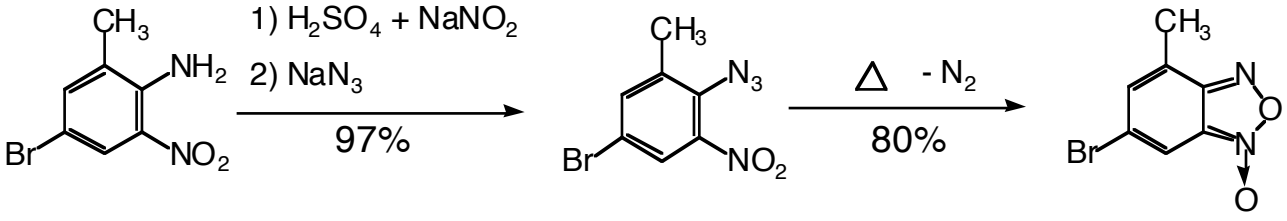
Abstract - 6-Bromo-4-methylbenzofuroxan (**3**) was prepared by the thermal decomposition of 4-bromo-2-methyl-6-nitrophenylazide in excellent yields. ^{1}H-NMR spectra showed that the compound (**3**) rapidly rearranges between the two unsymmetrical bicyclic structures. However, the methyl group and bromine may possibly function as a barrier against molecular rearrangement and so molecular rearrangement is slow enough that different chemical shifts are apparent at room temperature.

INTRODUCTION

Benzofuroxan (benzofurazan *N*-oxide) has been shown to have numerous pharmacological and industrial applications.[1a-d] As a part of benzofurazan chemistry, reactions of various benzofuroxans with active methylene compounds catalyzed by silica gel[2] or molecular sieves[3-4] yield the corresponding quinoxaline 1,4-dioxides, and the antibacterial activity of quinoxaline 1,4-dioxides has been reported.[5] Pyrido[2,3-*b*]pyrazine 1,4-dioxides have been obtained from pyrido[2,3-*c*]furoxan catalyzed by treatment with silica gel, alumina, or molecular sieves[6] and the antibacterial activity of

pyrido[2,3-*b*]pyrazine 1,4-dioxides has been reported.[7] Reactions of benzofuroxan with various phenolic compounds catalyzed by silica gel, alumina, or molecular sieves provide the corresponding phenazine 5,10-dioxide derivatives[8] and the antibacterial activity of phenazine 5,10-dioxide derivatives has been reported.[9] The toxicity of benzofurazans in *Escherichia coli* has been reported to be caused by an increase in intracellular flux of superoxide on aerobic incubation.[10] Superoxide production was confirmed using the cytochrome *c* reduction method and ESR spectra.[11] 4,7-Dimethylbenzofurazan was transformed by $^1O_2$ into 4,7-dimethylbenzofurazan 4,7-endoperoxide, in excellent yields.[12]

The main synthetic routes to benzofuroxan derivatives are oxidation of *o*-quinone dioximes, decomposition of *o*-nitroaryl azides and oxidation of *o*–nitroanilines. [1a-d] In this study, 6-bromo-4-methylbenzofuroxan (**3**) was synthesized in good yield from 4-bromo-2-methyl-6-nitroaniline (**1**). 4-Bromo-2-methyl-6-nitroaniline sulfate was diazotized by sodium nitrite. The diazo compound was converted to 4-bromo-2-methyl-6-nitrophenylazide (**2**) by treatment with sodium azide. The thermal decomposition of the azide (**2**) in diethylene glycol gave the corresponding compound (**3**) (see Scheme I).



1 **2** **3**

Scheme 1

The compound (**3**) has an interesting ^{1}H-NMR spectrum which showed two each of two kinds of singlets from δ 7.2 to 8.2 ppm at room temperature. The spectrum showed

different chemical shifts that look like devised from two compounds. The temperature-dependent ^{1}H-NMR spectra for compound (**3**) are shown in Figure 1. The two kinds of signals were broadened at 40 °C and then changed to one kind of signal at 60 °C. After cooling, the ^{1}H-NMR spectrum returned to the former room temperature spectrum. In general, benzofuroxan derivatives rapidly rearrange between the two unsymmetrical bicyclic structures via a transitional ring opened dinitroso form. [1a-d] We believe that the compound (**3**) must undergo the same molecular rearrangement as other benzofuroxans (see Figure 2).

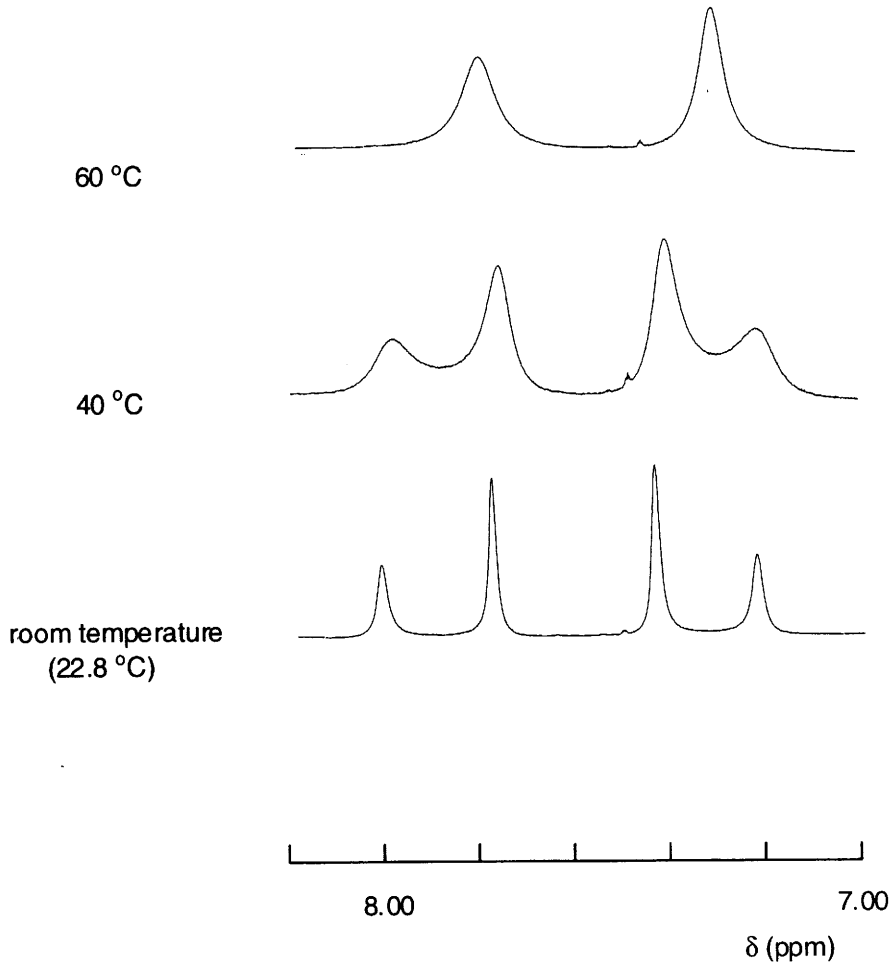
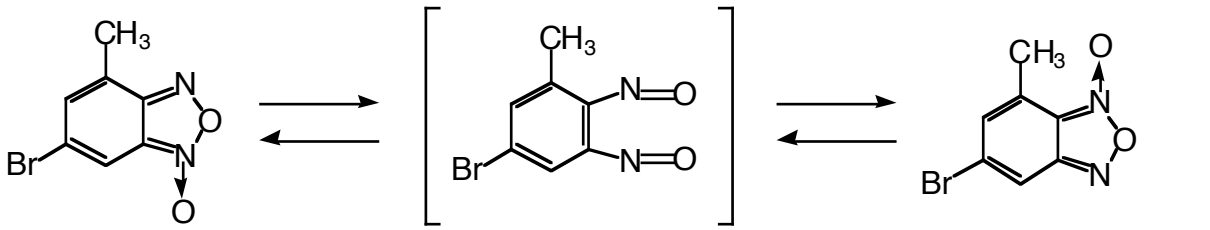


Figure 1

Then, the ^{1}H-NMR spectra of compound (**3**) at room temperature and at high temperature were obtained. The room temperature spectrum indicates the two equivalent unsymmetrical forms, and those at high temperature indicates the rapidly equilibrating mixture of the two equivalent unsymmetrical forms.



62 %
(in DMSO-d_6)

38 %
(in DMSO-d_6)

3a **3b**

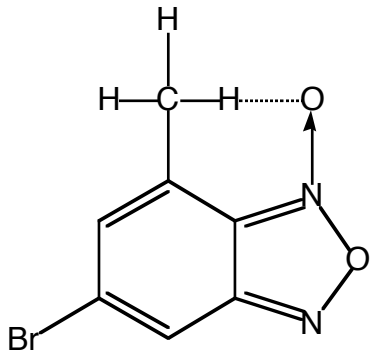
Figure 2

Thus in the ^{1}H-NMR spectrum at room temperature, the compound (**3**) showed two kinds of signals, two large peaks from the tautomer (**3a**) and two smaller signals from the tautomer (**3b**).

The above tautomer ratio in DMSO-d_6 at room temperature was determined from the aromatic proton integration.

The above extra phenomenon exhibited by the compound (**3**) can be explained in terms of a weak hydrogen bonding between *N*-oxide oxygen and the methyl group and the influence of the 6-position bromine as an electron-withdrawer. Ikekawa and Sato also reported the presence of a weak hydrogen bonding between the oxygen atom of *N*-oxide group and the hydrogen atom of the 2-methyl group as in the case of 2-methylpyridine 1-oxide.[13] The *N*-oxide oxygen of the compound (**3**) is attracted by the hydrogen atom of the methyl group. The methyl group may then possibly function as a barrier against molecular rearrangement and so molecular rearrangement is slow enough that different chemical shifts are apparent at room temperature. It is thus likely that one of the reason

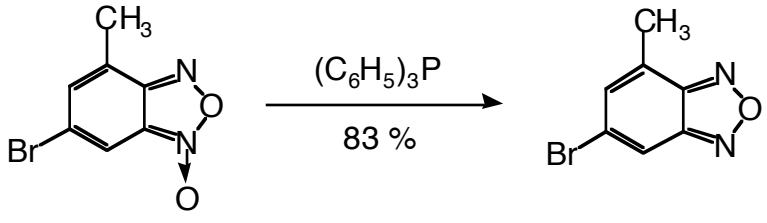
for slow molecular rearrangement is a weak hydrogen bonding between the oxygen atom of *N*-oxide group and the hydrogen atom of the methyl group (see Figure 3).



3b

Figure 3

Next, for comparison with chemical shift of aromatic protons of 6-bromo-4-methylbenzofurazan (**4**) which has no *N*-oxide and tautomerism, compound (**4**) was prepared by reduction of compound (**3**) with triphenylphosphine in excellent yield (see Scheme 2). ^{1}H-NMR spectrum of the compound (**4**) did not show two kinds of signals as in compound (**3**) but rather two doublets (δ 7.53, 8.30, $J_{5,7}$ = 1.1 Hz) at room temperature.

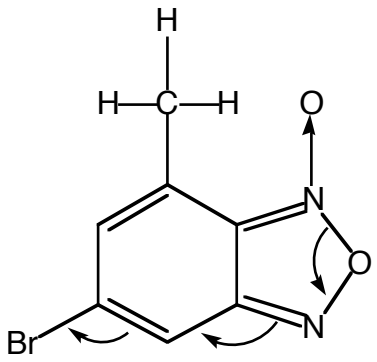


3 **4**

Scheme 2

It may be inferred that the effect of benzofuroxan tautomerism shows the two kinds of singnals in the ^{1}H-NMR spectrum of compound (**3**) at room temperature.

The electron-withdrawing 6-position bromine may produce the effect as shown in Figure 4. It is possible that the electron movement makes tautomer (**3b**) into an opened dinitroso form. The transformation to the ring opened dinitroso form from the tautomer (**3b**) may be made easier than from tautomer (**3a**) by influence of bromine. It is likely that this is one of the reasons why the tautomer (**3a**) ratio was greater than that of tautomer (**3b**) at room temperature**.**



3b

Figure 4

As a result of these effects of methyl group and bromine, it is thus understandable that slow molecular rearrangement occurs and that there is more tautomer (**3a**) present than tautomer (**3b**) at room temperature.

EXPERIMENTAL

Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were obtained by a JASCO ir-810 spectrophotometer. The ^{1}H-NMR spectra were obtained by a JNM-GSX 400 FT NMR System with TMS as the internal standard. The MS spectra were obtained by a Hitachi M-2000 and a JEOL

JMS-GCmate spectrometer with an electron beam energy of 70 eV. Microanalysis was performed at the microanalytical laboratory of the Center for Instrumental Analysis in College of Science & Technology, Nihon University.

4-Bromo-2-methyl-6-nitrophenylazide (**2**).

A solution of 4-bromo-2-methyl-6-nitroaniline (**1**) (2.31 g, 10 mmol) in glacial acetic acid (30 mL) and concentrated sulfuric acid (8 mL) was cooled until the temperature of solution was 0-5 ºC and then treated with sodium nitrite (0.95 g, 13.8 mmol) in water (10 mL). To the resulting solution of the diazonium ion was added sodium azide (1.50 g, 23 mmol) in water (10 mL) and the mixture maintained at 0-5 ºC. Stirring was then continued for 0.5 h at rt. The reaction mixture was then diluted with water. 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 4-bromo-2-methyl-6-nitrophenylazide (**2**) was eluted with n-hexane/dichloromethane (95:5), and purified by preparative TLC (Merck, Silica gel plate 60 F_{254} Art. 1.05717) with n-hexane/dichloromethane (9:1). Yield 2.48 g (97 %). Compound (**2**) had mp 61-62 ºC; IR (KBr): ν 2151, 1532, 1460, 1345 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.58 (s, 1H, H-5), 7.94 (s, 1H, H-7); HRMS (EI): Found: 255.9599. Calcd for $C_7H_5N_4O_2Br$(M): 255.9595; Anal. Calcd for $C_7H_5N_4O_2Br$: C,32.71; H,1.96; N,21.80. Found: C, 32.91; H, 2.10; N, 21.56.

6-Bromo-4-methylbenzofuroxan (**3**).

Compound (**2**) (2.31 g, 10.1mmol) was dissolved in diethylene glycol (20 mL) and heated at 150 ºC for 2 h and then this reaction mixture was poured onto crushed ice. The crude product was collected, washed with water, dried overnight. It was then added to a silica gel column and 6-bromo-4-methylbenzofuroxan (**3**) was eluted with n-hexane/dichloromethane (9:1). Yield 1.65 g (80 %). Recrystallization from n-hexane afforded light yellow needles. Compound (**3**) had mp 65-66 ºC; IR (KBr) : ν 1617, 1564, 1476, 1385 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 7.24 (s, 0.38H, H-5b) , 7.45 (s, 0.62H, H-5a) , 7.80 (s, 0.62H, H-7a) , 8.03 (s, 0.38H, H-7b), ^{1}H-NMR ($CDCl_3$)): δ 2.57 (s, 3H, CH_3), 6.95 (s, 0.33H, H-5b) , 7.15 (s, 0.67H, H-5a) , 7.42 (s,

0.67H, H-7a), 7.62 (s, 0.33H, H-7b); HRMS (EI): Found: 227.9554. Calcd for $C_7H_5N_2O_2Br$(M): 227.9533; Anal. Calcd for $C_7H_5N_2O_2Br$: C, 36.71; H, 2.20; N, 12.33. Found: C, 36.64; H, 2.27; N, 12.25.

6-Bromo-4-methylbenzofurazan (**4**)

A solution of compound (**3**) (114.5 mg, 0.5 mmol) and triphenylphosphine (135 mg, 0.515 mmol) in xylene (5 mL) was refluxed for 6 h. The mixture was then added to a silica gel column and 6-bromo-4-methylbenzofurazan (**4**) was eluted with n-hexane/dichloromethane (95:5), and purified by preparative TLC (Merck, Silica gel plate 60 F_{254} Art. 1.05717) with n-hexane/dichloromethane (9:1). Yield 88.4 mg (83 %). Compound (**4**) had mp 78-80 °C; IR (KBr) : ν 1606, 1551, 1462 ,1300 cm^{-1} ; ^{1}H-NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 7.53 (d, 1H, $J_{5,7}$ = 1.1 Hz, H-5) , 8.30 (d, 1H, $J_{5,7}$ = 1.1 Hz, H-7); HRMS (EI): Found: 211.9582. Calcd for $C_7H_5N_2OBr$(M): 211.9584; Anal. Calcd for $C_7H_5N_2OBr$: C,39.47; H,2.37 ; N, 13.15. Found: C, 39.69; H, 2.58; N, 12.99.

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* To whom correspondence should be addressed.

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