The Conformational Analysis of a Series of 4,8-Dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-Oxides Using NMR

Tomihiro NISHIYAMA, Yasushi NAKAI, Hideaki SHISHIBORI, and Fukiko YAMADA*

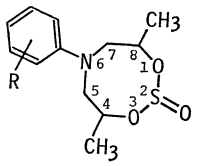
Department of Applied Chemistry, Faculty of Engineering, Kansai University, Senriyama, Suita, Osaka 564

(Received August 1, 1980)

The title compounds were prepared, and their ^{1}H- and ^{13}C-NMR spectra were examined. On the basis of the data for the benzene-solute collision complexes and the magnitudes of the γ shifts, five isomeric conformations of the compounds were discussed.

Recently, a number of conformational analyses of ethylene and trimethylene sulfites have been reported.[1-4] For example, Green and Hellier[1] have used the IR technique of the S=O stretching vibrations to study the conformation of trimethylene sulfites. They concluded that the higher wave number band (*ca.* 1195 cm^{-1}) is attributable to the chair form with an axial S=O function and/or flexible twist forms, while the lower wave number band (*ca.* 1234 cm^{-1}) is to be assigned to the chair form with an equatorial S=O group. Buchanan *et al.*[4] reported ^{13}C-NMR data on trimethylene sulfites and ten alkyl derivatives and concluded that these compounds exist in the chair form with an axial or equatorial S=O function and twist conformations.

In a previous paper,[5] we ourselves reported the reaction of *N,N*-bis(2-hydroxyethyl)anilines with thionyl chloride giving the 6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxides, which had a structure similar to that of the trimethylene sulfite skeleton. In order to obtain more stereochemical information about the 1,3,2,6-dioxathiazocine 2-oxide system, it seems desirable to prepare 1,3,2,6-dioxathiazocine 2-oxides with a ortho-, meta-, para-substituent on the *N*-phenyl ring and methyl group on the C-4 and C-8. In this paper we wish to report the conformational analyses of 4,8-dimethyl-6-phenyl-5,6,7,8-tetrahydro-4*H*-1,3,2,6-dioxathiazocine 2-oxides (**1**—**7**) by means of NMR spectroscopy.



1, R=H
2, R=*o*-CH_3
3, R=*m*-CH_3
4, R=*p*-CH_3
5, R=*o*-Cl
6, R=*m*-Cl
7, R=*p*-Cl

Experimental

Measurements. All the melting points are uncorrected. All the NMR spectra were determined at 100- and 60-MHz with JEOL JNM-PS-100 and JNM-PMX-60 spectrometers respectively. The ^{13}C-NMR spectra were obtained using a JNM-PS-100/EC-100 Fourier transform spectrometer operating at 25.15 MHz, with complete proton decoupling. The pulse width and repetition time were 10.2 μs for a 45° pulse and 6 s respectively. The spectra were observed as

TABLE 1. CHARACTERIZATION DATA OF THE 1,3,2,6-DIOXATHIAZOCINE 2-OXIDES

Compd No.	Yield/%	Mp/°C	IR, S=O ν/cm^{-1}	Found (Calcd) %		
				C	H	N
1a	18	205.0—206.0	1193	56.36 (56.45)	6.65 (6.71)	5.42 (5.48)
1b	8	122.0—122.7	1190	56.34	6.75	5.47
1c	6	88.2— 88.8	1182	56.24	6.80	5.47
2d	23	109.5—110.0	1190	58.09 (57.97)	7.14 (7.11)	5.11 (5.20)
2e	5	—[a]	1200	58.56	7.24	5.08
3a	2	137.8—138.0	1187	57.62	7.28	5.15
3b	13	80.2— 81.5	1187	58.20	7.14	5.05
3c	6	46.1— 47.0	1200	58.21	7.22	5.15
4a	50	182.0—182.9	1190	57.74	7.07	5.18
4b	8	93.9— 94.1	1182	57.12	7.35	5.13
4c	17	78.0— 79.0	1192	57.65	7.19	5.14
5d	12	87.5— 89.5	1187	49.64 (49.74)	5.55 (5.57)	4.89 (4.83)
5e	15	—[a]	1200	49.15	5.47	4.93
6a	5	158.0—158.9	1202	49.66	5.57	4.89
6b	7	125.0—125.5	1190	49.44	5.42	4.77
6c	15	90.0— 90.6	1200	49.78	5.43	4.78
7a	9	163.4—164.2	1195	49.43	5.51	4.79
7b	20	99.5—100.0	1190	49.45	5.54	4.79
7c	21	137.0—137.3	1198	49.56	5.43	4.88

a) Liquid.

2 mmol cm^{-3} solutions in $CDCl_3$ with a spectral width of 6250 Hz (data points : 8192). The chemical shifts were referred to the internal TMS as the standard. The IR spectra were recorded on a Shimadzu Model 27-G grating spectrophotometer on a KBr for the solid materials or on a NaCl plate for the liquid materials.

Compounds. The series of **1**—**7** was prepared by the reaction of the corresponding *N*,*N*-bis(2-hydroxypropyl)-anilines with thionyl chloride, as has been described in our previous paper.[5] The purification of the crude product by the use of a short silica gel column, with hexane or a hexane–benzene (1:1) mixture as an eluent, and subsequent recrystallization afforded two or three pure isomers as colorless crystals; these compounds gave satisfactory results for mass spectra and elemental analyses. The physical properties of the compounds of **1**—**7** are listed in Table 1.

Results and Discussion

S=O Frequencies. The IR spectra of **1**—**7** showed a characteristic band of the S=O function at 1190—1200 cm^{-1} (Table 1). Trimethylene sulfites prefer the chair form with an axial S=O group, and the same conformational preference is found for six-membered-ring sulfoxides.[6,7] In the case of trimethylene sulfites,[8] the S=O stretching band at 1190 cm^{-1} (CCl_4) to 1198 cm^{-1} (C_6H_{12}) indicates a axial S=O conformer, while 1233 (CS_2) to 1234 cm^{-1} (C_6H_{12}) is a equatorial conformer. Twist conformations apparently give intermediate values.

If this consideration can be extended to Compounds **1**—**7**, the position of the S=O stretching band of 1190—1120 cm^{-1} would indicate a predominance of the axial conformer or the twist conformer.

^{1}H-NMR Spectra. The NMR spectra of the heterocyclic protons of **5d**, **5e**, **7a**, **7b**, and **7c** are shown in Fig. 1. The NMR spectra of **7a** and **7b** consist of four distinct sets of multiplets, at *ca.* δ 4.7—4.9(m), 3.7—3.8(q), 3.1(q), and 1.3—1.4(d), for which a straightforward analysis was possible. In contrast, in Compounds **5d**, **5e**, and **7c**, the methylene protons for H-5 and H-7 gave complicated multiplets and were not easily analyzed. Striking differences in Compounds **5e** and **7c** compared with Compounds **5d**, **7a**, and **7b** are recognizable in the signals of the methine protons for H-4 and H-8. That is, two kinds of methine protons of H-4 and H-8 for **5e** and **7c** appeared at *ca.* δ 5.1 and 4.6 ppm. We subdivided the spectra into five types—A, B, C, D, and E, as can be seen in Fig. 1. The spectra of the compounds with an ortho-substituent may all be considered to belong to types A and B. Similarly, those without a substituent or with meta- and para-substituents belong to types C, D, and E. The methine proton for H-4 and/or H-8 of **5d**, **7a**, and **7b** shows one set of multiplets, while compounds of **5e** and **7c** show two sets of multiplets. We have, therefore, suggested that, in the case of Compounds **5d**, **7a**, and **7b**, the possible comformations are in the symmetric form, while, in contrast, Compounds **5e** and **7c** are asymmetric forms.

From the above considerations, the possible conformations of Types A, C, and D are illustrated in Scheme 1. For discussing the eight-membered-ring

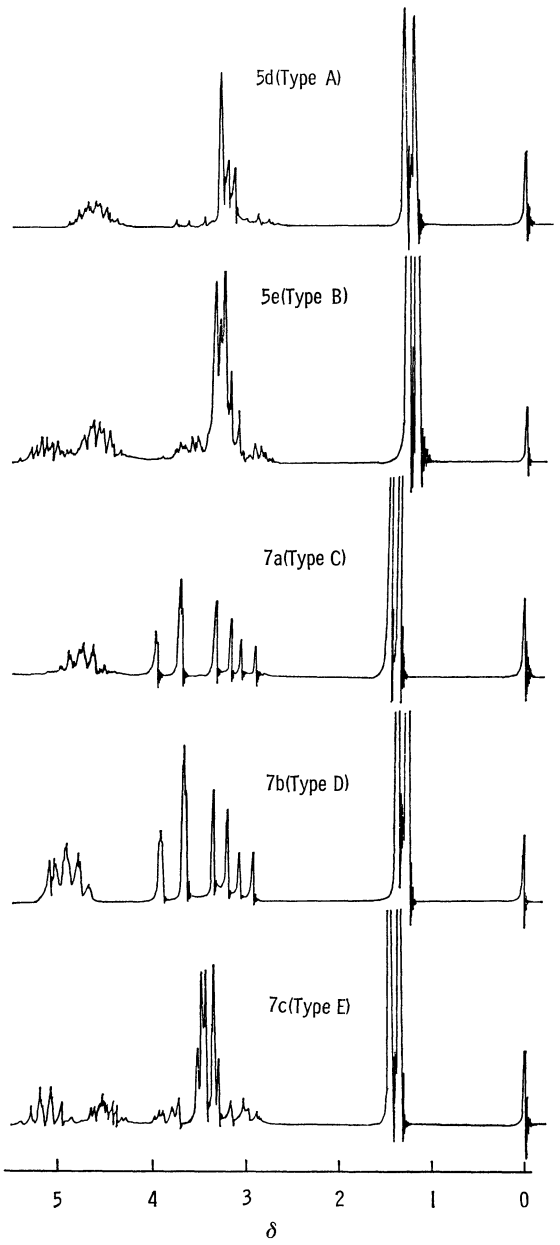
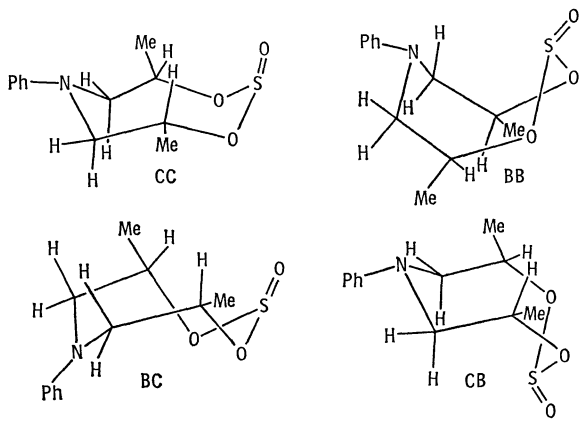


Fig. 1. NMR spectra of the heterocyclic and methyl protons of **5** and **7** in $CDCl_3$.



Scheme 1. Possible conformations of types A, C, and D.

stereochemistry, we used the nomenclature established for cyclooctane.[9]

For the geometry of solute-solvent collision complexes, Ledaal[10] proposed a common model with the dipole axis of the solute molecule located along the sixfold-symmetry axis of a benzene nucleus, with the positive end of the dipole nearest, and the negative end farthest away from, it. As for the aromatic solvent effect on the sulfoxides, our recent papers have also described the same type of collision complexes in connection with the stereochemistry of the 3-aryl-1,2,3-oxathiazolidine 2-oxides.[11,12]

Assuming that collision complexes of a similar geometry are formed between the benzene molecule (solvent) and the S=O bond in the compounds for chair-chair (CC), boat-boat (BB), boat-chair (BC), and chair-boat (CB) conformations, the following considerations are presented. For the CC conformation, benzene association should take place from the H-5 and H-7 axial protons of the solute molecule, *i.e.*, from the positively polarized end of the S=O bond. Consequently, the H-4 and H-8 axial protons are strongly deshielded. In the BB conformation, the benzene molecule should be formed from the H-4, H-5, H-7, and H-8 axial protons of the solute molecule; consequently, it is anticipated that all the protons of the heterocyclic ring will experience strong shielding effects in a benzene solution. Similar considerations are possible for the BC and CB conformations. That is, the axial protons of H-4, H-5, H-7, and H-8 are more deshielded than the remaining equatorial protons and methyl protons for the BC conformation. In the CB conformation, all the protons are shielded.

Table 2 shows the benzene-induced shift (Δ=

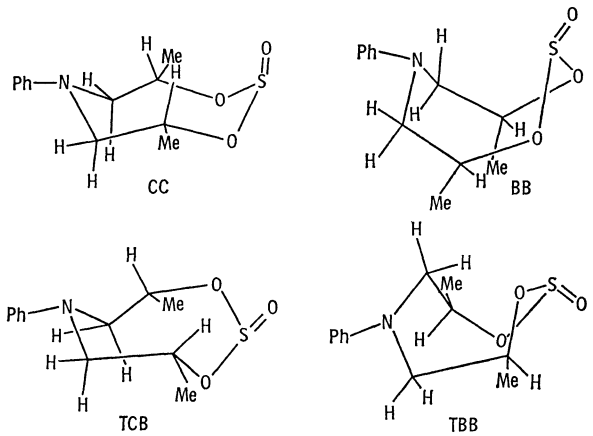
TABLE 2. ^{1}H-NMR CHEMICAL SHIFTS AND BENZENE-INDUCED SOLVENT SHIFTS FOR **1—7**

Compd No.	Chemical shifts, δ						
	H-4	H-8	H-5 and H-7		CH_3-4	CH_3-8	R
			axi-H	eq-H			
1a	4.78(m) (0.57)		3.85(q, J_{gem}=15.7, J_{vic}=1)[a] (0.57)[b]	3.08(q, J_{vic}=9.1) (0.60)	1.38(d, J=6.2) (0.52)		
1b	4.97(m) (0.01)		3.83(q, J_{gem}=15.0, J_{vic}=1) (0.33)	3.20(q, J_{vic}=8.5) (0.47)	1.28(d, J=6.2) (0.36)		
1c	5.10(m) (0.23)	4.53(m) (0.36)	3.8—3.1(m) (0.4—0.5)		1.37(d, J=6.2) (0.30) (0.45)		
2d	4.60(m) (0.27)		3.34—3.01(m) (0.3)		1.20(d, J=6.0) (0.23)		2.27(s) (0.17)
2e	5.12(m) (0.09)	4.43(m) (0.28)	3.65—2.73(m) (0.3)		1.18(d, J=6.0) (0.20) (0.26)		2.30(s) (0.09)
3a	4.73(m) (0.34)		3.85(q, J_{gem}=15.8, J_{vic}=1) (0.51)	3.04(q, J_{vic}=9.0) (0.49)	1.39(d, J=6.2) (0.46)		2.32(s) (0.09)
3b	4.93(m) (0.03)		3.80(q, J_{gem}=16.0, J_{vic}=1) (0.32)	3.08(q, J_{vic}=8.5) (0.42)	1.26(d, J=6.2) (0.40)		2.36(s) (0.16)
3c	5.10(m) (0.12)	4.57(m) (0.40)	3.98—2.85(m) (0.3—0.4)		1.42(d, J=6.0) (0.32) (0.47)		2.32(s) (0.10)
4a	4.77(m) (0.42)		3.81(q, J_{gem}=15.9, J_{vic}=1) (0.55)	3.06(q, J_{vic}=9.0) (0.65)	1.38(d, J=6.1) (0.54)		2.23(s) (0.02)
4b	4.95(m) (0.01)		3.80(q, J_{gem}=16.1, J_{vic}=1) (0.30)	3.08(q, J_{vic}=9.0) (0.35)	1.27(d, J=6.1) (0.37)		2.23(s) (0.00)
4c	5.15(m) (0.17)	4.57(m) (0.39)	3.81—2.98(m) (0.4)		1.38(d, J=6.2) (0.31) (0.45)		2.25(s) (0.05)
5d	4.60(m) (0.40)		3.45—2.87(m) (0.3—0.4)		1.25(d, J=6.0) (0.40)		
5e	5.19(m) (0.08)	4.60(m) (0.29)	3.77—2.85(m) (0.3)		1.23(d, J=6.2) (0.06) (0.25)		
6a	4.77(m) (0.54)		3.83(q, J_{gem}=16.0, J_{vic}=1) (0.63)	3.10(q, J_{vic}=9) (0.60)	1.25(d, J=6.0) (0.38)		
6b	4.90(m) (0.07)		3.80(q, J_{gem}=16.0, J_{vic}=1) (0.52)	3.20(q, J_{vic}=9.2) (0.59)	1.30(d, J=6.2) (0.50)		
6c	5.16(m) (0.28)	4.53(m) (0.53)	3.9—2.9(m) (0.5)		1.36(d, J=6.1) (0.35) (0.49)		
7a	4.73(m) (0.53)		3.79(q, J_{gem}=16.0, J_{vic}=1) (0.53)	3.07(q, J_{vic}=9.0) (0.63)	1.39(d, J=6.2) (0.54)		
7b	4.89(m) (0.13)		3.77(q, J_{gem}=16.0, J_{vic}=1) (0.54)	3.14(q, J_{vic}=8.2) (0.53)	1.32(d, J=6.2) (0.49)		
7c	5.13(m) (0.23)	4.48(m) (0.47)	3.7—2.9(m) (0.4—0.5)		1.36(d, J=6.0) (0.33) (0.43)		

a) Coupling constants, Hz. b) Benzene-induced solvent shifts, $\Delta=(\delta_{CDCl_3}-\delta_{C_6D_6})$.

$\delta_{CDCl_3}-\delta_{C_6D_6}$) with the chemical shift of Compounds **1**—**7** in $CDCl_3$. As can be seen in Table 2, the 4,8-protons of Compound **7b** are deshielded (the mean value is *ca.* +0.13 ppm). Only the CC conformation in Scheme 1 is compatible with these observations; therefore, compounds of Type D are considered to take the CC conformation. The spectra of Compounds **1b**, **3b**, **4b**, **6b**, and **7b** may all be considered to belong to Type D. On the other hand, all the protons of Compounds **5d** and **7a** are strongly deshielded (the mean values are *ca.* +0.4 and +0.5 ppm, respectively). Therefore, the BB or CB conformation is compatible with the above observations discussed for Compounds **5d** and **7a**. The differences between the signal patterns of Types A and C may be due to the different conformations of Compounds **5d** and **7a**. We thought, therefore, that, in Type C, the most reasonable conformation is BB in Scheme 1. In contrast, in the case of Type A, the CB conformation is more suitable than the BB conformation because of the steric hindrance between the S=O group and the ortho-substituent. The spectra of Compounds **1a**, **3a**, **4a**, **6a**, and **7a** may all be considered to belong to Type C, and those of Compounds **2d** and **5d**, to Type A.

On the other hand, some possible conformations of Types B and E are illustrated in Scheme 2; that is, the CC and BB conformations are obtained by the replacement of *syn*-axial hydrogen by a methyl group in the CC and BB conformations in Scheme 1, while TCB and TBB are twist forms of CB and BB. If we consider that the CC or BB conformations in Scheme 2 are for Types B and E, the chemical shifts of the axial and equatorial methyl protons may be said to appear at different positions because of the anisotropy of the S=O bond. Nikander *et al.*,[2] in reporting on chemical shifts for methyl-substituted 1,3,2-dioxathiane 2-oxides in which the methyl group is *syn*-axial to the S=O bond, said that there is only a minor shielding effect relative to its equatorial counterpart. As can be seen in Fig. 1 or Table 2, the two methyl groups attached to C-4 and C-8 of Types B and E are almost equivalent magnetically in $CDCl_3$, while the two methine protons are not. Marked differences between compounds of Types B and E are shown in the benzene-induced shifts of the two methine protons and two methyl protons attached to C-4 and/or C-8. For the compounds of Type B, the methine and methyl protons attached to C-4 or C-8 are shielded, while the remaining methine and methyl protons are only marginally affected. Judging from the examination of the molecular model, the TCB conformation will give rise to severe nonbonded interactions between the ortho-substituent of the phenyl ring and the S=O group. Thus, we concluded that compounds of Type B exist in the TCB conformation. The spectra of Compounds **2e** and **5e** may all be considered to belong to Type B. On the other hand, in the case of compounds of Type E, two methine and methyl protons are shielded. Therefore, it can be considered that compounds of Type E exist in the TBB conformation. The spectra of Compounds **1c**, **3c**, **4c**, **6c**, and **7c** may all be considered to belong to Type E.



Scheme 2. Possible conformations of types B and E.

^{13}C-NMR Spectra. The conformations of Compounds **1**—**7** are further illustrated by means of ^{13}C-NMR. The ^{13}C-NMR chemical shifts for the Compounds, **1**—**7**, examined in $CDCl_3$ solutions are presented in Table 3. The assignments of the carbons were made on the basis of: (1) the relative signal intensity, (2) the off-resonance decoupling technique, and (3) a comparison with the published data for trimethylene sulfites and ethylene sulfites.

The upfield shifts of 6—9 ppm at C-4 and/or C-8 of the CC-conformation compared with those in the CB and BB conformations are due to the γ-relationship between the axial S=O and axial hydrogens at the C-4 and/or C-8 in Scheme 1. Nonbonded interactions between the axial oxygen in CC conformation and the axial hydrogens at C-4 and/or C-8 are probably sufficient to perturb the electron distribution about

Table 3. ^{13}C chemical shifts of compounds **1**—**7**

Compd No.	Chemical shifts, δ				
	C-4	C-5 or C-7	C-8	4-Me or 8-Me	R
1a	74.0	60.1	74.0	18.3	—
1b	65.3	58.1	65.3	18.4	—
1c	67.5	55.9 55.5	71.2	19.8 19.1	—
2d	77.8	65.0	77.8	18.1	18.4
2e	69.7	61.6 60.2	73.6	19.6 19.4	18.6
3a	74.1	60.1	74.1	18.3	22.1
3b	65.4	58.2	65.4	18.4	22.1
3c	67.8	56.0 55.6	71.4	19.7 19.1	21.9
4a	74.1	60.1	74.1	18.2	20.1
4b	65.3	58.2	65.3	18.4	20.1
4c	68.1	56.2 55.9	71.5	19.7 19.1	20.1
5d	77.5	64.3	77.5	18.1	—
5e	69.5	60.0 59.4	73.4	19.5 19.2	—
6a	73.7	60.0	73.7	18.3	—
6b	65.0	58.2	65.0	18.4	—
6c	66.6	55.6 55.3	70.6	19.8 19.3	—
7a	73.7	60.1	73.7	18.3	—
7b	64.9	58.3	64.9	18.4	—
7c	66.9	55.8 55.6	70.7	19.8 19.2	—

C-4 and/or C-8 and increase their shieldings. These γ-shifts have already been reported for ethylene sulfites and propylene sulfites.[4,13] For example, Buchanan *et al.*[14] reported upfield shifts of 9.9 and 6.6 ppm at C-4 and C-6 of 4-phenyl-1,3,2-dioxathiane 2-oxide with an axial S=O bond relative to that of the equatorial S=O type. On the contrary, the chemical shifts of C-4 and C-8 in the TCB and TBB conformations appeared at different positions, as is shown in Table 3. The upfield shifts in C-4 indicate that the S=O function turned away to the axial hydrogen at C-4.

We concluded, in the light of all the available evidence, that Compounds **1**—**7** exist in five conformations, that is, CC, BB, CB, TCB, and TBB, as is shown in Schemes 1 and 2.

References

1) C. H. Green and D. G. Hellier, *J. Chem. Soc.*, **1972**, 458.
2) H. Nikander, V. Mukkala, T. Nurmi, and K. Pihlaja, *Org. Magn. Reson.*, **8**, 375 (1976).
3) D. G. Hellier and F. J. Webb, *Org. Magn. Reson.*, **9**, 347 (1977).
4) G. W. Buchanan, J. B. Stothers, and G. Wood, *Can. J. Chem.*, **51**, 3746 (1973).
5) T. Nishiyama, K. Ido, and F. Yamada, *J. Heterocycl. Chem.*, **16**, 597 (1979).
6) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *J. Chem. Soc., Chem. Commun.*, **1966**, 759.
7) C. R. Johnson and D. McCants, Jr., *J. Am. Chem. Soc.*, **86**, 2935 (1964); J. C. Martin and J. J. Uebel, *ibid.*, **86**, 2936 (1964).
8) D. G. Hellier and F. J. Webb, *J. Chem. Soc.*, **1977**, 612.
9) F. A. L. Anet and J. Krane, *Tetrahedron Lett.*, **1973**, 5029.
10) T. Ledaal, *Tetrahedron Lett.*, **1968**, 1683.
11) T. Nishiyama and F. Yamada, *Bull. Chem. Soc. Jpn.*, **44**, 3073 (1971).
12) F. Yamada, T. Nishiyama, and H. Samukawa, *Bull. Chem. Soc. Jpn.*, **48**, 1878 (1975).
13) G. W. Buchanan and D. G. Hellier, *Can. J. Chem.*, **54**, 1428 (1976).
14) G. W. Buchanan, C. M. E. Cousineau, and T. C. Mundell, *Tetrahedron Lett.*, **1978**, 2775.