Reactions of S-(1, 2-Benzisoxazol-3-yl)methyl-sulfoximides and the Related Compounds

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CONTENTS

General Introduction

Benzisoxazole has a close structural resemblance to indole. A number of naturally occurring and synthetic indole derivatives are well known to be biologically active and medicinally useful:[1] e.g., a Rauwolfia alkaloid reserpine and its certain derivatives are important tranquilizers and antihypertensives, serotonin is a vasoconstrictor and a chemical transmitter in the central nervous system (CNS), while indomethacine and pindolol are clinically used as a non-steroidal antiinflammatory agent and a β-adrenergic receptor blocking agent (β-blocker), respectively.

Giannella et al.[2] reported that 1,2-benzisoxazole nucleus (1) could substitute the indole ring of indole-3-acetic acid (2), which is an important plant growth regulator hormone known as "heteroauxin", retaining the auxin-like activity for 1,2-benzisoxazole-3-acetic acid (3).

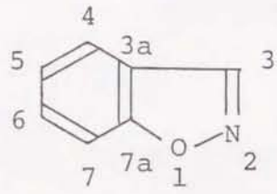
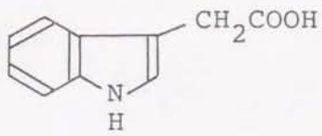


Fig. 1. The structure of 1,2-benzisoxazole 1



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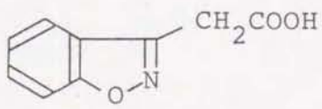
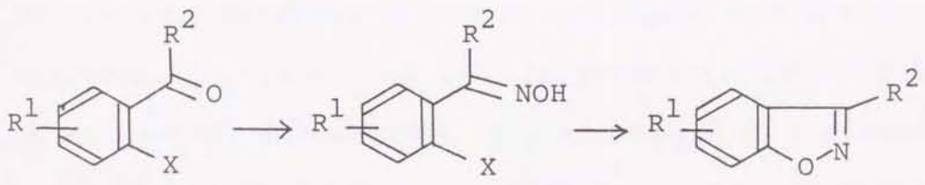


(3)

Although a number of 1,2-benzisoxazole derivatives have already been found to show some biological activities,[3] their chemical and biological properties have not yet been studied extensively in contrast to the indole derivatives. Therefore, in connection with the interesting chemical and potential biological activities of many indole derivatives, it appears to be of interest to study the properties of 1,2-benzisoxazole derivatives.

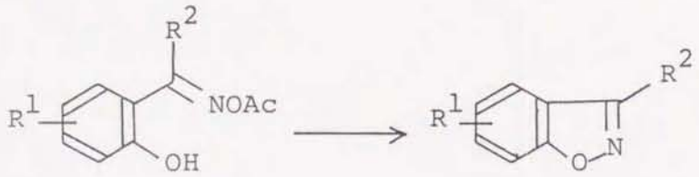
One of applicable methods for the synthesis of 1,2-benzisoxazole nucleus as shown in Eqs. 1-4[3] is the Posner reaction (Eq. 4),[4] between 4-hydroxycoumarine and hydroxylamine, which provides an excellent route to 1,2-benzisoxazole-3-acetic acids (3),[2,5] that can supply various 3-substituted 1,2-benzisoxazole derivatives.



(Eq. 1)

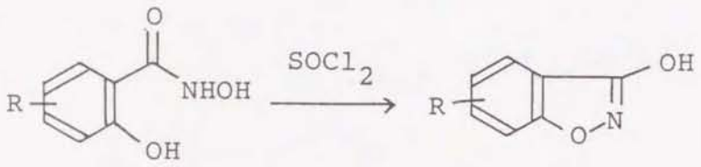
X: halogen, NO_2, OH

R^2: alkyl, Ar, $COOR^3$

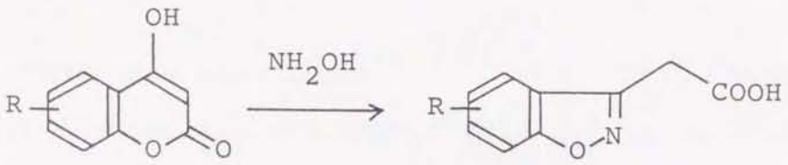


(Eq. 2)

R^2: H, alkyl, Ar



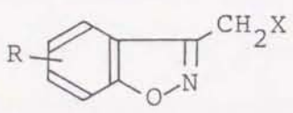
(Eq. 3)

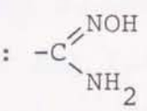
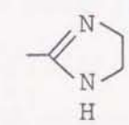


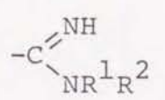
(Eq. 4)

(3)

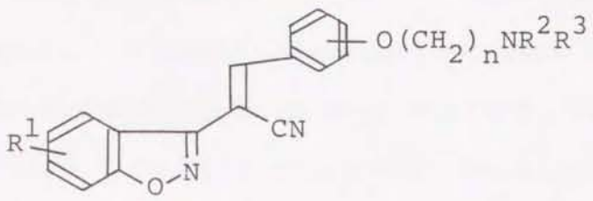
Uno et al.[6] have prepared various 3-substituted 1,2-benzisoxazole derivatives using 3 as the starting material and found that many of these derivatives possess interesting biological activities: amide oxime derivatives (4) and imidazolines (5) show antihypertensive and antidepressant activities; amidines (6) show antidepressant activity; sulfonamide derivatives (7) are promising anticonvulsants; β-aminoethyl derivatives (8), analogues of tryptamine and serotonin, show antihypertensive activity; and acrylonitriles (9) show antispasmodic activity, and so on.



X:  (4),  (5),

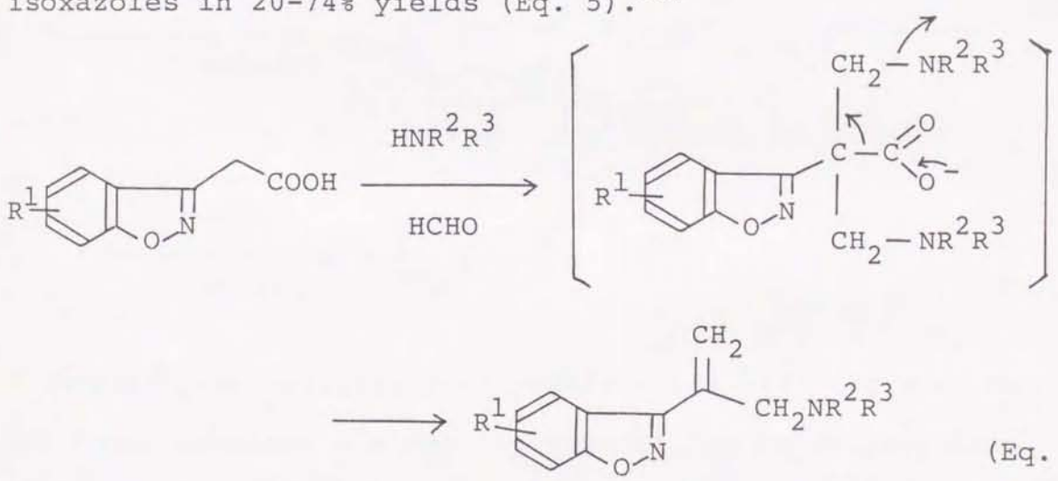
 (6), $-SO_2NH_2$ (7),

$-CH_2NR^1R^2$ (8)



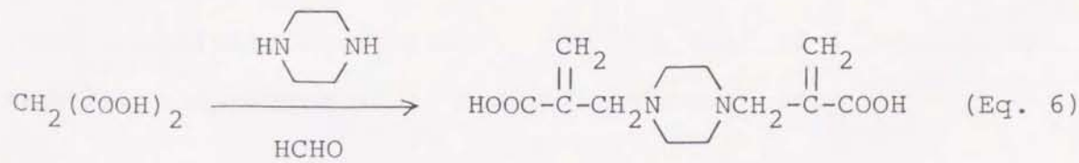
(9)

They have also found[6a,c,e] that the α-methylene group of 1,2-benzisoxazole-3-acetic acid (3) is unusually reactive to electrophiles, especially to halogenating and alkylating agents. Thus, the acetic acid 3 underwent the Mannich reaction on treatment with primary or secondary amines and formaldehyde to afford 3-(1-aminomethyl)vinyl-1,2-benzisoxazoles in 20-74% yields (Eq. 5).[6c]



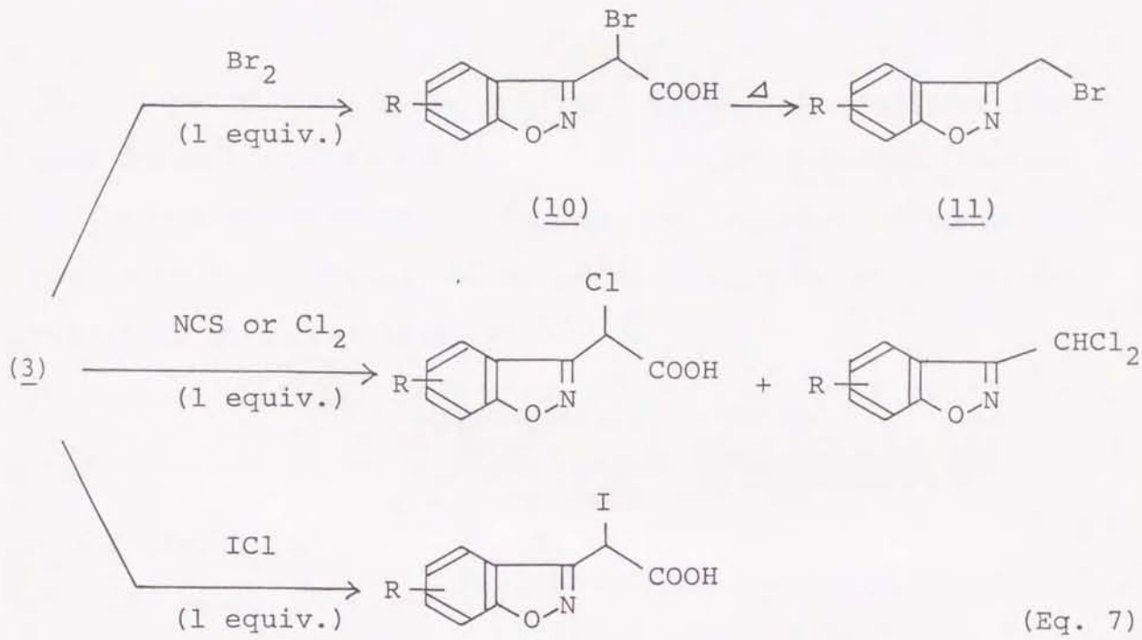
(Eq. 5)

A similar result was reported in the Mannich reaction of malonic acid with piperazine and formaline, yielding 1,4-bis(2-carboxy-2-propen-1-yl)piperazine in 85% yield (Eq. 6).[7]



(Eq. 6)

Although free carboxylic acids are generally inactive in α-halogenation without any catalyst such as PBr_3, except for those with relatively high enol content, such as malonic acid,[8] the free acid 3 readily underwent α-halogenation without any catalyst (Eq. 7).[6a,e,9]

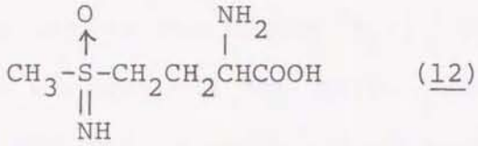


(Eq. 7)

α-Bromo-1,2-benzisoxazole-3-acetic acids (10) are very reactive and their bromines are readily substituted by nucleophiles such as amines,[6a,9] thiolates,[10] and chloride.[11] Moreover, the bromoacetic acids 10 undergo decarboxylation easily on pyrolysis to give 3-bromomethyl-1,2-benzisoxazoles (11).[6a,9]

These results described above suggest that the α-methylene group of 3 has a similar structural feature to the methylene group of malonic acid; namely, the C=N bond of 1,2-benzisoxazole ring has the nature of a "masked" carbonyl group.

Meanwhile, since Bentley et al.[12] discovered in 1950 the first sulfoximide (sulfoximine), methionine sulfoximide (12), as the compound responsible for the toxicity of wheat



(12)

flour treated with nitrogen trichloride, much attention has been focused on this new family of sulfur compounds because of its versatile functionalities, i.e., acidic hydrogens on α-carbon and nitrogen, basic and nucleophilic nitrogen, and chirality at sulfur (Fig. 2).[13]

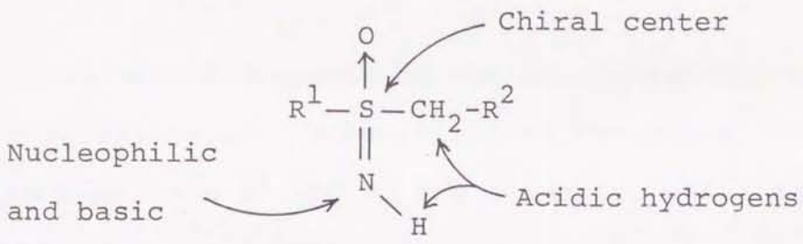
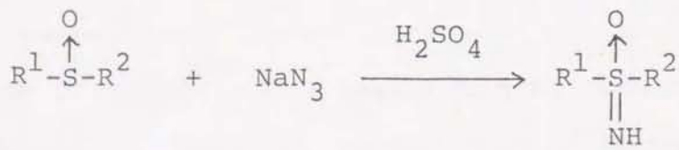


Fig. 2. The sulfoximide functional group

Sulfoximide derivatives have been prepared mainly by the following methods, but there is no generally applicable procedure to prepare all possible kinds of sulfoximides.

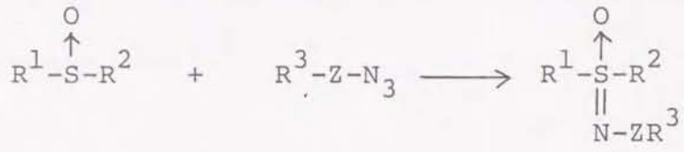
A) The reaction of sulfoxides with hydrazoic acid in the presence of concentrated sulfuric acid[14]



(Eq. 8)

This method is quite useful in the preparation of dialkyl and alkyl aryl N-unsubstituted (free) sulfoximides, but is unsuitable for diaryl, benzyl, and tert-alkyl derivatives, since diaryl sulfoxides are reluctant to react with hydrazoic acid and in the latter two cases, i.e., benzyl and tert-alkyl sulfoxides, the cleavage of the carbon-sulfur bond is often observed under the strong acidic conditions.[13c,15)]

B) The reaction of sulfoxides with acyl azide[14b,16)]

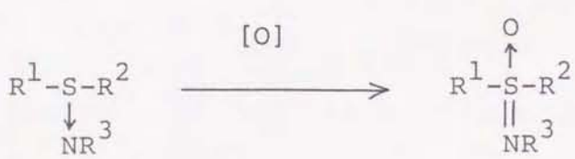


(Eq. 9)

Z: SO_2, CO

This method seems to be the most general procedure for the preparation of N-substituted sulfoximides, but the yield is low when both R^1 and R^2 are aromatic, while the preparation of acyl azide is somewhat limited.

C) The oxidation of sulfimides (sulfilimines)[12b,14b,17)]



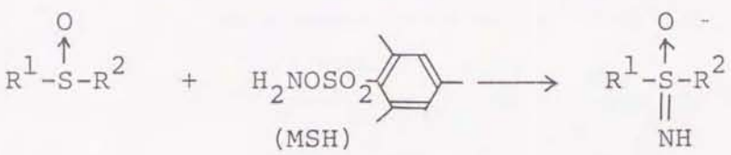
(Eq. 10)

R^3: H, alkyl, aryl, COR^4, SO_2R^5

This method can be accomplished by a variety of oxidants, such as potassium permanganate, m-chloroperbenzoic acid, sodium periodate, lead tetraacetate, sodium hypochlorite, and super oxide. However, in the case of N-p-toluenesulfonyl (tosyl)

sulfimides, typical oxidants such as potassium permanganate and peroxy acids frequently give the products in low yields owing to the low nucleophilicity of the sulfur atom.[16b] With the nucleophilic oxidants such as hypochlorite and super oxide, all kinds of N-tosylsulfimides are smoothly converted to the corresponding sulfoximides.[17c] The oxidation of N-arenesulfonylsulfimides proceeds with retention of configuration at the sulfur atom.[18]

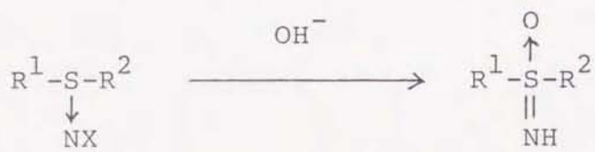
D) The reaction of sulfoxides with O-mesitylenesulfonyl-hydroxylamine (MSH)[19]



(Eq. 11)

This method is one of the most versatile procedures for the direct preparation of free sulfoximides, although the main restriction is the limited stability of MSH. The method has been used to prepare optically active "free" sulfoximides from optically active sulfoxides with retention of configuration at the sulfur atom.[20]

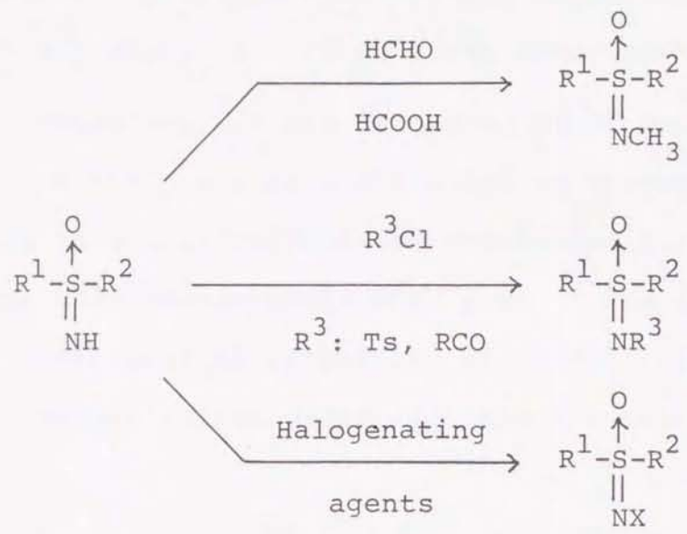
E) The alkaline hydrolysis of N-halosulfimides[21]



(Eq. 12)

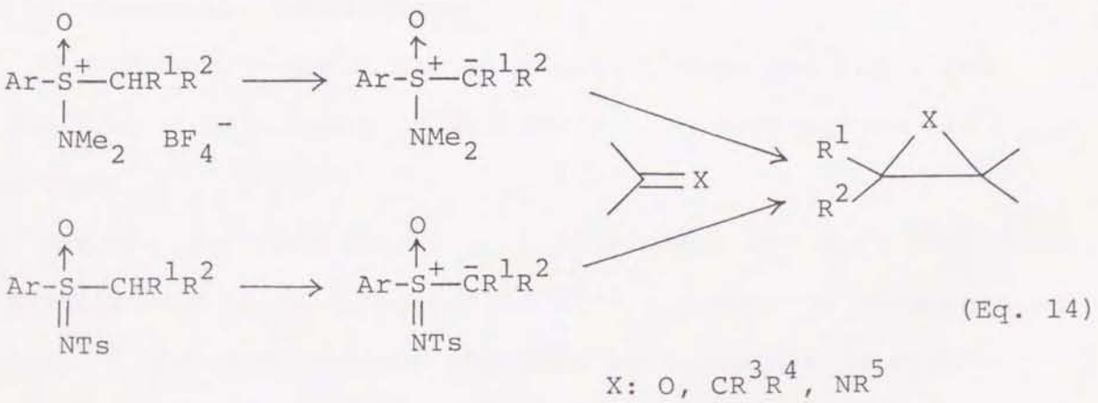
This method is quite useful for the preparation of diaryl free sulfoximides. The reaction proceeds with retention of configuration at the sulfur atom.[21b]

Free sulfoximides have been converted to various N-substituted derivatives by N-alkylation,[22] N-acylation,[23] and N-halogenation[24] (Eq. 13).



(Eq. 13)

Johnson et al.[13b,c,22] have demonstrated that the sulfoximidoyl-stabilized ylides and carbanions act as powerful nucleophilic alkylidene transfer agents upon reaction with compounds containing electrophilic double bonds such as ketones, imines, and α,β-unsaturated ketones, affording oxiranes, aziridines, and cyclopropanes, respectively (Eq. 14).

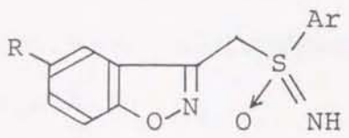


(Eq. 14)

X: O, CR^3R^4, NR^5

Many of sulfoximide derivatives have been found to possess a wide variety of interesting biological activities such as herbicidal, antibacterial, pesticidal, antispasmodic, muscle-stimulant, antihypertensive, CNS-depressant, anti-tumor, anti-secretory, and blood-sugar lowering activities.

Therefore, it was deemed to be of great interest to examine the chemical and biological properties of compounds which have both sulfoximide moiety and 1,2-benzisoxazole ring. Thus, this thesis deals with some of the interesting chemical and physiological properties of S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides (13) and the related compounds.



R: H, Br, MeO

Ar: Ph, p-MePh, p-ClPh

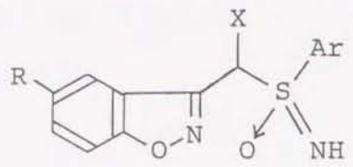
(13)

In Chapter 1, the synthesis and some chemical and pharmacological properties of the free sulfoximides 13 and their N-acyl derivatives are described. Several of their N-aminoacyl derivatives have been found to show mild antihypertensive and antispasmodic activities.

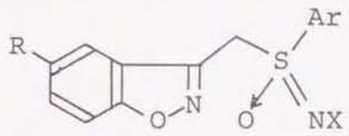
In Chapters 2 and 3, the interesting chemical behaviors of the free sulfoximides 13 and their halo derivatives are described.

Despite the fact that free sulfoximides are well known to undergo readily N-halogenation with a number of halogenating agents,[24] the reactions of the free sulfoximides 13 with N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) afford

the corresponding α-halogenated "free" sulfoximides 14 in good yields.



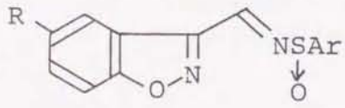
(14: X=Br, Cl)



(15: X=Br, Cl)

The α-bromination proceeded via a facile N-bromination followed by bromine transfer reaction of the resulting N-bromosulfoximide (15:X=Br), both in radical and ionic processes. The NCS chlorination, in contrast, proceeded via direct α-chlorination, but not via N-chlorination. The mechanisms of these reactions are discussed in detail in Chapter 2.

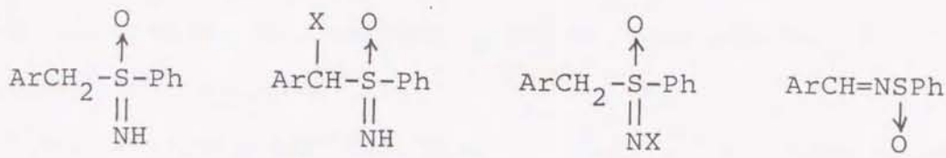
Meanwhile, the α- and N-halosulfoximides 14 and 15 have been found to undergo rearrangements on treatment with base to afford the same N-sulfinylimines (16). In Chapter 3, the mechanisms of these novel base-induced rearrangements are discussed.



(16)

As the extension of these interesting chemical behaviors of the 1,2-benzisoxazolylmethylsulfoximides described above, these reactions have been applied on the S-benzyl system in order to examine the generality of these chemical behaviors, and indeed similar chemical behaviors have been observed.

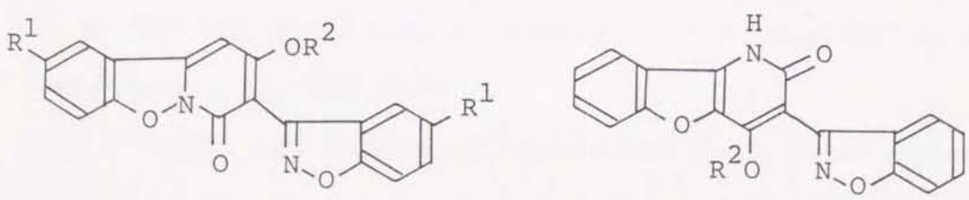
Thus, Chapter 4 deals with the halogenations of S-benzyl-S-phenylsulfoximides (17) and the rearrangements of their halo derivatives (18) and (19) to the corresponding N-sulfinyl-imines (20).



(17) (18) (19) (20)

Ar: Ph, p-NO_2Ph; X: Br, Cl

Chapter 5 deals with an interesting chemical behavior of 1,2-benzisoxazole-3-acetic acid (3). The acetic acid 3 undergoes dimerization on treatment with acyl chlorides in pyridine to give the novel ring system products, benzisoxazolo[2,3-a]-pyridines (21), indicating that 3 acts as an ambident nucleophile at the methylene carbon and the ring nitrogen. Furthermore, the pyridines 21 undergo photolytic ring transformation to give benzofuro[3,2-b]pyridines (22). The mechanisms of these reactions are discussed.



(21) (22)

R^1: H, MeO; R^2: H, Ts, Ac, PhCO

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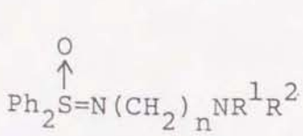
Chapter 1

Synthesis of S-Aryl-S-[(1,2-benzisoxazol-3-yl)methyl]-sulfoximides and Their N-Acyl Derivatives

Summary ----- The synthesis and some chemical and pharmacological properties of S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]-sulfoximide derivatives are described. Several of their N-aminoacyl derivatives have been found to possess mild antihypertensive and antispasmodic activities.

Introduction

Since the first sulfoximide, methionine sulfoximide, was discovered by Bentley et al.[1] in 1950, much attention has been focused on the synthesis and properties of sulfoximides and many derivatives have been found to possess a wide variety of interesting chemical and biological properties.[2] For example, N-alkylaminoalkylsulfoximides 1[3] have been claimed as antispasmodics, indole derivatives 2[4] as muscle-stimulants, pyridine derivatives 3[5] as anti-tumor agents, and so on.



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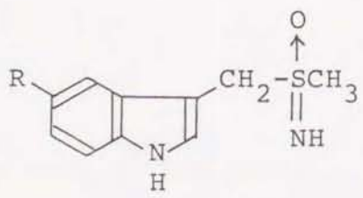

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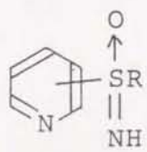


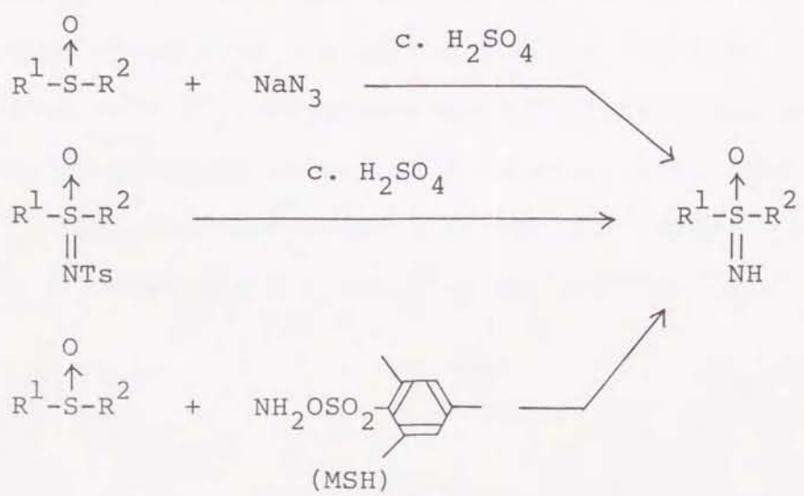
3

Meanwhile, many of 1,2-benzisoxazole derivatives have been found to possess interesting biological activities.[6] It appeared, therefore, to be of great interest to examine the biological properties of compounds containing both sulfoximide moiety and 1,2-benzisoxazole ring.

This Chapter deals with the synthesis and some chemical and pharmacological activities of S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides 4 and their N-acyl derivatives.

Synthesis of S-Aryl-S-[(1,2-benzisoxazol-3-yl)methyl]-sulfoximides 4

N-Unsubstituted (free) sulfoximides have been prepared by several methods, including reaction of sulfoxides with hydrazoic acid in the presence of concentrated sulfuric acid,[7] hydrolysis of N-tosylsulfoximides with concentrated sulfuric acid,[1b,8] and amination of sulfoxides with O-mesitylene-sulfonylhydroxylamine (MSH).[9]

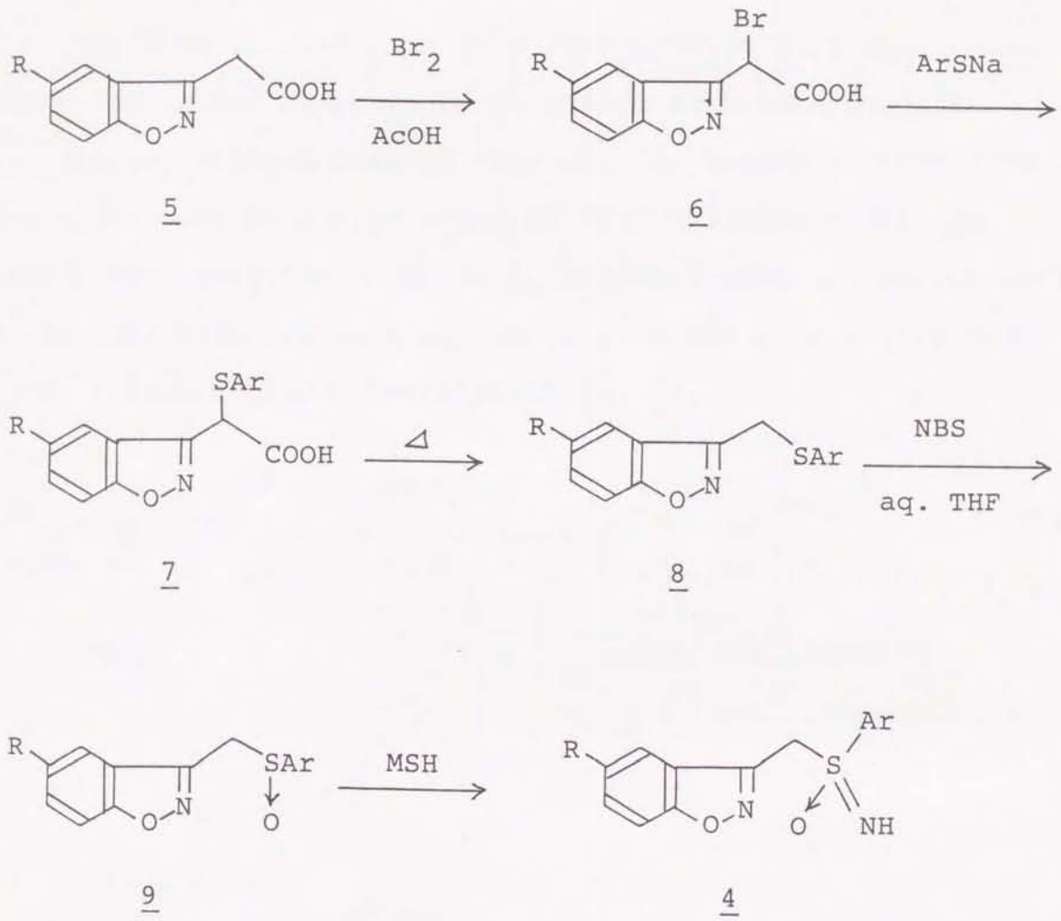


However, the former two methods are unsuitable for the preparation of derivatives labile to acid, e.g., S-benzyl, S-tert-alkyl, etc. sulfoximides, because the cleavage of the carbon-sulfur bond is often observed under the strong acidic conditions.[2c,10)]

Since the target "free sulfoximides 4" have an α-methylene group activated by 1,2-benzisoxazole ring, the hydrazoic acid method was unsuccessful in the preparation of 4. Therefore, the free sulfoximides 4 were prepared by using MSH under mild conditions, as shown in Chart 1.

(Chart 1)

1,2-Benzisoxazole-3-acetic acids 5 were treated with an equimolar amount of bromine in acetic acid to give α-bromo-1,2-benzisoxazole-3-acetic acids 6 in good yields.[6a,11)] Treatment of the bromoacetic acids 6 with sodium arylthiolate gave α-arylthio-1,2-benzisoxazole-3-acetic acids 7, which were readily decarboxylated on pyrolysis to give aryl (1,2-benzisoxazol-3-yl)methyl sulfides 8. The sulfides 8 were oxidized to aryl (1,2-benzisoxazol-3-yl)methyl sulfoxides 9 by using N-bromosuccinimide (NBS) in aqueous tetrahydrofuran (THF).[12)] Successive treatment of the sulfoxides 9 with MSH and base afforded the target "free sulfoximides 4".



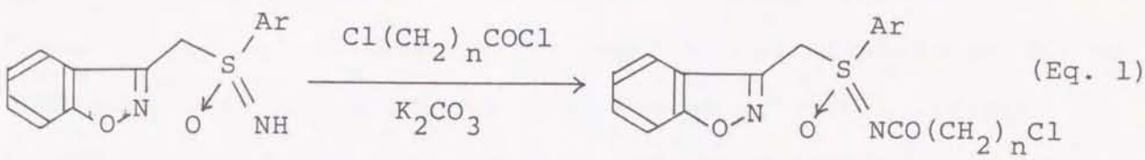
5 6 7 8 9 4

	a	b	c	d	e
R	H	H	H	Br	MeO
Ar	Ph	p-MePh	p-ClPh	Ph	Ph

Chart 1

Synthesis of the N-Acyl Derivatives of 4

The free sulfoximides 4a,c were treated with chloroacyl chlorides in the presence of potassium carbonate to give N-chloroacylsulfoximides 10 (Eq. 1). On treatment with bromoacetyl bromide in the presence of triethylamine (TEA), 4a gave N-bromoacetylsulfoximide 11 together with the corresponding quaternary ammonium salt 12, which gave the free sulfoximide 4a on alkaline (NaOH) hydrolysis (Eq. 2).



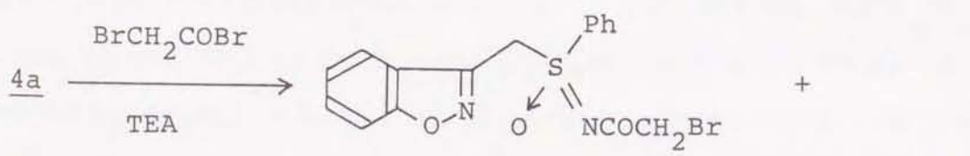
(Eq. 1)

4a,c

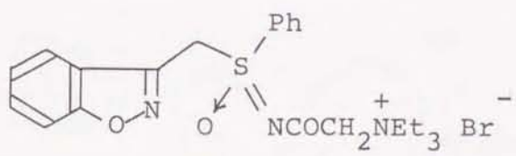
10a: n=1, Ar=Ph

b: n=1, Ar=p-ClPh

c: n=2, Ar=Ph



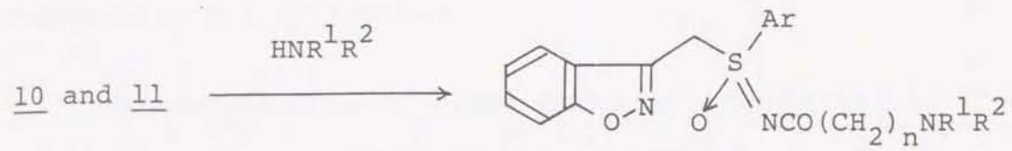
11



12

(Eq. 2)

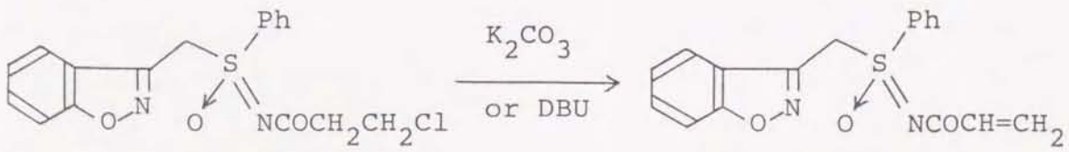
The reactions of the N-haloacylsulfoximides 10 and 11 with several secondary amines gave N-aminoacyl derivatives 13 and 14 (Table IV).



13: n=1

14: n=2

Meanwhile, the N-haloacetylsulfoximides 10a and 11 were treated with potassium carbonate to give the free sulfoximide 4a in almost quantitative yields. On the other hand, the N-chloropropionylsulfoximide 10c underwent elimination of HCl on treatment either with potassium carbonate or with 1,5-diazabicyclo[5.4.0]-5-undecene (DBU) to give an N-acryloylsulfoximide 15 (Eq. 3). The structure of 15 was confirmed by elemental and spectral analyses and also by the following chemical transformation. Thus, treatment of 15 with piperidine gave the N-piperidinopropionylsulfoximide 14b (Ar=Ph, NR^1R^2=N⟨⟩), whose IR and NMR spectra were in agreement with those of the sample prepared from the N-chloropropionylsulfoximide 10c and piperidine as described above.



10c 15 (Eq. 3)

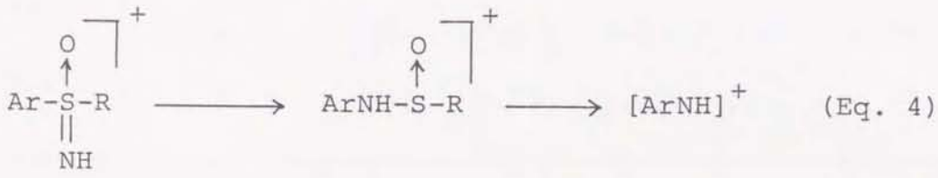
Pharmacological Activities

These compounds described above were subjected to the routine testing for pharmacological activities. Several of the N-aminoacyl derivatives 13 and 14 showed mild antihypertensive activities in spontaneously hypertensive rats (SHR) and antispasmodic activities examined by the inhibitory effects on the response of isolated ileum from guinea pig to transmural electrical stimulation (anti-TMS activity) and to acetylcholine (anti-ACh activity).

However, their activities are not so strong as expected and are also less potent than those of the drugs used clinically. Furthermore, these compounds have no other marked biological activities, e.g., neurotropic, analgesic, antiinflammatory, antibacterial, and other activities. Therefore, no further evaluation of these derivatives has been developed.

Mass Spectra of S-Aryl-S-[(1,2-benzisoxazol-3-yl)methyl]-sulfoximides 4a-e

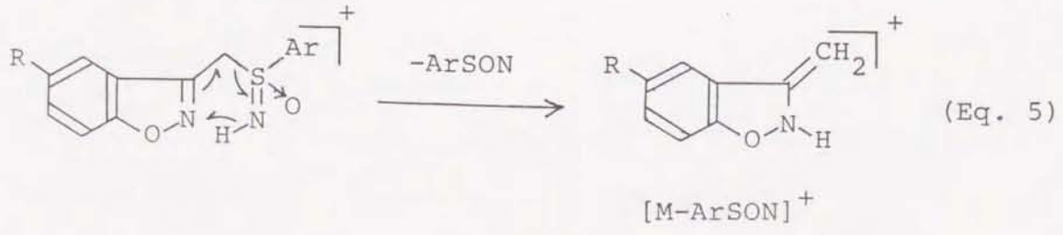
Fragmentations of dibutyl, aryl ethyl, aryl methyl, and diaryl "free" sulfoximides have been studied and reported to be markedly different from one another.[7b] Except for the dibutyl derivative, however, the peaks consistent with aryl-imide ions are observed as the base peaks or the markedly intense peaks, suggesting that the migration of an aryl group from the sulfur atom to the nitrogen atom is the important key step (Eq. 4).



(Eq. 4)

The results of the fragmentation analyses of the benz-isoxazolylmethylsulfoximides 4a-e are summarized in Table I.

The molecular ion peaks are clearly observed but are usually weak. The characteristic and intense peaks are observed at the mass units consistent with $[M-ArSON]^+$ ions which are considered to be generated by the McLafferty rearrangement of the molecular ions (Eq. 5).



(Eq. 5)

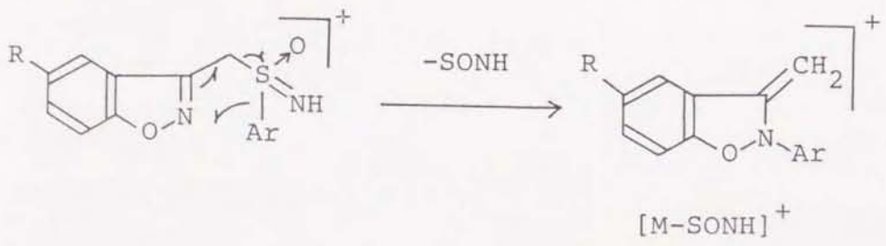
$[M-ArSON]^+$

Table I. Mass Spectra of 4a-e at 70 eV

Ion	Relative intensity				
	4a	4b	4c	4d	4e
$[M]^+$	0.04 (0.08)[a]	0.04	0.02	0.15	0.03
$[M-ArSON]^+$	0.81 (1.00)	0.37	1.00	0.98	0.11
$[M-SONH]^+$	0.08 (0.14)	0.18	0.07	0.03	0.03
$[ArSONH]^+$	0.43 (0.51)	0.97	0.25	0.22	0.75
$[ArNH]^+$	0.23 (0.12)	0.48	0.23	0.27	0.25
$[Ar]^+$	1.00 (0.20)	1.00	0.36	1.00	1.00
$[SONH]^+$	0.13 (0.03)	0.25	0.20	0.31	0.35

a) at 20 eV.

The other characteristic, but not so intense, peaks are observed at the mass units consistent with $[M-63]^+$ ions which are considered to be formed by migration of an aryl group to the ring nitrogen together with elimination of the SONH group in the molecular ions (Eq. 6): in the spectrum of 4a the metastable peak in this process is observed.



(Eq. 6)

$[M-SONH]^+$

The aryl ions observed as the base peaks are considered to be generated from the molecular and $[ArSONH]^+$ ions. Relatively intense peaks due to arylimide ions prove the migration of an aryl group to the imide nitrogen, which takes place in the molecular and/or $[ArSONH]^+$ ions, but these rearrangement paths no longer predominate. Thus, a possible fragmentation scheme for the benzisoxazolylmethylsulfoximides 4a-e is illustrated in Chart 2.

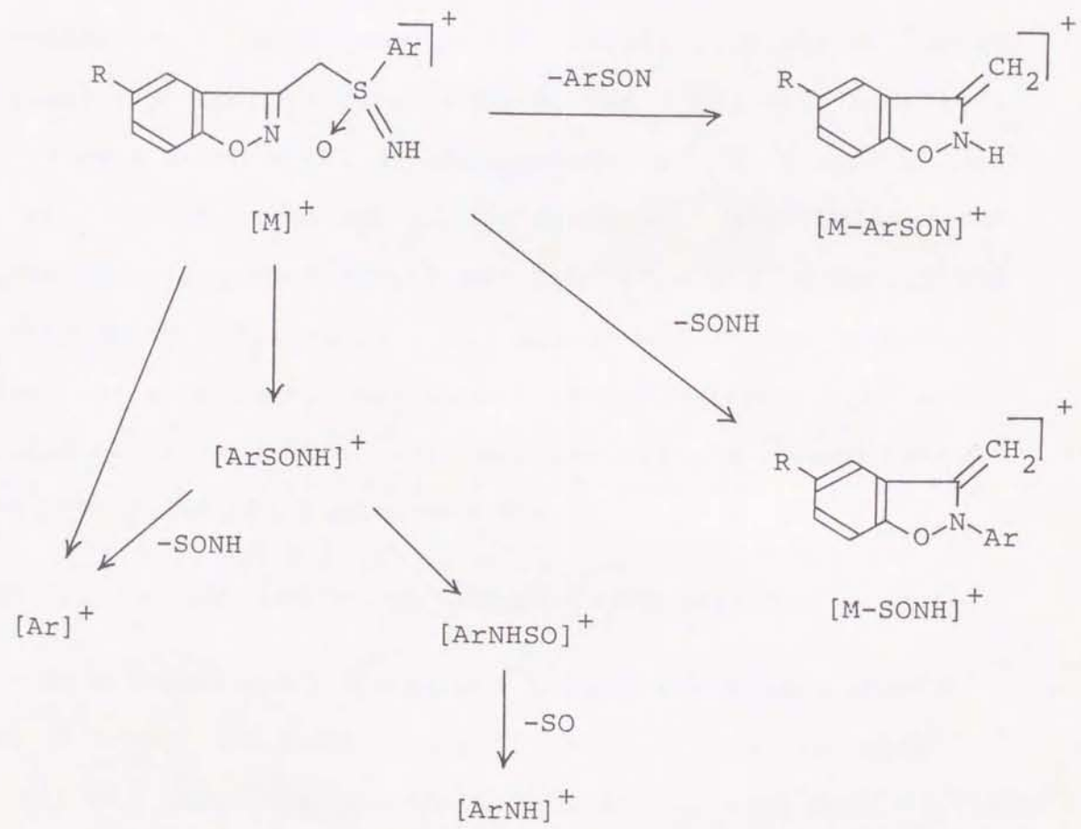


Chart 2

Experimental

The instruments and conditions used in this thesis are as follows. Melting points were measured on an Ishii micro melting point apparatus and are uncorrected. ^{1}H-Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-360 (60 MHz) spectrometer unless otherwise noted or a Varian HA 100D (100 MHz) spectrometer with tetramethylsilane as an internal standard in $CDCl_3$. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; dt, double triplet; br, broad. Infrared (IR) spectra were taken in KBr disks with a Hitachi EPI-G3 or a Jasco A-102 spectrophotometer. Mass spectra were recorded on a Hitachi RMU-6L spectrometer. High performance liquid chromatography (HPLC) was carried out on a Waters 204 machine using a nucleosil $_{10}C_{18}$ column and 2% aq. AcOH-EtOH (55:45) as an eluent. Gas-liquid chromatography (GLC) was carried out on a Yanaco G-180 machine using a column packed with 10% SP-1000 on Chromosorb WAW.

Aryl (1,2-Benzisoxazol-3-yl)methyl Sulfoxides 9

To a solution of α-bromo-1,2-benzisoxazole-3-acetic acid (0.1 mol) and NaOH (0.1 mol) in EtOH (100 ml)-water (40 ml) was added all at once a solution of aryl hydrosulfide (0.1 mol) and NaOH (0.1 mol) in EtOH (30 ml)-water (30 ml). After the mixture had been stirred for 1 hr at room temperature, the EtOH was evaporated off in vacuo. The residual aq. solution was washed with $CHCl_3$, acidified (pH ca. 2) with

conc. HCl, and then extracted with $CHCl_3$. The extract was dried and concentrated in vacuo. The residual crude 7 was heated at 120-130°C until the evolution of CO_2 ceased (about 20 min). After cooling, the resulting oil was dissolved in $CHCl_3$ and washed with aq. NaOH. The organic layer was dried and concentrated in vacuo. The resulting crude 8 was dissolved in THF (150 ml)-water (20 ml) and an excess of NBS was added. After the mixture had been stirred for 30 min at room temperature , the THF was evaporated off in vacuo and the resulting precipitates were extracted with $CHCl_3$. The extract was washed with aq. NaOH, dried, and concentrated in vacuo. The residual crystals were recrystallized from CH_2Cl_2-isopropyl ether to give pure sulfoxides 9a-e in total yields of 60-70%. Compounds 7 and 8, except for 7a and 8a,b, were not isolated as pure products. 7a: mp 85-86°C (ether-pet. ether). NMR: δ 5.43s(1H, CH), 7.1-8.1m(9H, arom), 9.7-10.5br(1H, COOH). Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91; S, 11.24. Found: C, 62.93; H, 3.99; N, 4.83; S, 11.34. 8a: mp 71-72°C (hexane). NMR: δ4.41s(2H, CH_2), 7.1-7.9m(9H, arom). Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.60; N, 5.81; S, 13.29. Found: C, 69.69; H, 4.55; N, 5.79; S, 13.22. 8b: mp 59-60°C (hexane). NMR: δ2.30s(3H, CH_3), 4.38s(2H, CH_2), 6.9-8.0m(8H, arom). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.55. Found: C, 70.43; H, 5.22; N, 5.56; S, 12.36. 9a: mp 109-110°C. NMR: δ4.45s(2H, CH_2), 7,0-7.9m(9H, arom). Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.33; H, 4.17; N, 5.57; S, 12.61. 9b: mp 117-119°C.

NMR: δ2.38s(3H, CH_3), 4.45s(2H, CH_2), 7.15-7.9m(8H, arom). Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.56; H, 4.62; N, 5.09; S, 11.62. 9c: mp 134-136°C. NMR: δ4.88s(2H, CH_2), 7.2-7.9m(8H, arom). Anal. Calcd for $C_{14}H_{10}NO_2SCl$: C, 57.64; H, 3.45; N, 4.80; S, 10.99; Cl, 12.15. Found: C, 57.74; H, 3.23; N, 5.11; S, 10.69; Cl, 12.37. 9d: mp 166-169°C. NMR: δ4.42s(2H, CH_2), 7.3-8.1m(8H, arom). Anal. Calcd for $C_{14}H_{10}NO_2SBr$: C, 50.01; H, 3.00; N, 4.17; S, 9.54; Br, 23.77. Found: C, 50.18; H, 3.00; N, 4.35; S, 9.26; Br, 23.99. 9e: mp 143-146°C. NMR: δ3.84s(3H, CH_3O), 4.45s (2H, CH_2), 6.9-7.9m(8H, arom). Anal. Calcd for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88; S, 11.16. Found: C, 62.57; H, 4.45; N, 4.69; S, 11.01.

The Free Sulfoximides 4

To a cooled solution of the sulfoxide 9 (0.05 mol) in 100 ml of CH_2Cl_2 was added 2-3 molar equiv. of MSH. The mixture was stirred for 10 hr at room temperature. Ether (50 ml) was added to the reaction mixture and the resulting white precipitates were collected by filtration. The dried precipitates were suspended in $CHCl_3$ and shaken with aq. NaOH. The organic layer was separated, dried, and concentrated in vacuo. The residual crystals were recrystallized from EtOH or CH_2Cl_2-isopropyl ether to give pure sulfoximides 4a-e (Table II).

Table II. S-Aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides 4

Compd	Mp (°C)	Yield (%)[a]	Formula	Analysis(%), Calcd/(Found) C	H	N	S	Hal	NMR, δ
4a	133-135	86	$C_{14}H_{12}N_2O_2S$	61.75	4.44	10.27	11.77	-	3.17s(1H, NH), 4.84s(2H, CH_2),
				(61.92	4.46	10.15	11.64	-)	7.2-8.2m(9H, arom)
4b	139-142	84	$C_{15}H_{14}N_2O_2S$	62.92	4.93	9.78	11.20	-	2.40s(3H, CH_3), 3.08s(1H, NH),
				(62.95	5.14	9.47	11.03	-)	4.79s(2H, CH_2), 7.1-8.0m(8H, arom)
4c	136-139	78	$C_{14}H_{11}N_2O_2SCl$	54.82	3.62	9.13	10.45	11.56	3.17s(1H, NH), 4.80s(2H, CH_2),
				(54.88	3.27	8.78	10.43	11.75)	7.2-8.1m(8H, arom)
4d	165-168	77	$C_{14}H_{11}N_2O_2SBr$	47.88	3.16	7.97	9.13	22.75	3.18s(1H, NH), 4.83s(2H, CH_2),
				(48.00	3.00	7.70	9.21	22.95)	7.3-8.2m(8H, arom)
4e	154-156	58	$C_{15}H_{14}N_2O_3S$	59.59	4.67	9.26	10.60	-	3.18s(1H, NH), 3.86s(3H, CH_3O),
				(59.88	4.54	9.24	10.47	-)	4.84s(2H, CH_2), 7.1-8.1m(8H, arom)

a) Based on the consumed sulfoxide.

The N-Haloacylsulfoximides 10 and 11

10a-c: To a solution of the free sulfoximide 4 (10 g) and K_2CO_3 (0.7 equiv.) in $CHCl_3$ (100 ml), a solution of chloroacyl chloride (1.2 equiv.) in $CHCl_3$ (20 ml) was added dropwise at room temperature. After the mixture had been stirred for 30 min, an additional acyl chloride (0.2 equiv.) was added and the stirring was continued for another 5 min. The reaction mixture was washed with water and the organic layer was dried. After the $CHCl_3$ had been evaporated off in vacuo, the residual crystals were recrystallized from MeOH to give 10a-c.

11: A solution of bromoacetyl bromide (13 g) in $CHCl_3$ (20 ml) was added dropwise to a stirred solution of 4a (15 g) and TEA (8.4 g) in $CHCl_3$ (150 ml). After the mixture had been treated as described above, the organic layer was subjected to silica gel column chromatography. The eluate with $CHCl_3$ was concentrated and the residue was recrystallized from MeOH to give 4.7 g of 11. From the eluate with 10%MeOH-$CHCl_3$, 13g (48% yield) of the salt 12 were obtained as a powder: NMR (DMSO-d_6), δ 1.22t(J= 7.0 Hz, 9H, CH_3 x 3), 3.53q(J= 7.0 Hz, 6H, CH_2CH_3 x 3), 4.29s(2H, CH_2CO), 5.92s(2H, CH_2S), 7.2-8.2m (9H, arom).

After the salt 12 (4.0 g) had been shaken with 10% aq. NaOH and $CHCl_3$ for 1 min, the $CHCl_3$ layer was dried and concentrated in vacuo to give the free sulfoximide 4a (2.0 g).

The N-haloacylsulfoximides 10a-c and 11 are summarized in Table III.

Table III. N-Haloacylsulfoximides 10 and 11

Compd	Mp (°C)	Yield (%)	Formula	Analysis(%), Calcd/(Found) C	H	N	S	Hal	NMR, δ
10a	138-139	92	$C_{16}H_{13}N_2O_3SCl$	55.10	3.76	8.03	9.19	10.16	4.15s(2H, $COCH_2$), 5.20d and 5.42d
				(55.10	3.75	8.09	9.26	10.43)	(AB q, J= 14.2Hz, 2H, CH_2S),
									7.2-8.05m(9H, arom)
10b	122-126	78	$C_{17}H_{15}N_2O_3SCl$	56.28	4.17	7.72	8.84	9.77	4.13s(2H, $COCH_2$), 5.22d and 5.42d
				(56.53	4.19	7.86	8.94	9.86)	(AB q, J= 14.2Hz, 2H, CH_2S),
									7.2-8.05m(8H, arom)
10c	145-147	71	$C_{16}H_{12}N_2O_3SCl_2$	50.14	3.16	7.31	8.37	18.50	2.91t(J= 6.7Hz, 2H, $CH_2\underline{CH_2}Cl$)
				(50.26	3.01	7.15	8.37	18.57)	3.83t(J= 6.7Hz, 2H, $CO\underline{CH_2}CH_2$)
									5.20d and 5.47d(AB q, J= 14.2Hz,
									2H, CH_2S), 7.2-8.2m(9H, arom)
11	134-138	22	$C_{16}H_{13}N_2O_3SBr$	48.87	3.33	7.12	8.15	20.32	3.96s(2H, $COCH_2$), 5.18d and 5.42d
				(48.65	3.43	7.13	8.11	20.36)	(AB q, J= 14.2Hz, 2H, CH_2S),
									7.2-8.1m(9H, arom)

The N-Aminoacylsulfoximides 13 and 14

A solution of the N-haloacylsulfoximide 10 or 11 (1.0-1.5 g) and a certain amine (2.1 equiv.) in $CHCl_3$ (30 ml) was refluxed for 2-6 hr. The rection mixture was washed with water and the organic layer was dried. The $CHCl_3$ was evaporated off in vacuo to give a crude product which was purified as a free base or a oxalate by recrystallization as summarized in Table IV.

The N-Acryloylsulfoximide 15

After a solution of the N-chloropropionylsulfoximide 10c (1.0 g) and K_2CO_3 (0.4 g) in EtOH (20 ml) had been refluxed for 40 min, the EtOH was evaporated off in vacuo and the residue was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated in vacuo. The residue was subjected to silica gel column chromatography with $CHCl_3$ as an eluent to give 0.5 g (59% yield) of 15. Mp 81-83°C (CH_2Cl_2-isopropyl ether). Anal. Calcd for $C_{17}H_{14}N_2O_3S$: C, 62.53; H, 4.32; N, 8.58; S, 9.82. Found: C, 62.38; H, 4.33; N, 8.16; S, 9.60. NMR (100 MHz): δ 5.21d and 5.46d(AB q, J= 14.2 Hz, 2H, CH_2S), 5.76dd(J= 3.8 and 8.4 Hz, 1H, $COCH=CH_EH$), 6.29dd (J= 8.4 and 17.0 Hz, 1H, $COCH=CH_2$), 6.40dd(J= 3.8 and 17.0 Hz, 1H, $COCH=CH_ZH$), 7.2-8.0m(9H, arom). Mass: m/z 326 (M^+, 2%), 125 ($PhSO^+$, 33%), 77 (Ph^+, 100%), 55 ($COCH=CH_2^+$, 88%).

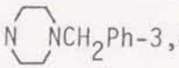
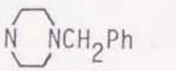
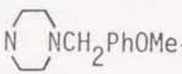
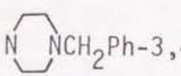
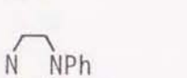
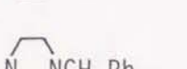
A solution of 15 (0.1 g) and piperidine (2 equiv.) in $CHCl_3$ (5 ml) was refluxed for 30 min and then the reaction

Table IV. N-Aminoacyl-S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides 13(n=1) and 14(n=2)

Copmd	Ar	NR_2	mp(°C)[a] (Solvent)[b]	Yield (%)	Formula[c]	Analysis(%),Calcd/(Found) C	H	N	S	Cl
13a	Ph	NEt_2	201-204* (M-IP)	65[d]	$C_{20}H_{23}N_3O_3S \cdot 0x$	55.57	5.30	8.84	6.74	-
						(55.62	5.21	8.74	6.99	-)
13b	Ph		109-111** (C-IP)	74	$C_{20}H_{21}N_3O_3S$	62.64	5.52	10.96	8.36	-
						(62.84	5.66	11.00	8.37	-)
13c	Ph		136-137** (EtOH)	78	$C_{21}H_{23}N_3O_3S$	63.46	5.83	10.57	8.07	-
						(63.19	5.80	10.48	8.12	-)
13d	Ph		155-157** (MeOH)	60[d]	$C_{20}H_{21}N_3O_4S$	60.13	5.30	10.52	8.03	-
						(60.33	5.21	10.32	7.92	-)
13e	Ph		207-210* (MeOH)	34	$C_{21}H_{24}N_4O_3S \cdot 20x$	50.67	4.76	9.46	5.41	-
						(50.54	4.84	9.33	5.31	-)
13f	Ph		173-175** (C-IP)	58[d]	$C_{26}H_{26}N_4O_3S$	65.80	5.52	11.81	6.76	-
						(66.06	5.68	11.67	6.89	-)
13g	Ph		215-219* (EtOH)	57	$C_{27}H_{28}N_4O_3S \cdot 20x$	55.68	4.82	8.38	4.79	-
						(55.51	4.68	8.54	4.84	-)
13h	Ph		139-142** (C-IP)	62	$C_{28}H_{30}N_4O_4S$	64.84	5.83	10.80	6.18	-
						(64.51	5.81	10.56	6.18	-)

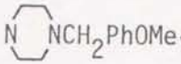
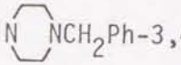
(continued)

Table IV. (continued)

Compd	Ar	NR_2	mp	Yield	Formula	C	H	N	S	Cl
13i	Ph		208-215* (MeOH)	62	$C_{28}H_{28}N_4O_5S \cdot 20x$	53.93 (53.80	4.53 4.19	7.86 7.82	4.50 4.51	- -)
13j	p-ClPh		210-215* (MeOH)	67	$C_{27}H_{27}N_4O_3S \cdot 20x$	52.96 (53.09	4.44 4.41	7.97 7.67	4.56 4.44	5.04 5.06)
13k	p-ClPh		199-204* (MeOH)	42	$C_{28}H_{29}N_4O_4S \cdot 20x$	52.43 (53.16	4.54 4.39	7.64 7.54	4.37 4.14	4.84 4.89)
13l	p-ClPh		198-205* (MeOH)	60	$C_{28}H_{27}N_4O_5S \cdot 20x$	51.44 (50.81	4.18 4.08	7.50 7.62	4.29 4.44	4.74 4.76)
14a	Ph		110-112** (C-IP)	59	$C_{21}H_{23}N_3O_3S$	63.46 (63.48	5.83 5.85	10.57 10.34	8.07 8.13	- -)
14b	Ph		98-101.5** (H-IP)	76	$C_{22}H_{25}N_3O_3S$	64.21 (63.89	6.12 5.87	10.21 10.13	7.79 7.92	- -)
14c	Ph		97-100** (A-IP)	73	$C_{21}H_{23}N_3O_4S$	61.00 (60.88	5.61 5.49	10.16 10.27	7.75 7.89	- -)
14d	Ph		136-139** (EtOH)	75	$C_{27}H_{28}N_4O_3S$	66.37 (66.23	5.78 5.61	11.47 11.16	6.56 6.26	- -)
14e	Ph		124-126** (C-IP)	73	$C_{28}H_{30}N_4O_3S$	66.91 (67.08	6.02 5.98	11.15 10.96	6.38 6.53	- -)

(continued)

Table IV. (continued)

Compd	Ar	NR_2	mp	Yield	Formula	C	H	N	S	Cl
14f	Ph		205-210* (EtOH)	67	$C_{29}H_{32}N_4O_4S \cdot 2Ox$	54.24 (54.74	5.24 4.99	7.67 7.64	4.39 4.58	-)
14g	Ph	 e)	198-205* (MeOH)	72	$C_{29}H_{30}N_4O_5S \cdot 2Ox$	54.54 (54.07	4.72 4.77	7.71 7.67	4.41 4.48	- -)

a) *mono- or dioxalate; **free base.

b) A, AcOEt; C, CH_2Cl_2; H, hexane; IP, isopropyl ether; M, MeOH.

c) Ox, oxalate.

d) Prepared from 11.

e) 3,4-Methylenedioxybenzylpiperazinyl.

mixture was directly subjected to silica gel column chromatography to give 0.1 g (79% yield) of the piperidinopropionylsulfoximide 14b.

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Chapter 2

Halogenations of S-Aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides

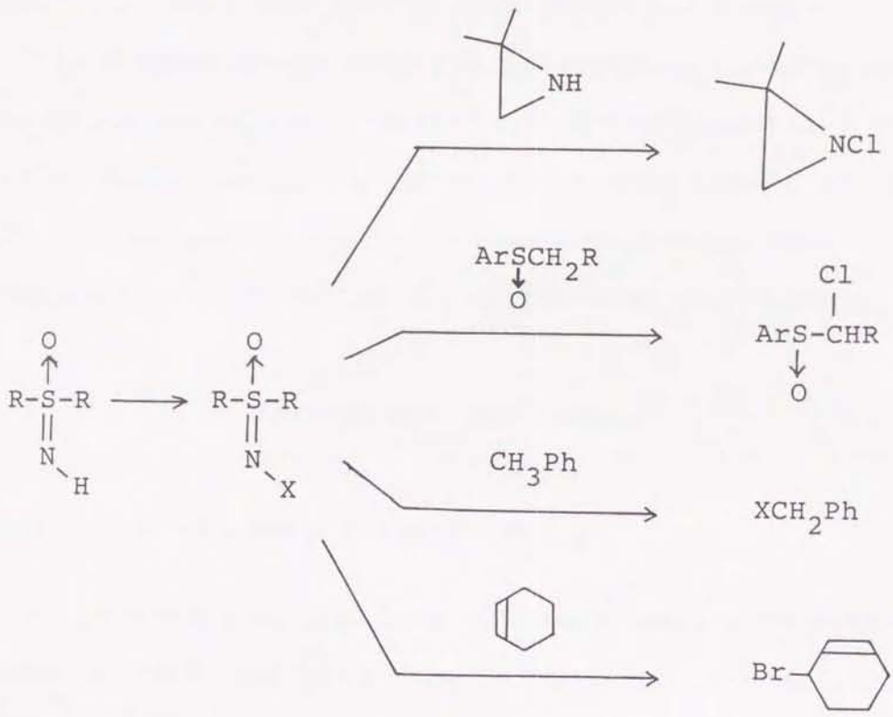
Summary ----- The reactions of the title free sulfoximides with N-bromosuccinimide (NBS) and with N-chlorosuccinimide (NCS) afforded unexpectedly the corresponding α-halogenated "free" sulfoximides in good yields. The NBS bromination proceeded via a facile N-bromination followed by bromine transfer reaction of the resulting N-bromosulfoximide to give the α-bromosulfoximide. The NCS chlorination, in contrast, proceeded via direct α-chlorination, not via N-chlorination. However, in the presence of potassium carbonate or silica gel, N-chlorination occurred predominantly in the NCS chlorination. The mechanisms of these reactions are discussed in detail.

Introduction

Among numerous publications on the synthesis and properties of sulfoximide derivatives which possess a wide variety of chemical and biological interest, only a few dealt with the reactivities of the halo derivatives, especially the α-halo derivatives.[1)]

N-Unsubstituted (free) sulfoximides are well known to undergo readily N-halogenation with a number of halogenating agents such as bromine,[1a)] aqueous sodium hydroxide-bromine,[1h)]

aqueous sodium hypochlorite[1h] and hypobromite,[1c] N-chlorobenzotriazole,[1b] and tert-butyl hypochlorite (BHC),[1d] and the resulting N-halosulfoximides have been used as the halogenating agents in the halogenations of aziridine derivative,[1b] sulfoxides,[1f] toluene,[1g] and olefins.[1c,h]



It was expected, therefore, that N-halosulfoximide containing an active methylene or a benzyl group could undergo rearrangement of the halogen atom to the active or benzylic methylene group. However, no research has been carried out on this possibility.

Meanwhile, Uno et al.[2] have found that the α-methylene group of 1,2-benzisoxazole-3-acetic acid is unusually reactive in the electrophilic substitutions, suggesting that the C=N

bond of the 1,2-benzisoxazole ring has the nature of a "masked" carbonyl group.

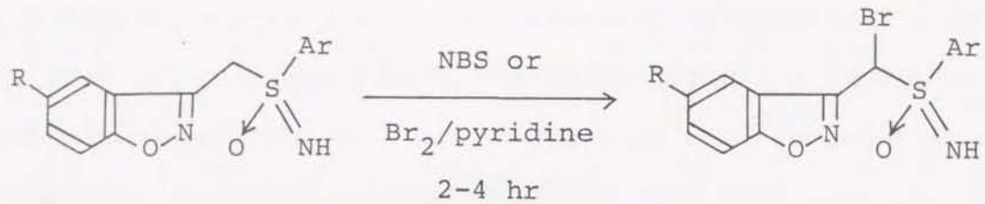
Therefore, it appeared to be quite interesting to examine the halogenation of the sulfoximide derivative having an α-methylene group activated with 1,2-benzisoxazole ring in connection with the possibility described above.

This Chapter deals with the interesting chemical behaviors in the halogenations of S-aryl-S-[(1,2-benzisoxazol-3-yl)-methyl]sulfoximides 1, including the rearrangement of their N-halo derivatives to the corresponding α-halo derivatives, and the direct α-chlorination of the free sulfoximides 1.

Results and Discussion

Bromination of the Free Sulfoximides 1

The reactions of the free sulfoximides 1 with N-bromo-succinimide (NBS) and with bromine/pyridine in commercial chloroform for 2-4 hr at room temperature gave α-bromo "free" sulfoximides, S-aryl-S-[(1,2-benzisoxazol-3-yl)bromomethyl]-sulfoximides 2, in ca.60% and 80-90% yields, respectively, as a mixture of diastereomers, whose NMR spectra showed two distinct methine singlets (see "Experimental").



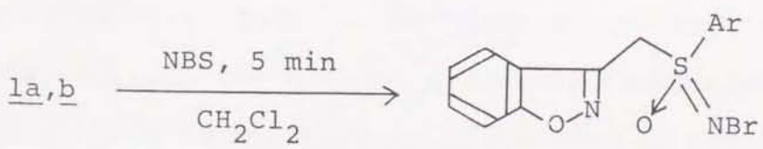
1 2

	a	b	c	d	e
R	H	H	H	Br	MeO
Ar	Ph	p-MePh	p-ClPh	Ph	Ph

This result is surprising in view of the fact that "free" sulfoximides readily undergo N-halogenation with various halogenating agents as described before, but would not be unexpected if the α-bromosulfoximides 2 were produced via the corresponding N-bromosulfoximides.

In order to confirm the above expectation, N-bromo-S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides 3 were prepared and their behaviors were examined.

When the free sulfoximides 1a,b were treated with NBS in dichloromethane for 5 min at room temperature, followed by silica gel column chromatography, the desired N-bromosulfoximides 3a,b were obtained in isolated yields of 90%.



3a: Ar= Ph

b: Ar= p-MePh

This finding suggests that the foregoing α-bromination of the free sulfoximides 1 with NBS proceeded via a facile N-bromination followed by bromine transfer reaction of the resulting N-bromosulfoximide 3. Thus, the decomposition of the N-bromosulfoximide 3 was carried out under several conditions and, as expected, the bromine transfer reaction of 3 was found to proceed easily to give the α-bromosulfoximide 2 as shown in Table I.

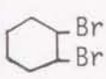
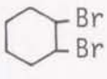
(Table I)

Inspection of the data summarized in Table I reveals an interesting feature of this rearrangement. In the dark, no reaction occurred, whereas in the presence of a light source, even a room light (a fluorescent lamp), the bromine transfer reaction easily proceeded at room temperature and showed a clear induction period as shown in Fig. 1, seemingly ruling out any ionic mechanism.

(Fig. 1)

The effect of solvent, however, was remarkable; an increase in the concentration of ethanol in the solvent enhanced the rate of this reaction and decreased the yields of radical products. Thus, in dichloromethane and in refluxing carbon tetrachloride the N-bromo-S-(p-tolyl)sulfoximide 3b gave the S-(p-bromomethylphenyl)sulfoximides 1f and 2f in 10-25% yields either in the presence or in the absence of a radical initiator (BPO), while in chloroform containing

Table I. Decomposition of the N-Bromosulfoximides 3[a)]

Compd.	Reaction Conditions	Products and Yields(%)[b)]			
		1a	2a		
	5%EtOH-$CHCl_3$,[c)] 1.5 hr	38.5	56.6		
	1%EtOH-$CHCl_3$,[c)] 2.5 hr	35.2	58.1		
	CH_2Cl_2, 10 hr	31.5	58.5		
3a	1%EtOH-$CHCl_3$, dark, 1 week	no decomposition			
	5%EtOH-$CHCl_3$,  ,[d)] 7 hr[e)]	65.7	7.7		22.2[f)]
	CH_2Cl_2,  ,[d)] 24 hr	-[g)]	-[g)]		36.8[f)]

		1b	1f[h)]	2b	2f[h)]
	5%EtOH-$CHCl_3$, 1.5 hr	43.4	trace	47.1	trace
	1%EtOH-$CHCl_3$, 2.5 hr	34.1	2.5	47.8	5.1
3b	CH_2Cl_2, 10 hr	24.5	25.4	22.5	16.8
	CCl_4, reflux, 10 hr	31.2	18.5	18.6	9.9
	CCl_4, BPO(5%), reflux, 3 hr	26.0	15.1	20.6	11.2

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise stated.

b) Determined by HPLC.

c) Chloroform containing 5% or 1% ethanol.

d) 10 equiv.

e) The other product is 1-bromo-2-ethoxycyclohexane[1c)] (23.3%).[f)]

f) Determined by GLC.

g) Yields of 1a and 2a were not determined.

h) 1f: R=H, Ar=p-$BrCH_2Ph$; 2f: R=H, Ar=p-$BrCH_2Ph$.

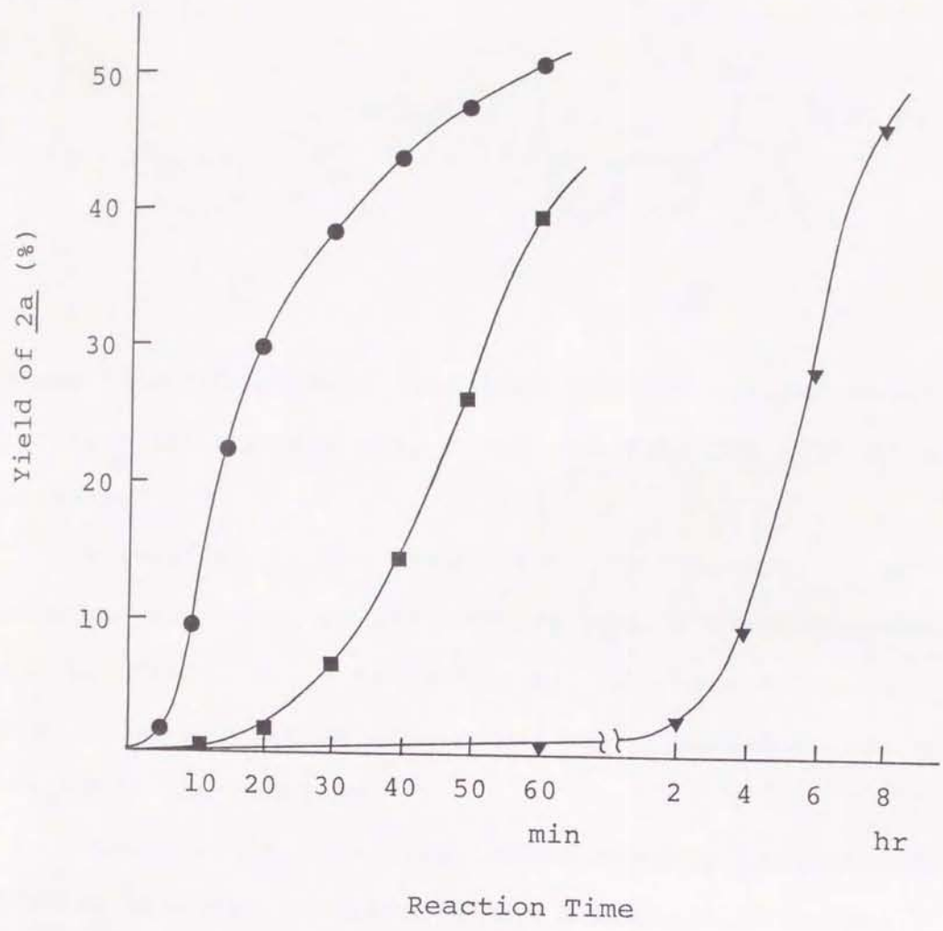
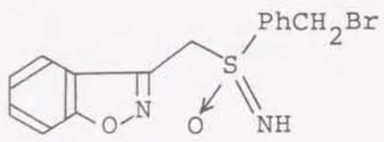


Fig. 1. Change of Yield of the α-Bromosulfoximide 2a with Time in the Decomposition of the N-Bromosulfoximide 3a in the Presence of a Light Source

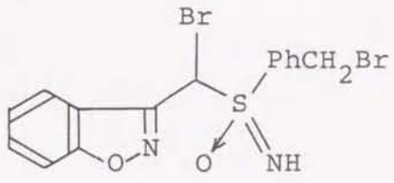
● : in 5%EtOH-$CHCl_3$, ■ : in 1%EtOH-$CHCl_3$,

▼ : in CH_2Cl_2

5% ethanol (5%EtOH-$CHCl_3$) the yields of these radical products decreased to only trace amounts.



1f



2f

These findings suggest that this bromine rearrangement proceeds through not only a radical path but also an ionic process.

Meanwhile, in the presence of cyclohexene, 4a gave 1,2-dibromocyclohexane in 36% and 22% yields in dichloromethane and in 5%EtOH-$CHCl_3$, respectively; in the absence of cyclohexene the liberation of bromine was observed in the early stages of the reaction.

These results described above clearly indicate that the bromine transfer reaction of the N-bromosulfoximides 3 proceeds through an initial photo-induced radical process (an induction period) followed by a bromination process in which the bromine molecule formed in the initial step should act as the active brominating species both in radical and ionic processes.

The radical bromination process is considered to proceed via a chain process like the "Goldfinger mechanism"[3] in which bromine molecule acts as a chain carrier, but not via that involving the sulfoximidoyl radical, as shown in Chart 1.

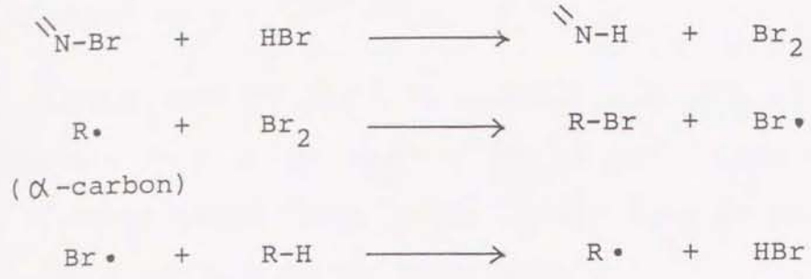


Chart 1

Similar results have been reported in bromination of olefins[1h] and toluene[1g] with N-bromo-S,S-diphenylsulfoximide.

The ionic bromination process involves the electrophilic attack of bromine molecule on the active α-methylene group and seems to be mainly operative in solvents containing ethanol. The activation of the α-methylene group of 1 to an electrophile (bromine molecule) may be explained in terms of the strong electron-withdrawing inductive effect and/or (more likely) the tautomerizm of the 1,2-benzisoxazole ring whose C=N bond shows the nature of a "masked" carbonyl group,[2] as illustrated in Chart 2.

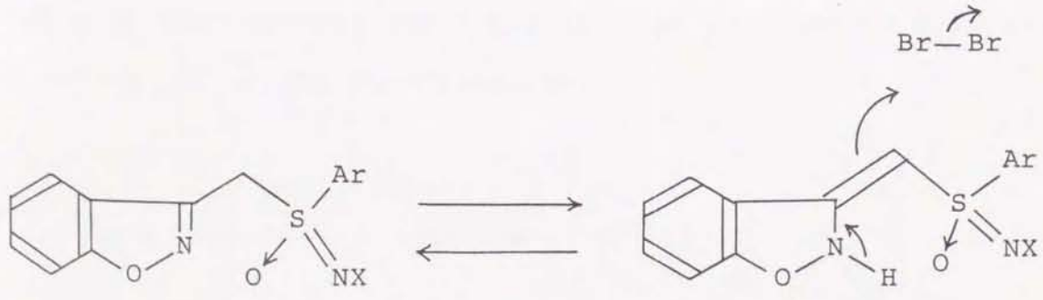
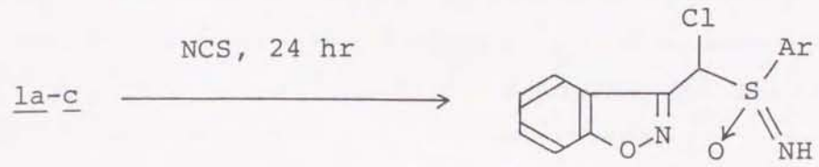


Chart 2

Chlorination of the Free Sulfoximides 1

The reaction of the free sulfoximides 1a-c with N-chlorosuccinimide (NCS) in chloroform for 24 hr at room temperature gave α-chlorinated "free" sulfoximides 4a-c in ca. 70% yields as a mixture of diastereomers.

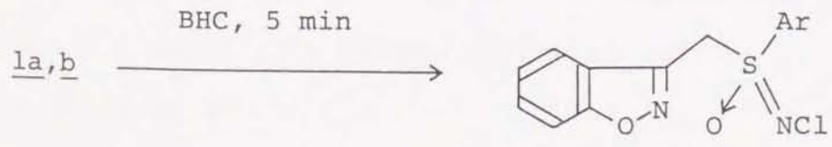


4a: Ar= Ph

b: Ar= p-MePh

c: Ar= p-ClPh

By analogy, this α-chlorination was presumed to proceed via the corresponding N-chlorosulfoximide in the same manner as the NBS bromination described above, although the N-chloro derivative could not be isolated in this reaction, in contrast to the NBS reaction. The N-chlorosulfoximides 5a,b, however, were easily obtained in 90% yields on treatment of 1a,b with BHC in dichloromethane for 5 min at room temperature followed by silica gel column chromatography.



5a: Ar= Ph

b: Ar= p-MePh

In order to examine whether the N-chlorosulfoximide 5 is an intermediate in the α-chlorination of 1 with NCS, the decomposition of 5 was carried out under several conditions. The results summarized in Table II, however, show an unexpected feature of this reaction.

Table II. Decomposition of the N-Chlorosulfoximides 5[a)]

Compd	Reaction Conditions	Products and Yields(%)[b)]	
		1a	4a
5a	5%EtOH-$CHCl_3$, 24 hr	81.3	6.1
	1%EtOH-$CHCl_3$, 48 hr	66.6	12.7
	CH_2Cl_2, 1 week	32.8	22.5
	CH_2Cl_2, dark, 2 weeks	No decomposition	
		1b	4b
5b	5%EtOH-$CHCl_3$, 48 hr	78.5	3.9
	1%EtOH-$CHCl_3$, 120 hr	63.7	8.0
	CH_2Cl_2, 1 week	34.1	9.1

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise noted.

b) Determined by HPLC.

The N-chlorosulfoximide 5 decomposed at room temperature to give the free sulfoximide 1 and the α-chlorosulfoximide 4 in the presence of a light source, suggesting that the reaction was photochemically initiated, as in the case of the N-bromo derivative 3, though the rate was strongly dependent on the solvent used. In every case examined, however, the yields of the α-chlorosulfoximides 4 were very low (4-22% yields) in comparison with those of the NCS chlorination of 1. This result seems to be contrary to the expectation stated above.

In order to clarify this point, the reaction of the free sulfoximides 1a,b with NCS was examined under several conditions and the results summarized in Table III are in contrast to those of the decomposition of the N-chlorosulfoximides 5 in Table II.

(Table III)

Either in the presence or in the absence of a light source, the reaction of 1 with NCS proceeded smoothly at room temperature to give the α-chlorosulfoximide 4 in good yields and was found to complete within 24 hr, regardless of the solvent used. For example, even in the dark the free sulfoximide 1a reacted with NCS in dichloromethane for 24 hr to give the α-chlorosulfoximide 4a in 71% yield, whereas in the dark the N-chlorosulfoximide 5a which was presumed to be an intermediate in this reaction was stable for 2 weeks in dichloromethane (see Table II). Furthermore, the NMR inspection during the course of the α-chlorination of 1a with NCS in chloroform-d_1 ($CDCl_3$) indicated that no detectable amount of

Table III. Reaction of the Free Sulfoximides 1 with NCS[a)]

Compd.	Reaction Conditions	Product(s) and Yields(%)[b)]	
		4a	5a
1a	$5\%EtOH-CHCl_3$, 24 hr	68.1	
	$1\%EtOH-CHCl_3$, 24 hr	64.6	
	CH_2Cl_2, 24 hr	68.2	
	$5\%EtOH-CHCl_3$, dark, 24 hr	68.0	
	$1\%EtOH-CHCl_3$, dark, 24 hr	64.9	
	CH_2Cl_2, dark, 24 hr	71.2	
	$CDCl_3$, dark, 24 hr	(77)	(0)
	$CDCl_3$, 0°, dark, 1 week[c)]	(60)	(20)
	$CDCl_3$, p-quinone(1 equiv.), 24 hr	(75)	(0)
	$CDCl_3$, CCl_3COOH(10%), 12 hr	(76)	(0)
	$CDCl_3$, pyridine-d_5(10%), 24 hr	(74)	(0)
	$CDCl_3$, trans-stilbene(1.5 equiv.), 24 hr	(73)	(0)
	$CDCl_3$, K_2CO_3(1 equiv.), 10 min[d)]	(0)	(50)
	$CDCl_3$, SiO_2,[e)] 2 hr	(10)	(72)
		4b	
1b	$5\%EtOH-CHCl_3$, 24 hr	72.5	
	$1\%EtOH-CHCl_3$, 24 hr	70.5	
	CH_2Cl_2, 24 hr	72.0	
	$5\%EtOH-CHCl_3$, dark, 24 hr	69.2	
	$1\%EtOH-CHCl_3$, dark, 24 hr	71.0	
	CH_2Cl_2, dark, 24 hr	65.9	

(continued)

Table III. (continued)

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise stated.

b) Determined by HPLC and values in parentheses by NMR.

c) The reaction was approximately 90% completed.

d) The reaction was approximately 55% completed: prolonged reaction caused the further rearrangement of 5a to the corresponding N-sulfinylimine.[4)]

e) Kieselgel 60(70-230 mesh)(Merck)1.0 g/ 1a 300 mg.

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the N-chlorosulfoximide 5a was produced. These observations appear to exclude the possibility of the intermediacy of the N-chlorosulfoximide 5 in the α-chlorination of 1 with NCS.

The rate of this α-chlorination was strongly affected by the reaction temperature; at 0°C the reaction of 1a with NCS required over 1 week for completion. The addition of acids such as trichloroacetic or p-toluenesulfonic acid apparently enhanced the rate of this reaction. The presence of p-quinone, however, had little effect. These findings seem to indicate that this α-chlorination is not a radical process, but is an ionic process. The function of the acid is in all likelihood to generate a more powerful electrophilic reagent by protonation of the oxygen of NCS[5)] and/or to activate the α-methylene group of 1 to an electrophile by protonation of the imino nitrogen of 1.

Meanwhile, the addition of pyridine or trans-stilbene also had little effect, suggesting that in this α-chlorination NCS itself acts as the active chlorinating species, not merely as a controlled source of chlorine molecule.[6)]

On the basis of the results described above, the α-chlorination of the free sulfoximide 1 with NCS is considered to proceed through the direct electrophilic α-attack of NCS, not via N-chlorination, in contrast to the α-bromination of 1 with NBS.

Although it is difficult to explain why the imino group of the free sulfoximide 1 is less reactive to NCS than to BHC and NBS, there are two possible explanations. One is that the nucleophilicity of the imino group of 1 is decreased because of the electron-withdrawing inductive effect of the 1,2-benzisoxazole ring. The other is that NCS is too much less electrophilic than BHC and NBS to react with the deactivated imino group. It seems likely, therefore, that at room temperature the NCS chlorination of 1 can occur at the α-position activated by the 1,2-benzisoxazole ring as mentioned above. At a lower temperature (0°C), N-chlorination may be able to compete with α-chlorination because the rate of α-chlorination is retarded.

On the other hand, in the presence of potassium carbonate or, interestingly, silica gel, N-chlorination occurred predominantly in the reaction of 1a with NCS as shown in Table III. The function of potassium carbonate or silica gel is likely to be to increase the nucleophilicity of the imino nitrogen

by deprotonation or adsorption of the imino proton, respectively.

The α-halogenations of sulfoximide derivatives have been reported only on chlorination of N-methyl,[1d] N-chloro,[1d] and N-tosyl derivatives[1d,7] and bromination of cyclic derivatives,[8] while the synthesis of α-halo "free" sulfoximides has been reported only by Johnson and Corkins,[1d] including reduction of N,α-dichlorosulfoximides with sodium sulfite, and amination of α-halosulfoxides with O-mesitylenesulfonylhydroxylamine (MSH).

Therefore, the reactions described in this Chapter are the first example on the rearrangement of N-halosulfoximide to the corresponding α-halosulfoximide and on the α-halogenation of "free" sulfoximide.

Experimental

The α-Halo Free Sulfoximides 2 and 4

A solution of the free sulfoximide 1 (6 mmol) and a slight excess of Br_2/pyridine, NBS, or NCS in 20 ml of commercial $CHCl_3$ was stirred for 2-3 hr, 3-4 hr, or 24 hr, respectively, at room temperature under a room light. The reaction mixture was washed with dilute aq. K_2CO_3, and then the organic layer was dried and concentrated in vacuo. The residual oil was chromatographed on a silica gel column using $CHCl_3$ as an eluent to afford 2 or 4. Recrystallization from CH_2Cl_2-isopropyl ether gave pure products (Table IV). All α-halosulfoximides 2a-e and 4a-c were isolated as mixtures of diastereomers; the NMR spectra showed two distinct methine singlets, as shown in Table IV.

(Table IV)

The N-Halosulfoximides 3 and 5

An equimolar amount of NBS or BHC was added to a stirred solution of 1 in 20 ml of CH_2Cl_2 at room temperature, and the mixture was stirred for 5 min. The rection mixture was directly subjected to silica gel column chromatography and eluted with CH_2Cl_2 to afford 3 or 5. Recrystallization from CH_2Cl_2-isopropyl ether gave pure products (Table V).

(Table V)

Table IV. S-Aryl-S-[(1,2-benzisoxazol-3-yl)halomethyl]sulfoximides 2[a] and 4

Compd	Mp (°C)	Yield (%)	Formula	Analsis(%), Calcd/(Found) C	H	N	S	Br	Cl	NMR, δ
2a	162-168	86 (61)[b]	$C_{14}H_{11}N_2O_2SBr$	47.88 (47.81	3.16 3.06	7.97 7.90	9.13 8.89	22.75 22.98	- -)	3.57s and 4.00s(1H, NH), 6.16s and 6.22s(1H, CH), 7.2-8.4m(9H, arom)
2b	144-147	83 (60)	$C_{15}H_{13}N_2O_2SBr$	49.33 (49.35	3.59 3.37	7.67 7.63	8.78 8.60	21.88 22.15	- -)	2.42s and 2.45s(3H, CH_3), 3.53s and 3.97s(1H, NH), 6.17s and 6.24s(1H, CH), 7.1-8.4m(8H, arom)
2c	153-156	82 (60)	$C_{14}H_{10}N_2O_2SBrCl$	43.60 (43.62	2.61 2.46	7.26 7.13	8.31 8.05	20.72 20.57	9.19 9.13)	3.60s and 4.01s(1H,NH), 6.17s and 6.25s(1H, CH), 7.3-8.4m(8H, arom)
2d	163-167	80	$C_{14}H_{10}N_2O_2SBr_2$	39.10 (39.16	2.34 2.16	6.51 6.40	7.45 7.31	37.16 36.96	- -)	3.56s and 4.01s(1H, NH), 6.13s and 6.19s(1H, CH), 7.3-8.4m(8H, arom)
2e	147-149	89	$C_{15}H_{13}N_2O_3SBr$	47.26 (47.06	3.44 3.23	7.35 7.17	8.41 8.47	20.96 21.06	- -)	3.90s(1H, NH), 3.91s(3H, CH_3O), 6.16s and 6.21s(1H, CH), 7.1-8.2m(8H, arom)

(continued)

Table IV. (continued)

Compd	Mp	Yield	Formula	C	H	N	S	Br	Cl	NMR, δ
4a	156-160	71	$C_{14}H_{11}N_2O_2SCl$	54.82	3.62	9.13	10.45	-	11.56	3.50s and 3.83s(1H, NH),
				(55.22	3.45	9.00	10.21	-	12.13)	6.12s and 6.14s(1H, CH),
										7.2-8.4m(9H, arom)
4b	151-153	64	$C_{15}H_{13}N_2O_2SCl$	56.16	4.08	8.73	9.99	-	11.05	2.43s(3H, CH_3), 3.50s(1H, NH),
				(56.54	3.86	8.70	9.89	-	11.05)	6.05s and 6.08s(1H, CH),
										7.1-8.2m(8H, arom)
4c	142-145	70	$C_{14}H_{10}N_2O_2SCl_2$	49.28	2.95	8.21	9.40	-	20.78	3.50s and 3.85s(1H, NH),
				(49.36	2.75	7.86	9.53	-	21.23)	6.13s and 6.14s(1H, CH),
										7.2-8.3m(8H, arom)

a) Data for compounds 2 prepared by using bromine/pyridine are listed.

b) Yields in parentheses are based on the reaction with NBS.

Table V. N-Halo-S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides 3 and 5

Compd	Mp (°C)	Yield (%)	Formula	Analysis(%), Calcd/(Found) C	H	N	S	Br	Cl	NMR, δ
3a	105-109	89	$C_{14}H_{11}N_2O_2SBr$	47.88	3.16	7.97	9.13	22.75	-	5.13d and 5.15d(AB q, J= 14Hz,
				(48.32	3.05	8.07	9.16	22.69	-)	2H, CH_2), 7.2-8.1m(9H, arom)
3b	121-124	90	$C_{15}H_{13}N_2O_2SBr$	49.33	3.59	7.67	8.78	21.88	-	2.43s(3H, CH_3), 5.10d and 5.13d
				(49.74	3.43	7.65	8.77	22.06	-)	(AB q, J= 14Hz, 2H, CH_2),
										7.2-8.1m(8H, arom)
5a	107-112	91	$C_{14}H_{11}N_2O_2SCl$	54.82	3.62	9.13	10.45	-	11.56	5.10d and 5.12d(AB q, J= 14Hz,
				(54.46	3.54	9.16	10.17	-	11.39)	2H, CH_2), 7.1-8.1m(9H, arom)
5b	110-114	89	$C_{15}H_{13}N_2O_2SCl$	56.16	4.08	8.73	9.99	-	11.05	2.39s(3H, CH_3), 5.04d and 5.06d
				(55.99	3.94	8.65	9.89	-	11.13)	(AB q, J= 14 Hz, 2H, CH_2),
										7.1-8.0m(8H, arom)

The S-(p-Bromomethylphenyl)sulfoximides 1f and 2f

1f: A solution of (1,2-benzisoxazol-3-yl)methyl phenyl sulfide (3.0 g), NBS (2.1 g), and a catalytic amount of benzoyl peroxide (BPO) in CCl_4 (30 ml) was refluxed for 1.5 hr. After cooling, the precipitates were filtered off and the filtrate was concentrated in vacuo. The residual oil was dissolved in THF (50 ml)-water (10 ml) and NBS (2.0 g) was added. After stirring for 1 hr at room temperature, the reaction mixture was worked up in the same manner as described in Chapter 1 to give 1.0 g of crystals whose NMR spectrum showed it to be a mixture of (1,2-benzisoxazol-3-yl)methyl p-bromomethylphenyl sulfoxide (80%) and (1,2-benzisoxazol-3-yl)methyl phenyl sulfoxide (20%). NMR: δ 2.39s(3H x 0.2, CH_3), 4.45s and 4.49s(ca. 3.6H, SCH_2 and $BrCH_2Ph$), 7.2-7.9m(8H, arom).

To this mixture of the sulfoxides (0.9 g) in 10 ml of CH_2Cl_2 was added MSH (2.0 g) and then the mixture was stirred for 10 hr. The reaction mixture was worked up in the manner described in Chapter 1 to yield 0.37 g of crystals. This product was revealed to be a mixture of 1f (90%) and 1b (10%) by HPLC and NMR (100 MHz) analyses. NMR: δ 2.42s(3H x 0.1, CH_3 of 1b) 2.8s(1H, NH), 4.48s(2H x 0.9, $BrCH_2Ph$), 4.82s(2H, SCH_2), 7.2-7.9m(8H, arom).

2f: The above-mentioned mixture of the sulfoximides 1f and 1b (300 mg) was added to a cooled solution of Br_2 (130 mg) and pyridine (65 mg) in $CHCl_3$ (3 ml) and the mixture was stirred for 1.5 hr at room temperature. The reaction mixture was worked up in the same manner as described above to afford

160 mg of crystals. This product was revealed to be a mixture of 2f (95%) and 2b (5%) by HPLC analysis. The NMR (100 MHz) spectrum of this mixture showed 2f to be a mixture of diastereomers: δ 2.41s and 2.44s(trace, CH_3 of 2b), 3.5-4.0br (1H, NH), 4.46s and 4.49s(2H, $BrC\underline{H}_2Ph$), 6.12s and 6.18s(1H, CH), 7.2-8.2m(8H, arom).

Decomposition of the N-Halosulfoximides 3 and 5 (Tables I and II)

The reaction was carried out using a 0.1M solution of the N-halosulfoximide under the conditions stated in Tables I and II. After an appropriate reaction time, the reaction mixture was washed with 5% aq. K_2CO_3. The organic layer was dried and concentrated in vacuo. The residual crystals were dissolved in 1 ml of $CHCl_3$ and 19 ml of EtOH and then subjected to HPLC analysis. GLC analysis was carried out using the reaction mixture without the treatment described above.

Reaction of the Free Sulfoximides 1 with NCS (Table III)

The reaction was carried out using a 0.1M solution of 1 with an equimolar amount of NCS under the conditions stated in Table III, except for the reaction in $CDCl_3$. HPLC analysis was run after the reaction mixture had been worked up as described above. The reaction in $CDCl_3$ was carried out using a 0.2M solution of 1 with an equimolar amount of NCS, and the reaction mixture was directly subjected to NMR analysis.

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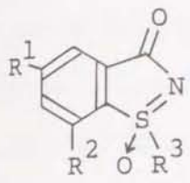
Chapter 3

Base-Induced Rearrangements of α- and N-Halo Derivatives of S-Aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides to the Corresponding N-Sulfinylimines

Summary ----- The title α- and N-halosulfoximides undergo novel rearrangements on treatment with base to give the corresponding N-sulfinylimines, suggesting that these rearrangements involve the same three-membered cyclic sulfoximide intermediate, a thiazirine S-oxide, which has a novel three-membered ring system with an endocyclic S=N group.

Introduction

Much attention in the sulfoximide chemistry has been focused on the synthesis of new heterocycles containing the sulfoximide moiety and many of cyclic sulfoximide derivatives with four- to seven-membered rings and an exo- or endocyclic S=N group have been synthesized.[1)] Several of these derivatives have been claimed to have a wide variety of pharmacological activities; e.g., blood-sugar lowering (1),[2)] antihypertensive (2),[1b,q)] anti-secretory (3),[3)] CNS-depressant (4),[1b)] and other activities.



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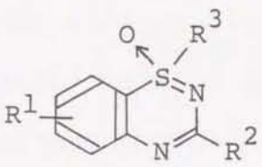

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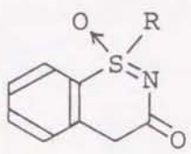

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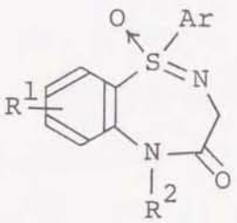
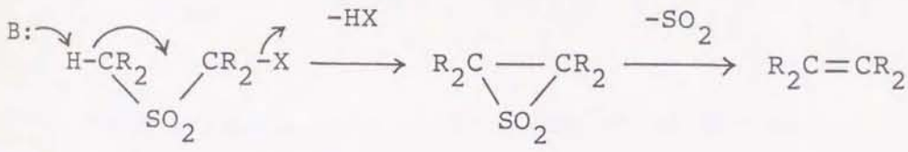


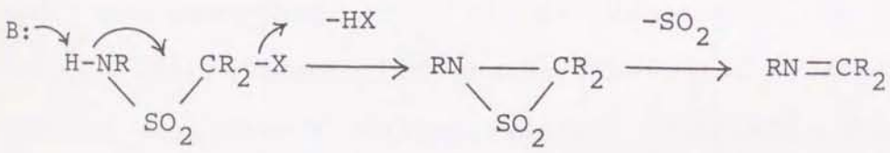
4

Meanwhile, α-halosulfones[4] and α-halosulfonamides[4,5] are well known to undergo the Ramberg-Backlund rearrangements which involve the intermediacy of three-membered heterocycles, an episulfone 5 and an α-sultam 6, giving alkenes and imines (or their degradation products), respectively, as shown in Eqs. 1 and 2.



(Eq. 1)

5

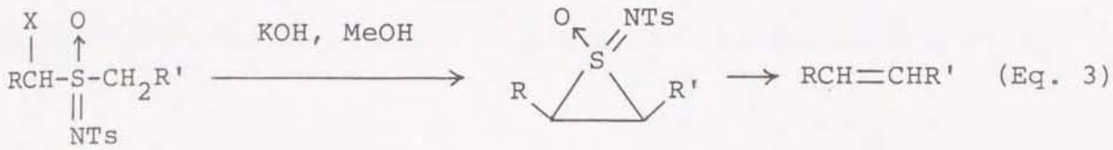


(Eq. 2)

6

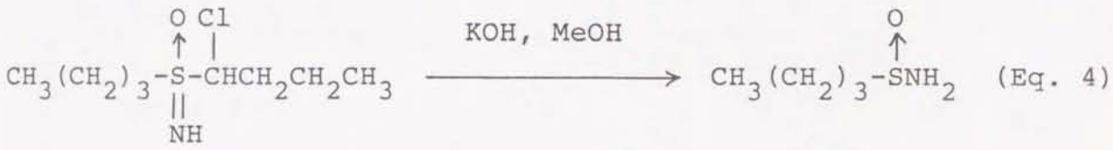
Recently, Johnson and Corkins[6] reported that α-halo-N-(p-toluenesulfonyl)sulfoximides underwent a similar 1,3-elimination to give alkenes, suggesting the intermediacy of a three-membered cyclic sulfoximide with an exocyclic S=N group (an episulfoximide 7) (Eq. 3), and also that the reaction of S-butyl-S-(1-chlorobutyl)sulfoximide with potassium hydroxide

in refluxing methanol gave 1-butanesulfinamide (Eq. 4), the production of which could be rationalized in a number of ways, including a three-membered S-N heterocyclic intermediate, though the available data were not sufficient to justify this speculation.



(Eq. 3)

7

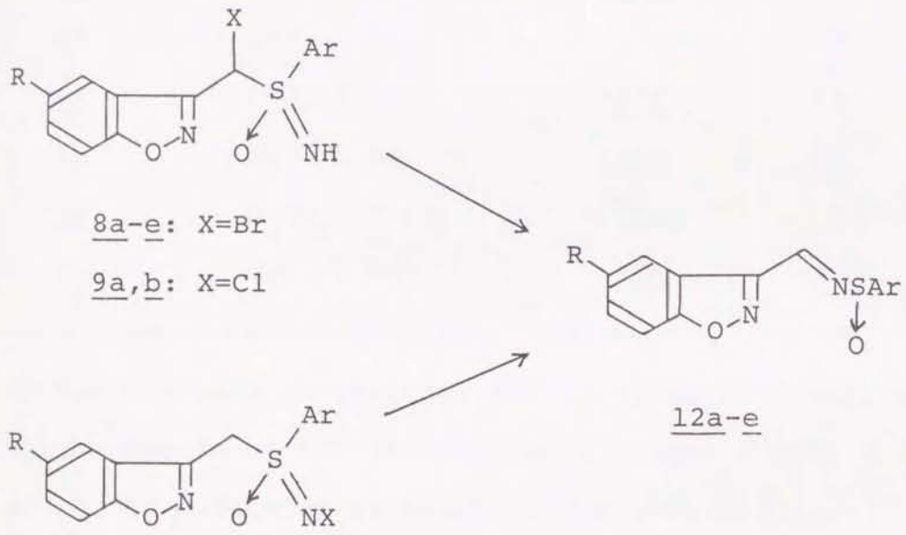


(Eq. 4)

In Chapter 2, the rearrangement of N-halo derivatives of S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides 10 and 11 to the corresponding α-halo derivatives 8 and 9 was described. This Chapter deals with the novel base-induced rearrangements of the halosulfoximides 8-11 to give the corresponding N-sulfinylimines, undoubtedly suggesting the intermediacy of a three-membered cyclic sulfoximide with an endocyclic S=N group.

Results and Discussion

The halosulfoximides 8-11 were treated either with 1,5-diazabicyclo[5.4.0]-5-undecene (DBU) or with potassium carbonate to give the same N-sulfinylimines, 3-arylsulfinyliminomethyl-1,2-benzisoxazoles 12 (Chart 1). The results of these interesting rearrangements are summarized in Tables I and II.



8a-e: X=Br

9a,b: X=Cl

12a-e

10a,b: X=Br

11a,b: X=Cl

	a	b	c	d	e
R	H	H	H	Br	MeO
Ar	Ph	p-MePh	p-ClPh	Ph	Ph

Chart 1

Table I. Rearrangement of the α-Halosulfoximides 8 and 9 with Base[a)]

Compd	Reaction Conditions	Product	Yield(%)[b)]
8a	DBU, 2 hr	12a	86
8a	K_2CO_3, 6 hr	12a	22[c)]
8b	DBU, 2 hr	12b	83
8c	DBU, 2 hr	12c	80
8d	DBU, 2 hr	12d	70
8e	DBU, 4 hr	12e	74
9a	DBU, 5 hr	12a	15[d)]
9a	K_2CO_3, 7 hr	12a	8[c)]
9b	DBU, 5 hr	12b	16[d)]

a) The reaction was carried out in chloroform with a slight excess of DBU at room temperature or with 2 molar equiv. of potassium carbonate under reflux unless otherwise noted.

b) Isolated yield after column chromatography.

c) Recoveries of 8a and 9a were 65% and 85%, respectively.

d) Under reflux. Recoveries of 9a and 9b were 65% and 63%, respectively.

Table II. Rearrangement of the N-Halosulfoximides 10 and 11 with Base[a)]

Compd	Reaction Conditions	Product	Yield(%)[b)]
10a	DBU, 5 min	12a	56[c)]
10a	K_2CO_3, 5 hr	12a	85
10b	K_2CO_3, 5 hr	12b	85
11a	DBU, 5 min	12a	83
11a	K_2CO_3, 3.5 hr	12a	85
11b	DBU, 5 min	12b	85
11b	K_2CO_3, 3.5 hr	12b	85

a) The reaction was carried out in dichloromethane at room temperature with a slight excess of DBU or 2 molar equiv. of potassium carbonate.

b) Isolated yield after column chromatography.

c) S-[(1,2-Benzisoxazol-3-yl)methyl]-S-phenylsulfoximide was also obtained in 22% yield.

As shown in Table I, the α-bromosulfoximides 8a-e were found to rearrange readily into 12a-e in good yields on treatment with DBU at room temperature. The α-chlorosulfoximides 9a,b underwent no rearrangement under the same mild conditions; however, under reflux in chloroform for 5 hr, 9a,b gave 12a,b in 15% and 16% yields, respectively. Meanwhile, treatment of the α-halosulfoximides 8 and 9 with potassium carbonate at room temperature caused no reaction, whereas under reflux in chloroform for 6-7 hr, 8a and 9a gave 12a in 22% and 8% yields, respectively.

In contrast, the N-halosulfoximides 10 and 11 readily underwent the rearrangement on treatment either with DBU or with potassium carbonate at room temperature to afford the N-sulfinylimines 12 in good yields, though in the reaction of the N-bromosulfoximide 10a with DBU the free sulfoximide was also obtained in 22% yield, as shown in Table II.

The N-sulfinylimine structure of 12 was deduced from elemental and spectral analyses. The IR spectra of 12 showed strong bands at around 1610 and 1110 cm^{-1} which are considered to be due to the C=N and SO groups, respectively, but have no characteristic bands of the sulfoximide structure at around 1220, 1110, and 1000 cm^{-1} due to the NSO group.[7] Their NMR spectra showed a singlet peak of the CH=N group at δ 9.25-9.28. Their mass spectra showed the base peaks due to the $ArSO^{+}$ ions.

Further evidence for the structural assignment of 12 was provided by the following chemical transformations of the

representative 12a (Chart 2).

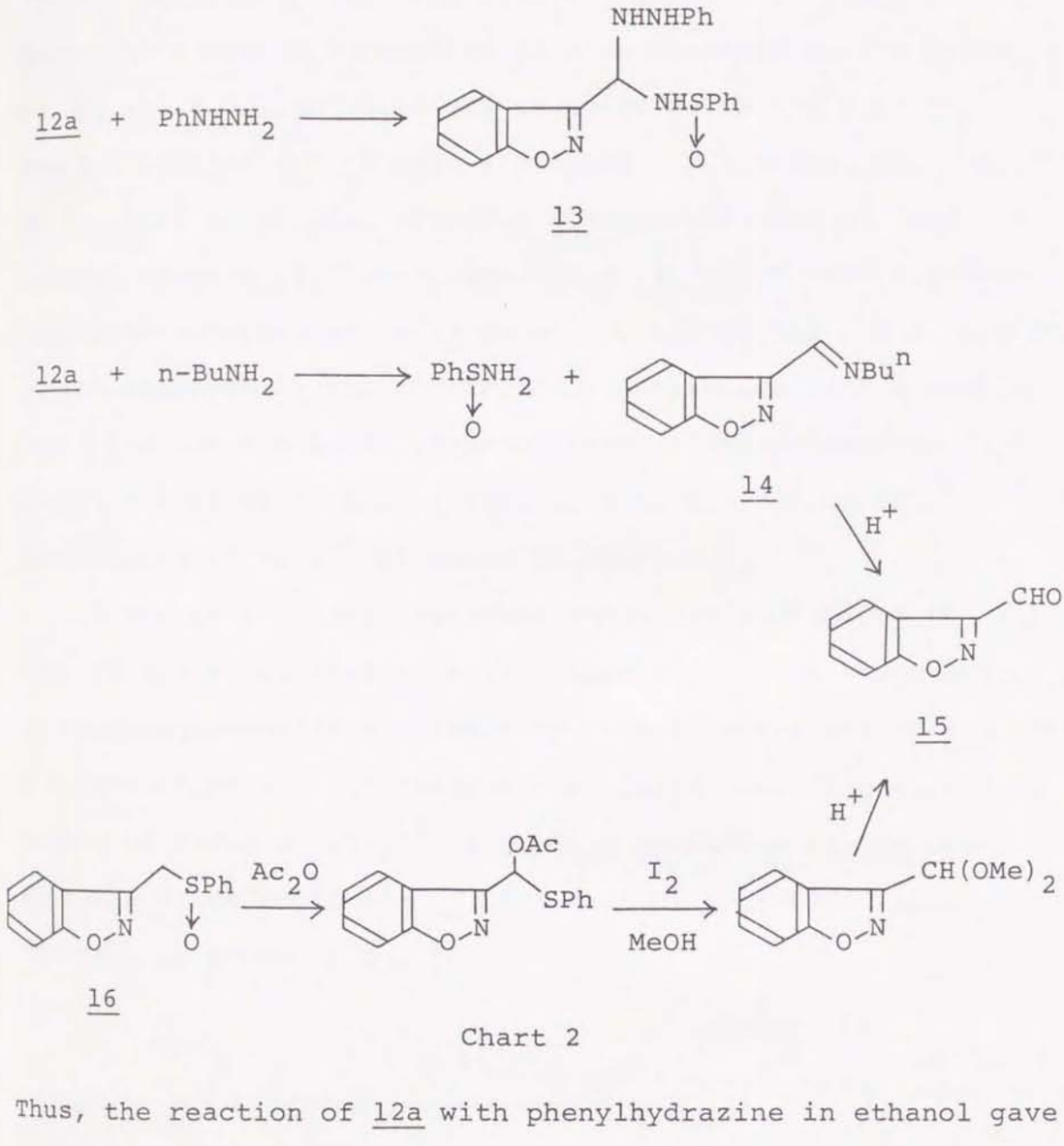
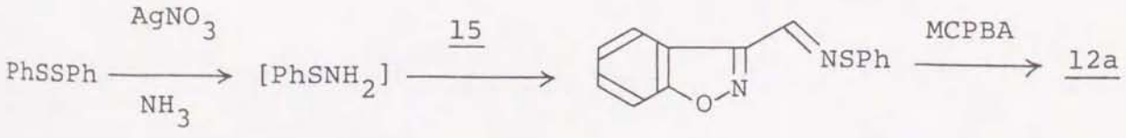


Chart 2

Thus, the reaction of 12a with phenylhydrazine in ethanol gave an adduct, N-[(1,2-benzisoxazol-3-yl)(2-phenylhydrazino)methyl]-benzenesulfinamide 13. The structure of 13 was confirmed by elemental and spectral analyses. Its IR spectrum showed strong bands at 3050(NH), 1601(C=N), 1025 and/or 1040(SO) cm^{-1}. Furthermore, its NMR spectrum (100 MHz) showed the presence of the partial structure PhNHNHCHNH-: δ6.7-8.1m(14H, arom),

6.24s(1H, PhNH), 5.92dd(J= 8.1 and 9.7 Hz, 1H, NHCHNH), 5.56d (J= 9.7 Hz, 1H, CHNHS), and 4.20d(J= 8.1 Hz, 1H, NHNHCH); deuteration with D_2O resulted in disappearance of the peaks at δ6.24, 5.56, and 4.20 and in collapse of the double doublet peak at δ 5.92 into a singlet. Meanwhile, the reaction of 12a with butylamine afforded benzenesulfinamide[8] and 3-butyliminomethyl-1,2-benzisoxazole 14, which gave 1,2-benzisoxazole-3-carbaldehyde 15 on acidic hydrolysis. The structure of the aldehyde 15 was confirmed by comparison with a sample which was alternatively prepared from (1,2-benzisoxazol-3-yl)-methyl phenyl sulfoxide 16 according to the method of Strandtmann et al.,[9] as shown in Chart 2.

Although the data described above are sufficient to support the N-sulfinylimine structure of 12, the structure of 12 was unequivocally confirmed by direct comparison of 12a with a sample which was alternatively prepared according to the method of Davis et al.,[10] including oxidation of the corresponding N-sulfenylimine 17 with m-chloroperbenzoic acid (MCPBA), as shown in Eq. 5.



17 (Eq. 5)

Interestingly, the α-methylene and methine protons of the halosulfoximides 8-11 were found to be exchangeable with the deuterium of chloroform-d_1 ($CDCl_3$) in the presence of DBU.

Thus, the reactions of 8-11 with DBU were carried out in $CDCl_3$ at room temperature, the α-bromosulfoximides 8 and the N-halosulfoximides 10 and 11 underwent partial H-D exchange reactions of their methine and methylene protons together with the rearrangements, whereas the α-chlorosulfoximides 9 underwent only nearly complete H-D exchange in 6-7 hr.
These results clearly suggest the formation of the α-carbanions of the halosulfoximides 8-11 under the rearrangement conditions.

On the basis of the results described above, plausible mechanisms for these interesting rearrangements are illustrated in Chart 3.

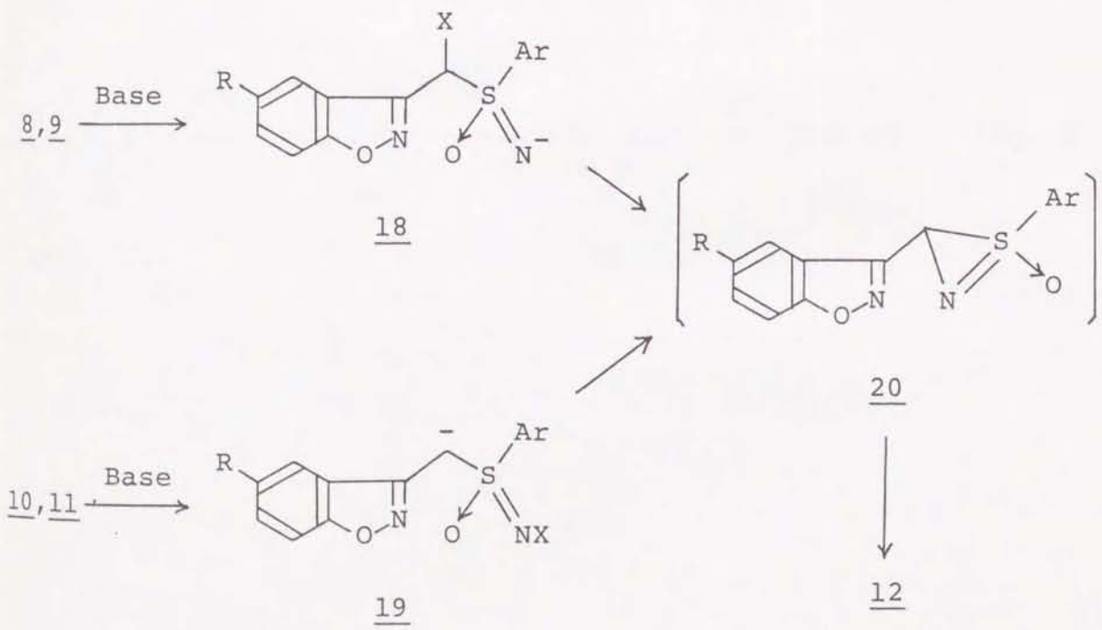
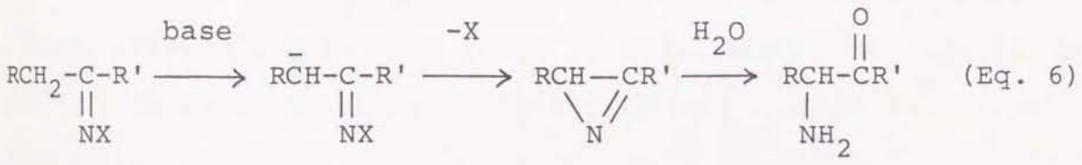


Chart 3

The initial step involves the reversible formation of the sulfoximidoyl anion 18 or the α-carbanion 19, followed by an internal 1,3-substitution of halide ion to afford the same cyclic intermediate, a thiazirine S-oxide 20, which has a novel three-membered ring system with an endocyclic S=N group. The intermediate 20, in turn, undergoes spontaneous ring opening without loss of the sulfur component to give the N-sulfinylimine 12. The formation of the thiazirine intermediate 20 is mechanistically analogous to that of the α-sultam intermediate 6 in the Ramberg-Backlund reaction of α-halosulfonamides (Eq. 2) and that of the azirine intermediate 21 in the Neber reaction[11] of ketoxime tosylates and N-chloroimines (Eq. 6).



(Eq. 6)

X=Ts, Cl

21

Experimental

The N-Sulfinylimines 12

Rearrangements of the Halosulfoximides 8-11 with Base (Tables I and II) --- The reaction was carried out using a 0.15-0.2M solution of the halosulfoximide under the conditions stated in Tables I and II. After an appropriate reaction time, the reaction mixture was subjected to silica gel column chromatography and eluted with $CHCl_3$ to afford 12. Recrystallization from acetonitrile gave a pure product. The elemental analyses and NMR spectral data are summarized in Table III. The IR and mass spectral data are as follows. 12a: IR ν cm^{-1}: 1608, 1593(C=N), 1106(SO); mass: m/z 270(M^+), 125($PhSO^+$). 12b: IR ν cm^{-1}: 1613, 1593(C=N), 1105(SO); mass: m/z 284(M^+), 139($TolSO^+$). 12c: IR ν cm^{-1}: 1615, 1595(C=N), 1115, 1105, and/or 1089(SO); mass: m/z 304(M^+), 159($ClPhSO^+$). 12d: IR ν cm^{-1}: 1606(C=N), 1119(SO). 12e: IR ν cm^{-1}: 1618, 1598(C=N), 1107(SO).

Alternative Synthesis of 12a --- The N-sulfenylimine 17 was prepared in 5% yield according to the procedure of Davis et al.[10a] NMR: δ 7.2-8.5m(9H, arom), 8.79s(1H, CH=N). Oxidation of 17 with MCPBA in a two phase system containing chloroform and water-sodium bicarbonate[10b] gave the N-sulfinylimine 12a in 53% yield. The IR and NMR spectra of this product were in agreement with those of the compound described above.

N-[(1,2-Benzisoxazol-3-yl)(2-phenylhydrazino)methyl]benzenesulfinamide 13

A solution of 12a (1.1 g) and phenylhydrazine (1.0 g) in

Table III. 3-Arylsulfinyliminomethyl-1,2-benzisoxazoles 12[a)]

Compd	Mp (°C)	Formula	Analysis(%), Calcd/(Found) C	H	N	S	Hal	NMR, δ
12a	135-137	$C_{14}H_{10}N_2O_2S$	62.21	3.73	10.36	11.86	-	9.28s(1H, CH=N),
			(62.28	3.51	10.45	12.13	-)	7.2-8.4m(9H, arom)
12b	114-115	$C_{15}H_{12}N_2O_2S$	63.36	4.26	9.85	11.28	-	9.28s(1H, CH=N),
			(63.61	4.19	10.00	10.98	-)	7.2-8.4m(8H, arom),
								2.41s(3H, CH_3)
12c	151-153	$C_{14}H_9N_2O_2SCl$	55.18	2.98	9.19	10.52	11.63	9.25s(1H, CH=N),
			(55.18	2.68	9.26	10.50	11.61)	7.3-8.4m(8H, arom)
12d	128-130	$C_{14}H_9N_2O_2SBr$	48.15	2.60	8.02	9.18	22.88	9.26s(1H, CH=N),
			(48.21	2.51	8.15	8.98	23.11)	7.3-8.5m(8H, arom)
12e	143-145	$C_{15}H_{12}N_2O_3S$	59.99	4.03	9.33	10.67	-	9.27s(1H, CH=N),
			(60.02	3.98	9.33	10.38	-)	7.1-8.1m(8H, arom)
								3.89s(3H, CH_3O)

a) Data for compounds 12 prepared from 8 with DBU are listed.

EtOH (25 ml) was stirred for 10 min at 50°C. After the reaction mixture had been cooled, the precipitates were collected by filtration and washed with cold EtOH to give 0.92 g of 13. Mp 127-131°C (CH_3CN). Anal. Calcd for $C_{20}H_{18}N_4O_2S$: C, 63.47; H, 4.79; N, 14.81; S, 8.47. Found: C, 63.45; H, 4.74; N, 14.97; S, 8.53.

1,2-Benzisoxazole-3-carbaldehyde 15

Reaction of 12a with Butylamine --- After a solution of 12a (540 mg) and butylamine (300 mg) in EtOH (15 ml) had been stirred for 1.5 hr at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in isopropyl ether and cooled in an ice-bath. The precipitates were collected and washed with cold isopropyl ether to give 250 mg (89% yield) of benzenesulfinamide,[8] mp 122-124°C. The filtrate was concentrated and the residual oil was subjected to silica gel column chromatography, giving 320 mg of 3-butyliminomethyl-1,2-benzisoxazole 14 as a light yellow oil. NMR (100 MHz): δ 0.99t(J= 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 1.3-2.0m(4H, $CH_2C\underline{H}_2C\underline{H}_2CH_3$), 3.76dt(J= 1.4 and 6.4 Hz, 2H, $CH{=}NC\underline{H}_2CH_2$), 7.2-8.4m(4H, arom), 8.64t(J= 1.4 Hz, 1H, $C\underline{H}{=}NCH_2$). A solution of 14 (320 mg) in 1N HCl (10 ml) was stirred for 1 hr at room temperature and extracted with $CHCl_3$. The extract was concentrated in vacuo and the residue was subjected to silica gel column chromatography, giving 200 mg (68% yield) of the aldehyde 15. Mp 64-65°C (pet. ether). Anal. Calcd for $C_8H_5NO_2$: C, 65.40; H, 3.43; N, 9.52. Found: C, 64.89; H, 3.36; N, 9.53. NMR: δ 7.2-8.4m(4H, arom), 10.47s (1H, CHO). IR ν cm^{-1}: 1703(CHO), 1609(C=N). Mass: m/z 147(M^+).

Alternative Synthesis of 15 --- After a mixture of (1,2-benzisoxazol-3-yl)methyl phenyl sulfoxide 16 (9.5 g) and acetic anhydride (90 ml) had been refluxed for 3.5 hr, the reaction mixture was concentrated. The residue was dissolved in $CHCl_3$ and washed with water. The organic layer was dried and concentrated in vacuo. The residue was subjected to silica gel column chromatography, giving 9 g of [(1,2-benzisoxazol-3-yl)(phenylthio)methyl] acetate as a colorless oil. NMR: δ 2.18s(3H, Ac), 7.2-8.0m(10H, CH and arom). After a solution of the acetate (9 g) and iodine (2 g) in MeOH (100 ml) had been refluxed for 14 hr, 2 g of iodine were added and the refluxing was continued for another 10 hr. The reaction mixture was concentrated and the residue was dissolved in $CHCl_3$ and washed with aq. sodium thiosulfate. The organic layer was dried and concentrated. The residue was subjected to silica gel column chromatography, giving 3.9 g of 1,2-benzisoxazole-3-carbaldehyde dimethyl acetal as a colorless oil. NMR: δ 3.51s(6H, 2 x CH_3O), 5.78s(1H, CH), 7.1-8.1m(4H, arom). After a suspension of the acetal (3.9 g) in 20% aq. HCl (20 ml) had been stirred for 1 hr at room temperature, the reaction mixture was extracted with $CHCl_3$. The extract was dried and concentrated in vacuo to give 2.1 g of the aldehyde 15, whose IR and NMR spectra were in agreement with those of the product described above.

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Chapter 4

Halogenations of S-Benzyl-S-phenylsulfoximides and Rearrangements of Their N- and α-Halo Derivatives to N-Sulfinylimines

Summary ----- The reactions of S-benzyl- and S-(p-nitrobenzyl)-S-phenylsulfoximides with N-bromosuccinimide and t-butyl hypochlorite gave the corresponding N-halosulfoximides in good yields. The N-bromo-S-(p-nitrobenzyl)sulfoximide decomposed in the presence of a light source to give the corresponding α-bromosulfoximide, whereas the other N-halosulfoximides did not give the corresponding α-halosulfoximides. On treatment with N-chlorosuccinimide the p-nitrobenzylsulfoximide underwent both N- and α-chlorinations, while the benzylsulfoximide underwent only N-chlorination. Meanwhile, the halosulfoximides underwent base-induced rearrangements under varying conditions to give the corresponding N-sulfinylimines. The mechanisms of these reactions are discussed.

Introduction

In Chapters 2 and 3, the rearrangements of N-halosulfoximides to α-halosulfoximides and of the N- and α-halosulfoximides to the corresponding N-sulfinylimines were described. However, these results are based on the reactions of "special" sulfoximide derivatives, S-aryl-S-[(1,2-benzisoxazol-3-yl)-methyl]sulfoximides 1c (Ar= 1,2-benzisoxazol-3-yl).

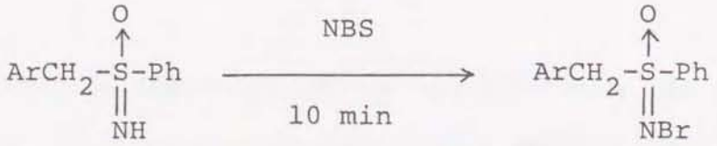
Therefore, in order to examine the generality of these interesting chemical behaviors of the 1,2-benzisoxazolylmethylsulfoximides, these reactions have been applied on the benzyl system and similar results have been obtained. Thus, this Chapter deals with the halogenations of S-benzyl-S-phenylsulfoximides 1a,b and the rearrangements of their N- and α-halo derivatives 2-5 into the corresponding N-sulfinylimines, N-benzylidenebenzenesulfinamides 6.

Results and Discussion

The free sulfoximides, S-benzyl- and S-(p-nitrobenzyl)-S-phenylsulfoximides 1a,b, were prepared by amination of the corresponding sulfoxides[1] with O-mesitylenesulfonylhydroxylamine (MSH).[2]

Bromination of the Free Sulfoximides 1a,b

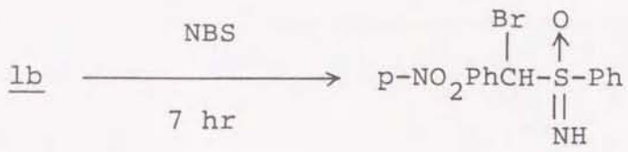
The reaction of 1a,b with N-bromosuccinimide (NBS) for 10 min at room temperature gave N-bromo-S-benzyl-S-phenylsulfoximides 2a,b in isolated yields of 90% and 86%, respectively.



1a,b 2a,b

a: Ar=Ph; b:Ar=p-NO_2Ph

However, the reaction of the p-nitrobenzylsulfoximide 1b with NBS was allowed to continue for 7 hr in the presence of a light source (a room light), affording S-(α-bromo-p-nitrobenzyl)-S-phenylsulfoximide 3 in 30% yield instead of 2b.



3

These findings suggest that the α-bromosulfoximide 3 was produced via a facile N-bromination followed by bromine transfer reaction of the resulting N-bromosulfoximide 2b. As shown in Table I, in fact, the N-bromosulfoximide 2b decomposed in 5-24 hr at room temperature in the presence of a light source to give the α-bromosulfoximide 3 in 16-36% yields, depending on the solvent used. In early stages of the reactions examined there was a clear induction period in which the liberation of bromine was observed (Fig. 1). In the absence of a light source no decomposition occurred.

(Table I)

(Fig. 1)

The results described above suggest that the rearrangement of the N-bromo-S-(p-nitrobenzyl)sulfoximide 2b was photochemically initiated and the bromine molecule formed in the induction period acts as the active brominating species. The bromination process with bromine molecule is considered to

Table I. Decomposition of the N-Bromosulfoximide 2b[a)]

Reaction Conditions	Products and Yields(%)[b)]	
	1b	3
CH_2Cl_2, 24 hr	27.8	36.9
1%EtOH-$CHCl_3$, 10 hr	57.5	24.0
5%EtOH-$CHCl_3$, 5 hr	72.9	16.0
1%EtOH-$CHCl_3$, dark, 1 week	No decomposition	

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise noted.

b) Yields were determined by HPLC. p-Nitrobenzyl bromide was also obtained in 5-8% yields as another characterizable product.

proceed both in radical and ionic processes as in the case of the N-bromo derivatives of the 1,2-benzisoxazolylmethylsulfoximides described in Chapter 2.

On the other hand, N-bromo-S-benzylsulfoximide 2a decomposed in the presence of a light source, as with 2b, to give 1a in ca. 80% yield, but did not give the corresponding α-bromosulfoximide as an isolable and characterizable product.

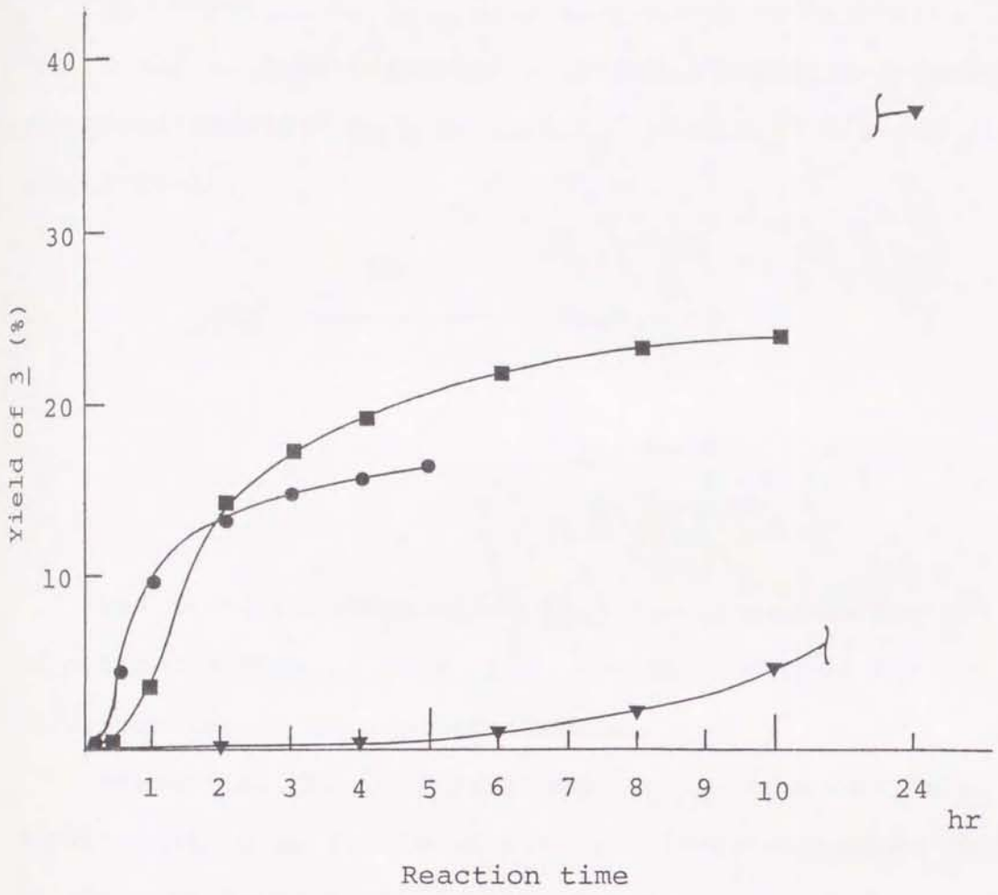


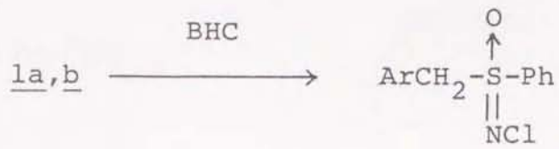
Fig. 1. Change of Yield of the α-Bromosulfoximide 3 with Time in the Decomposition of the N-Bromosulfoximides 2b in the Presence of a Light Source.

● : in 5%EtOH-$CHCl_3$, ■ : in 1%EtOH-$CHCl_3$,

▼ : in CH_2Cl_2.

Chlorination of the Free Sulfoximides 1a,b

The reaction of 1a,b with tert-butyl hypochlorite (BHC) for 10 min at room temperature afforded N-chloro-S-benzyl-S-phenylsulfoximides 4a,b in isolated yields of 88% and 73%, respectively.



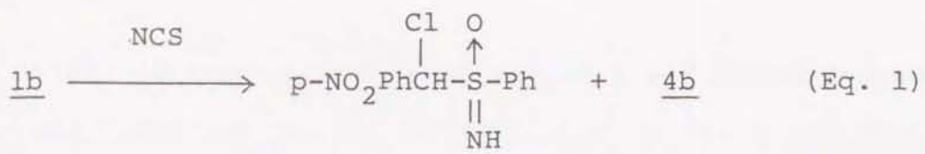
4a: Ar=Ph

b: Ar=p-NO_2Ph

The N-chlorosulfoximides 4a,b decomposed in the presence of a light source to give 1a,b, but did not give the corresponding α-chlorosulfoximides.

Meanwhile, the benzylsulfoximide 1a underwent only N-chlorination on treatment with N-chlorosuccinimide (NCS) to give the N-chlorosulfoximide 4a, reguiring over a week for completion at room temperature.

On the other hand, the p-nitrobenzylsulfoximide 1b underwent both N- and α-chlorinations on treatment with NCS (Eq. 1 and Table II). This reaction proceeded either in the presence or in the absence of a light source, though the absence of a light source appears to retard the rate and to increase the yield of the α-chlorosulfoximide 5. Althuogh the reason of this effect of a light source is not clear, the α-chlorination of 1b with NCS seems to proceed in the



1b → (NCS) → p-NO_2PhCH(Cl)-S(→O)-Ph (NH) + 4b (Eq. 1)

5

Table II. Reaction of the p-Nitrobenzylsulfoximide 1b with NCS[a)]

Reaction Conditions	Products and Yields(%)[b)]		
	4b	5	1b(recovered)
CH_2Cl_2, 24 hr	-	45.9	47.2
1%EtOH-$CHCl_3$, 24 hr	-	38.2	51.2
5%EtOH-$CHCl_3$, 24 hr	-	48.4	44.2
CH_2Cl_2, dark, 48 hr	-	60.2	34.9
1%EtOH-$CHCl_3$, dark, 48 hr	-	52.9	40.1
5%EtOH-$CHCl_3$, dark, 48 hr	-	55.7	40.4
$CDCl_3$, 15 hr[c)]	(33)	(35)	
$CDCl_3$, dark, 24 hr[d)]	(32)	(42)	

a) The reaction was carried out at room temperature in the presence of a room light unless otherwise noted.

b) Yields were determined by HPLC after the treatment described in "Experimental", during which 4b was converted to 1b, and those in parentheses by NMR using the reaction mixture without any treatment.

c) The reaction was approximately 73% completed: prolonged reaction caused partial decomposition of 4b.

d) The reaction was approximately 77% completed: prolonged reaction caused partial N-chlorination of 5.

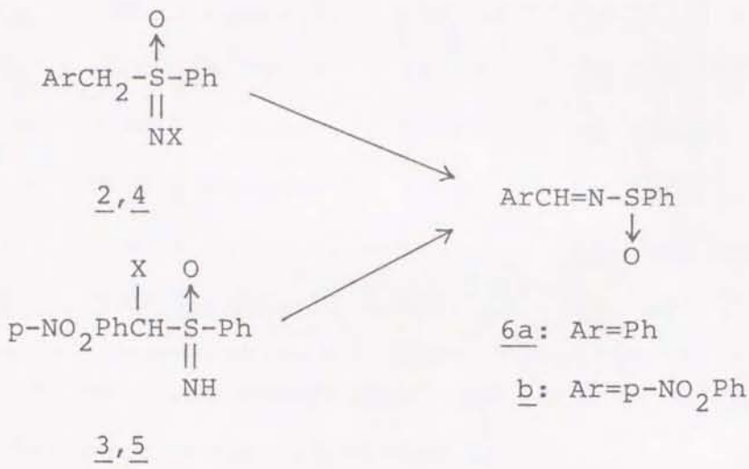
same manner as the NCS chlorination of the 1,2-benzisoxazolylmethylsulfoximides described in Chapter 2, i.e., via the direct α-attack of NCS, on the basis of the results described above.

In the α-halogenations of the sulfoximide derivatives examined in Chapter 2 and this Chapter, the order of reactivity is S-(1,2-benzisoxazol-3-yl)methyl- (1c) > S-(p-nitrobenzyl)- (1b) > S-benzylsulfoximide (1a), indicating that the reactivity appears to be controlled by the degree of activation of the α-position, i.e., α-CH acidity. This idea is consistent with the NMR findings and deuterium exchange reaction of these methylene protons. The NMR chemical shift (60 MHz in $CDCl_3$) of the methylene group of 1c (δ 4.84) appears at a 0.5 or 0.4 ppm lower field than that of 1a (δ 4.34) or 1b (δ 4.44), respectively. In acetonitrile-d_3 containing ca. 100 molar equiv. of deuterium oxide at 35°C, the methylene protons of 1c were ca. 50% exchanged with deuterium in 24 hr, whereas under the same conditions those of 1b required ca. 1 week for 50% deuterium exchange and those of 1a underwent no significant deuterium exchange even after 2 weeks.

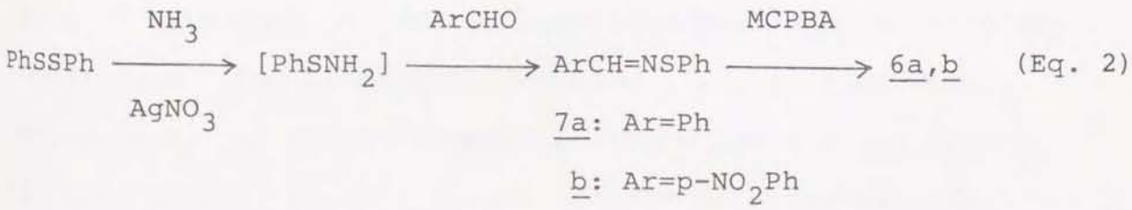
Alternative approaches to prepare the α-halo derivatives of the S-benzylsulfoximide 1a were unsuccessful according to the method of Johnson and Corkins,[3] which involves amination of the corresponding α-halosulfoxides with MSH and α-chlorination of the corresponding N-halosulfoximides with BHC.

Base-Induced Rearrangements of the Halosulfoximides 2-5

As with the halo derivatives of the 1,2-benzisoxazolylmethylsulfoximides described in Chapter 3, the halosulfoximides 2-5 underwent base-induced rearrangements to give the corresponding N-sulfinylimines, N-benzylidenebenzenesulfinamides 6.



The structure of 6 was confirmed by direct comparison with samples which were alternatively prepared according to the method of Davis et al.,[4] including oxidation of the corresponding N-sulfenylimines 7 with m-chloroperbenzoic acid (MCPBA) in a two phase system containing chloroform and water-sodium bicarbonate, as shown in Eq. 2.



(Eq. 2)

The results of these rearrangements are summarized in Table III.

Table III. Rearrangements of the Halosulfoximides 2-5 with Base[a)]

Compd	Reaction Conditions	Product(s) and Yields(%)[b)]			
2a	DBU(2 equiv.), 10 min	6a	54	1a	38
2a	K_2CO_3(5 equiv.), 24 hr	6a	81.5		
2b	DBU(1.2 equiv.), 10 min	6b	62	1b	26
2b	K_2CO_3(3 equiv.), 10 hr	6b	78		
4a	DBU(2 equiv.), 5 min	6a	93		
4a	K_2CO_3(5 equiv.), 24 hr	6a	55(85)[c)]		
4b	DBU(1.2 equiv.), 5 min	6b	94.5		
4b	K_2CO_3(3 equiv.), 3 hr	6b	96		
3	DBU(3 equiv.), 4 hr	6b	65(76.5)[c)]		
5	DBU(3 equiv.), 5 hr	6b	10[d)]		

a) The reaction was carried out in dichloromethane at room temperature unless otherwise noted.

b) Isolated yields after column chromatography.

c) Based on the unrecovered halosulfoximide.

d) Under reflux in chloroform. The recovery of 5 was 78%.

All the N-halosulfoximides 2a,b and 4a,b underwent rearrangement on treatment either with 1,5-diazabicyclo[5.4.0]-5-undecene (DBU) or with potassium carbonate at room temperature to give 6a,b in good to excellent yields under varying conditions. The α-bromosulfoximide 3 was treated with 3 molar equiv. of DBU at room temperature for 4 hr to give 6b in good yield. Under the same conditions, however, the α-chlorosulfoximide 5 underwent no rearrangement, but under reflux in chloroform for 5 hr, 5 gave 6b in 10% yield.

When the reaction of the N-chlorosulfoximides 4a,b with DBU was carried out in chloroform-d_1 ($CDCl_3$), 4a,b underwent partial hydrogen-deuterium exchange of their methylene protons with the deuterium of $CDCl_3$ together with the rearrangement: in the NMR spectra of the reaction mixtures the peak height of non-deuterated chloroform increased 2-4 times the original peak height. Similarly, under the same conditions the α-bromosulfoximide 3 underwent partial H-D exchange together with the rearrangement, whereas the α-chlorosulfoximide 5 underwent only H-D exchange. These findings clearly suggest the formation of the α-carbanion under the rearrangement conditions.

On the basis of the results described above, these rearrangements may proceed in a manner similar to that of the Neber[5] or the Ramberg-Backlund reaction[6] to afford the same intermediate of a three-membered cyclic sulfoximide, a thiazirine S-oxide 8, followed by spontaneous ring opening without loss of the sulfur component to give 6, as shown in Chart 1.

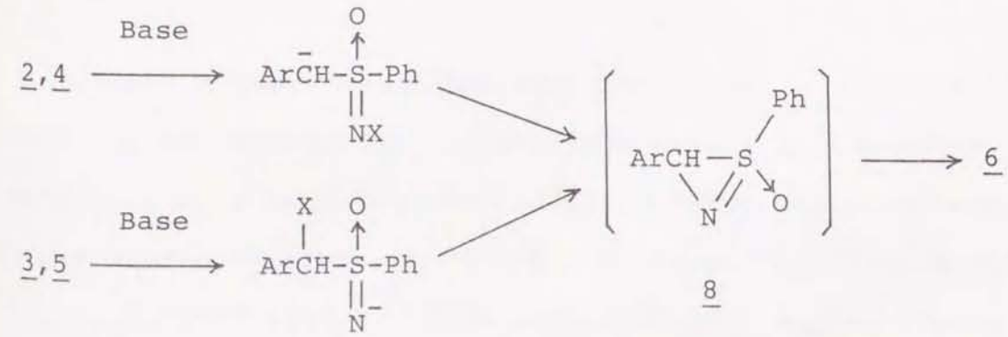
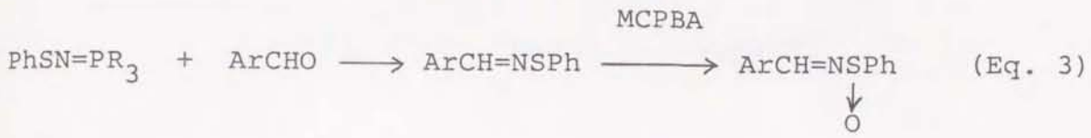
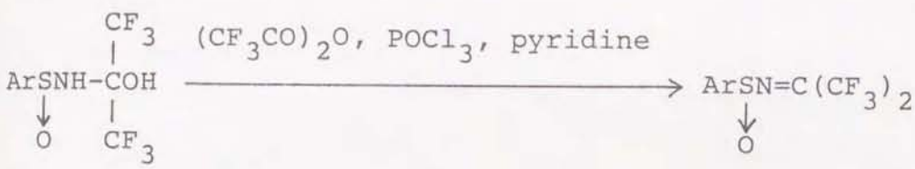


Chart 1

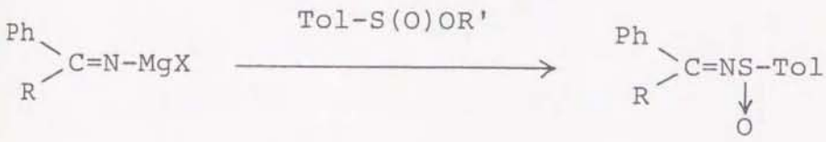
Although N-sulfinylimines (N-alkylidenesulfinamides) are a relatively new family of reactive sulfur compounds, they have been synthesized by several procedures (Eqs. 2-6)[4b,7] and demonstrated to be useful intermediates for organic synthesis,[4b,7c,8] including a mild, high-yield source of unstable sulfenic acids (Eq. 7).[4b,9]



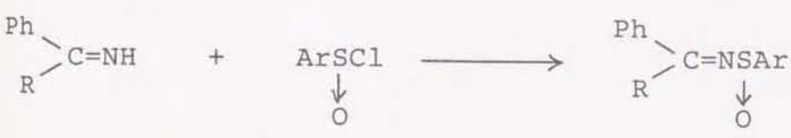
(Eq. 3)



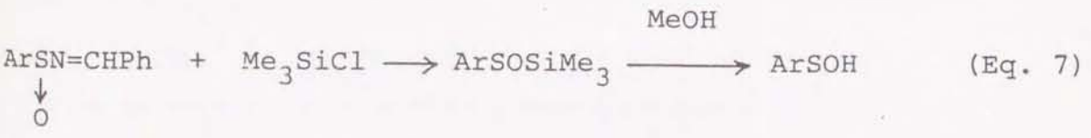
(Eq. 4)



(Eq. 5)



(Eq. 6)



(Eq. 7)

Since it has become apparent in Chapter 3 and this Chapter that the halosulfoximide derivatives having an α-active methylene or a benzyl group readily undergo rearrangement under mild conditions to give the corresponding N-sulfinylimines in good yields, these rearrangements appear to be able to offer a useful method for the preparation of this interesting family of sulfur compounds.

Mass Spectra of the S-Benzyl-S-phenylsulfoximides 1a,b

The results of the fragmentation analyses of the benzylsulfoximides 1a,b are summarized in Table IV.

Table IV. Mass Spectra of 1a,b

	Relative intensity			
	1a		1b	
Ion	70 eV	20 eV	70 eV	20 eV
$[M]^+$	0.01	0.01	0.02	0.03
$[ArCH_2NH]^+$	0.37	1.00	0.08	0.15
$[ArCH_2]^+$	1.00	0.90	0.10	0.11
$[PhSONH]^+$	0.08	0.04	1.00	1.00
$[PhNH]^+$	0.01	0.10	0.26	0.26
$[Ph]^+$	0.20	0.03	0.92	0.34
$[C_6H_6]^+$	0.06	0.07	0.60	0.35
$[SONH]^+$	0.07	0.01	0.26	0.09

The fragment ions observed intensely in the fragmentation of the benzylsulfoximide 1a are also observed, but not so intensely, at the corresponding mass units in that of the p-nitrobenzylsulfoximide 1b, and vice versa, suggesting that the key fragmentation steps of 1a and 1b are different from each other.

In the case of 1a, the base peak is m/z 91 or 106 at 70 or 20 eV, respectively. The peak of m/z 91 is due to benzyl ion which is considered to be formed directly from the molecular ion, since no definite peaks due to $[PhCH_2SONH]^+$ and $[PhCH_2SO]^+$ ions are observed. For the same reasons, the ion at m/z 106 consistent with benzylimide ion is considered to be generated from N-benzylbenzenesulfinamide ion which is formed by an initial benzyl migration to the imide nitrogen in the molecular ion. The peak due to phenylimide ion at m/z 92 is absent or weak, indicating that a phenyl to nitrogen migration process no longer predominates in contrast to alkyl aryl sulfoximides whose key fragmentation steps have been shown to be this type of rearrangement.[10)]

In the case of 1b, the base peak is m/z 140 due to $[PhSONH]^+$ ion at both 70 and 20 eV. Other intense peaks are observed at m/z 92, 78, 77, and 63 due to phenylimide, benzene, phenyl, and $[SONH]^+$ ions, respectively. All these ions are considered to be generated from the base peak ion $[PhSONH]^+$, since no other marked ion is observed.

Thus, the fragmentation scheme for the benzylsulfoximides 1a,b may be illustrated in Chart 2. The fragmentation of 1a involves two key steps (Paths A and B) and that of 1b involves Path C as the key step.

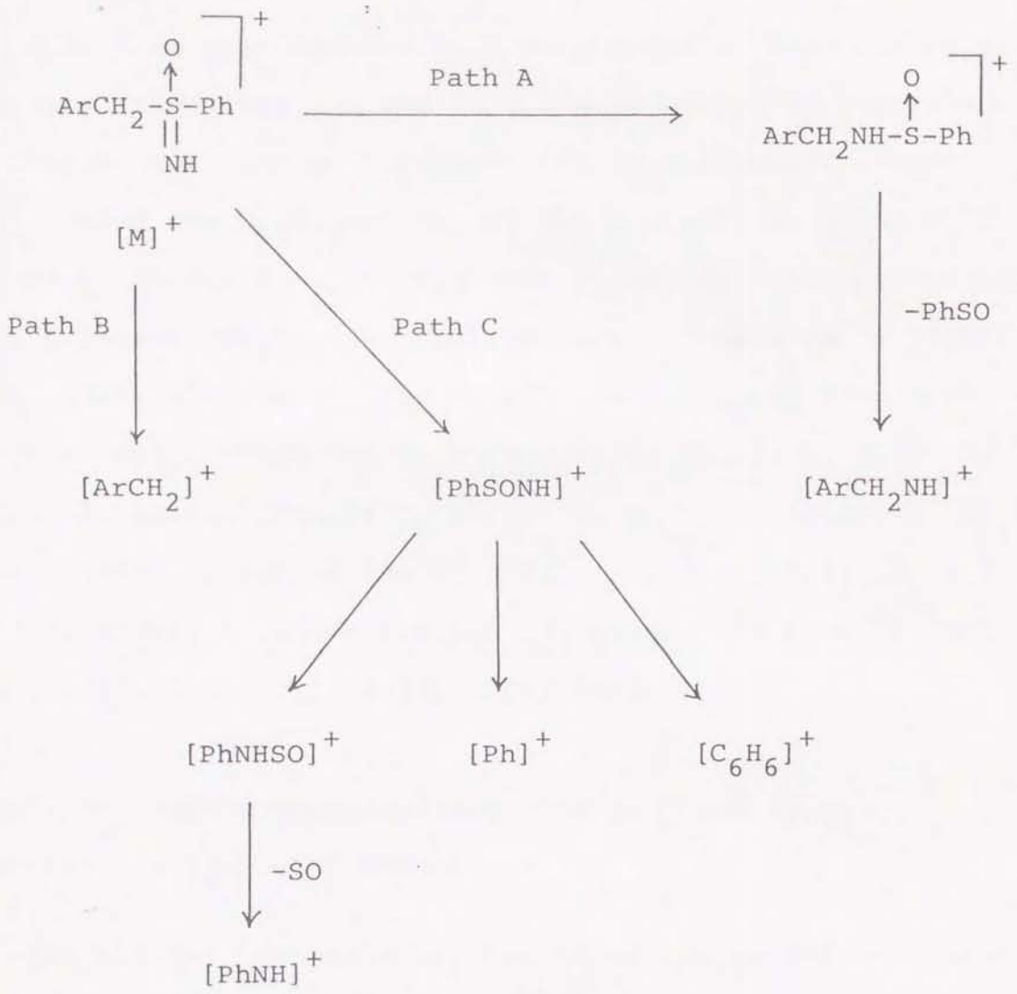

ArCH2-S-Ph
O
NH
Path A
ArCH2NH-S-Ph
[M]+
Path B
Path C
-PhSO
[ArCH2]+
[PhSONH]+
[ArCH2NH]+
[PhNHSO]+
[Ph]+
[C6H6]+
-SO
[PhNH]+

Chart 2

Experimental

S-Benzyl- and S-(p-Nitrobenzyl)-S-phenylsulfoximides 1a,b

The free sulfoximides 1a,b were prepared from the corresponding sulfoxides and MSH in the same manner as described in Chapter 1. 1a: mp 109-112°C (CH_2Cl_2-isopropyl ether). Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66; N, 6.06; S, 13.86. Found: C, 67.41; H, 5.55; N, 5.95; S, 13.84. NMR: δ 2.90s(1H, NH), 4.34s(2H, CH_2), 6.9-8.0m(10H, arom). IR ν cm^{-1}: 3320(NH), 1216, 1109, 972(NSO). 1b: mp 163-165°C (CH_2Cl_2-isopropyl ether). Anal. Calcd for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.32; H, 4.31; N, 10.22; S, 11.60. NMR: δ 2.92s(1H, NH), 4.44s(2H, CH_2), 7.1-8.0m, 7.30d(J= 9.0 Hz)(7H, arom), 8.15d(J= 9.0 Hz, 2H, arom). IR ν cm^{-1}: 3325 (NH), 1513, 1345(NO_2), 1224, 1109, 940(NSO).

N-Halo-S-benzyl-S-phenylsulfoximides 2a,b and 4a,b. Reaction of 1a,b with NBS or BHC

2a and 4a: An equimolar amount of NBS or BHC was added to a solution of 1a (1.0 g) in CH_2Cl_2 (10 ml) at room temperature and the mixture was stirred for 10 min in the dark. The reaction mixture was directly subjected to silica gel column chromatography using $CHCl_3$ as an eluent to give 2a or 4a in 90% or 88% yield, respectively. Recrystallization from CH_2Cl_2-hexane gave pure products.

2b and 4b: After a mixture of equimolar amounts of 1b (1.0 g) and NBS or BHC in $CHCl_3$ (10 ml) had been stirred for

10 min at room temperature in the dark, the precipitates were collected by filtration and washed with cold $CHCl_3$ to give 2b or 4b in 86% or 73% yield, respectively. Recrystallization from CH_2Cl_2-isopropyl ether gave pure products.

2a: mp 97-105°C. Anal. Calcd for $C_{13}H_{12}BrNOS$: C, 50.33; H, 3.90; Br, 25.76; N, 4.52; S, 10.33. Found: C, 50.24; H, 3.84; Br, 25.54; N, 4.24; S, 10.18. NMR: δ 4.68s(2H, CH_2), 6.9-7.9m(10H, arom). IR ν cm^{-1}: 1212, 1089, 971(NSO).

2b: mp 131-133°C. Anal. Calcd for $C_{13}H_{11}BrN_2O_3S$: C, 43.96; H, 3.12; Br, 22.50; N, 7.89; S, 9.03. Found: C, 44.13; H, 2.93; Br, 22.71; N, 7.89; S, 8.78. NMR: δ 4.70s(2H, CH_2), 7.24d, 8.09d(J= 8.6 Hz, each 2H, NO_2Ph), 7.4-7.9m(5H, Ph). IR ν cm^{-1}: 1512, 1344(NO_2), 1212, 1089, 973(NSO).

4a: mp 86-89°C. Anal. Calcd for $C_{13}H_{12}ClNOS$: C, 58.75; H,4.55; Cl, 13.34; N, 5.27; S, 12.06. Found: C, 58.63; H, 4.56; Cl, 13.56; N, 5.24; S, 12.09. NMR: δ 4.61s(2H, CH_2), 6.9-7.9m (10H, arom). IR ν cm^{-1}: 1212, 1089, 973(NSO). 4b: mp 128-130°C. Anal. Calcd for $C_{13}H_{11}ClN_2O_3S$: C, 50.25; H, 3.57; Cl, 11.41; N, 9.01; S, 10.32. Found: C, 50.18; H, 3.63; Cl, 11.21; N, 8.92; S, 10.24. NMR: δ 4.71s(2H, CH_2), 7.25d, 8.09d(J= 9.0 Hz, each 2H, NO_2Ph), 7.4-7.9m(5H, Ph). IR ν cm^{-1}: 1512, 1342 (NO_2), 1216, 1088, 972(NSO).

When the above reactions were carried out in $CDCl_3$ at room temperature, the NMR analyses of the reaction mixtures showed that the yields of the N-halosulfoximides 2 and 4 were quantitative.

S-(α-Bromo-p-nitrobenzyl)-S-phenylsulfoximide 3

A slight excess of NBS was added to a stirred solution of 1b (2.0 g) in $CHCl_3$ (50 ml) and the resulting suspension was allowed to stir for 7 hr at room temperature under a room light. The reaction mixture was washed with dilute aq. K_2CO_3, and then the organic layer was dried and concentrated in vacuo. The residue was chromatographed on a silica gel column using $CHCl_3$ as an eluent to afford 0.8 g (30% yield) of 3 together with 0.9 g of the recovered 1b. The NMR spectrum of 3 showed it to be a mixture of diastereomers: two distinct methine singlets were observed.
3: mp 116-124°C (CH_2Cl_2-isopropyl ether). Anal. Calcd for $C_{13}H_{11}BrN_2O_3S$: C, 43.96; H, 3.12; Br, 22.50; N, 7.89; S, 9.03. Found: C, 44.06; H, 3.13; Br, 22.23; N, 7.86; S, 9.16. NMR: δ 3.3s, 3.6s(1H, NH), 5.77s, 5.81s(1H, CH), 7.25-8.3m (9H, arom). IR ν cm^{-1}: 3275(NH), 1513, 1346(NO_2), 1242, 1135, 950(NSO).

Decomposition of the N-Halosulfoximides 2 and 4

The reaction was carried out with a 0.05M solution of the N-halosulfoximide. After an appropriate reaction time, an aliquot portion (1-2 ml) of the reaction mixture was taken up, washed with 5% aq. K_2CO_3 (5 ml), and extracted with $CHCl_3$ (5 ml). The organic layer was dried and concentrated in vacuo. The residue was dissolved in 1 ml of $CHCl_3$ and 19 ml of EtOH, and then subjected to HPLC analysis.

The results for the decomposition of N-bromo-S-(p-nitrobenzyl)-S-phenylsulfoximide 2b are summarized in Table I. The other N-halosulfoximides 2a and 4a,b decomposed in 7 hr, 55 hr, and 24 hr, respectively, in 5%EtOH-$CHCl_3$ to give 1a,b in ca. 80% yields together with a small amount of the corresponding benzyl halide, but no other characterizable product was obtained.

Reaction of 1a,b with NCS

1a: The reaction of 1a (60 mg) with an equimolar amount of NCS was carried out in $CDCl_3$ (1 ml) at room temperature in a sealed tube in the dark. After a week the NMR analysis of the reaction mixture indicated that the reaction was approximately 88% completed and the yield of the N-chlorosulfoximide 4a was ca. 84%.

1b: The results for the reaction of 1b with NCS are summarized in Table II. The reaction was carried out using a 0.1-0.2M solution of 1b with an equimolar amount of NCS. HPLC analysis was run after the reaction mixture had been worked up as described above. NMR analysis was carried out with the reaction mixture without any treatment.

S-(α-Chloro-p-nitrobenzyl)-S-phenylsulfoximide 5 was isolated as a mixture of diastereomers by silica gel column chromatography and recrystallized from CH_2Cl_2-isopropyl ether: mp 125-131°C. Anal. Calcd for $C_{13}H_{11}ClN_2O_3S$: C, 50.25; H, 3.57; Cl, 11.41; N, 9.01; S, 10.32. Found: C, 49.99; H, 3.46; Cl, 11.57; N, 8.93; S, 10.36. NMR: δ3.30s(1H, NH), 5.74s, 5.77s(1H, CH), 7.3-8.1m(7H), 8.18d(J= 9.0 Hz, 2H)(arom).

IR ν cm^{-1}: 3275(NH), 1515, 1347(NO_2), 1242, 1137, 952(NSO).

N-Benzylidene- and N-(p-Nitrobenzylidene)benzenesulfinamides 6a,b. Rearrangements of the Halosulfoximides 2-5 with Base

The reaction was carried out with a 0.1-0.2M solution of the halosulfoximide under the conditions stated in Table III: the reaction of the N-halosulfoximides 2 and 4 with K_2CO_3 was carried out in the dark to avoid partial decomposition of the N-halosulfoximide described above. After an appropriate reaction time, the reaction mixture was directly subjected to silica gel column chromatography and eluted with $CHCl_3$ to give 6. 6a: mp 80-83°C (hexane) (lit.[4b] mp 78-79°C). Anal. Calcd for $C_{13}H_{11}NOS$: C, 68.10; H, 4.84; N, 6.11; S,13.98. Found: C, 68.35; H, 4.75; N, 6.11; S, 14.05. NMR: δ 7.2-8.1m (10H, arom), 8.79s(1H, CH=N). IR ν cm^{-1}: 1604(C=N), 1099(SO). 6b: mp 154-157°C (CH_3CN). Anal. Calcd for $C_{13}H_{10}N_2O_3S$: C, 56.92; H, 3.67; N, 10.21; S, 11.69. Found: C, 57.30; H, 3.72; N, 10.45; S, 11.70. NMR: δ 7.3-7.9m(5H, Ph), 8.02d, 8.30d(J= 9.0 Hz, each 2H, NO_2Ph), 8.85s(1H, CH=N). IR ν cm^{-1}: 1590 (C=N), 1519, 1341(NO_2), 1101(SO).

Alternative Preparation of the N-Sulfinylimines 6a,b

N-Benzylidene- and N-(p-nitrobenzylidene)benzenesulfenamides 7a,b were prepared in 72% and 5% yields, respectively, according to the procedure of Davis et al.[4a] 7a: mp 45-47°C (hexane) (lit.[7a] mp 35-36°C). Anal. Calcd for $C_{13}H_{11}NS$: C, 73.20; H, 5.20; N, 6.57; S, 15.03. Found: C, 72.93; H, 5.24;

N, 6.50; S, 14.74. NMR: δ7.1-8.1m(10H, arom), 8.49s(1H, CH=N). 7b: mp 80-81°C(EtOH). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85; S, 12.41. Found: C, 60.71; H, 4.11; N, 10.85; S, 12.44. NMR: δ7.1-8.1m(7H), 8.27d(J= 9.0 Hz, 2H)(arom), 8.48s(1H, CH=N).

The above N-sulfenylimines 7a,b were oxidized by MCPBA to give 6a,b in 93% and 77% yields, respectively, according to the method of Davis et al.[4b,c] The IR and NMR spectra of these samples were in agreement with those of the products in the rearrangements of the halosulfoximides 2-5 described above.

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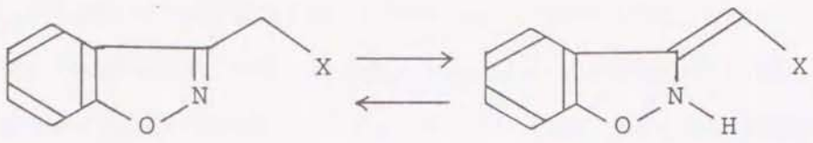
Chapter 5

Synthesis of 4-Oxo-4H-benzisoxazolo[2,3-a]pyridines and Their Ring Transformations to 2-Oxobenzofuro[3,2-b]pyridines

Summary ----- 1,2-Benzisoxazole-3-acetic acids underwent dimerization on treatment with acyl chlorides in pyridine to give 4-oxo-4H-benzisoxazolo[2,3-a]pyridines which, in turn, underwent photo-induced ring transformation to afford 2-oxo-1,2-dihydrobenzofuro[3,2-b]pyridines.

Introduction

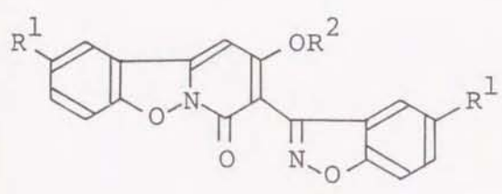
The α-methylene group of 1,2-benzisxoazole-3-acetic acids 1 has been found to be unusually reactive in the electrophilic substitutions, i.e., halogenations,[1)] sulfonation,[1c)] and the Mannich reaction,[2)] suggesting that the C=N bond of 1,2-benzisoxazole ring functions as a "masked" carbonyl group. In Chapter 2, the methylene group of S-aryl-S-[(1,2-benzisoxazol-3-yl)methyl]sulfoximides was described also to be active to halogen electrophiles. Although the reasons for the high reactivities of these methylene groups to electrophiles are as yet unexplained exactly, there is a plausible explanation which involves the imine-enamine tautomerizm, as shown in Eq. 1.



(Eq. 1)

This assumption suggests that 1,2-benzisoxazoles with a methylene group at the 3-position promise to act as an ambident nucleophile at the methylene carbon and the ring nitrogen.

As expected, 1,2-benzisoxazole-3-acetic acids 1 have been found to undergo dimerization on treatment with acyl chlorides in pyridine to give 4-oxo-4H-benzisoxazolo[2,3-a]pyridines 2, indicating that one molecule of 1 acts as a nitrogen nucleophile and another as a carbon nucleophile. The pyridines 2 have been found to undergo photo-induced ring transformation to afford 2-oxo-1,2-dihydrobenzofuro[3,2-b]pyridines 3.



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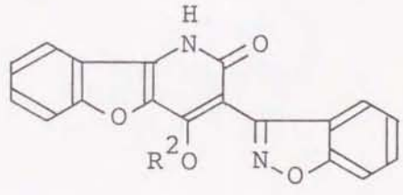
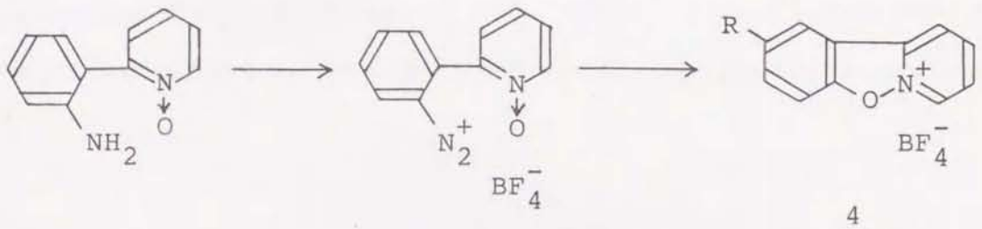


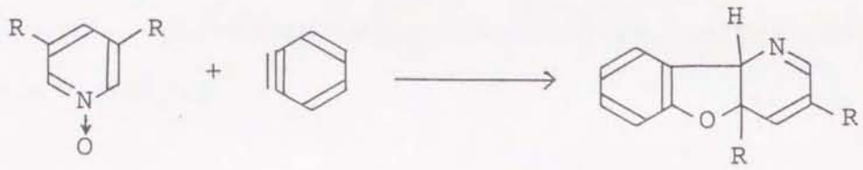
3

The former ring system 2 was yet unknown, though the pyridinium analogue 4 has been synthesized from 2-(o-aminophenyl)pyridine 1-oxide via the diazonium tetrafluoroborate.[3)]

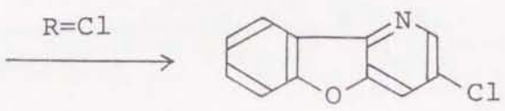


4

The latter ring system 3 has hitherto been prepared only by a few following reactions, i.e., the reaction of pyridine 1-oxides with benzyne (Eq. 2),[4] the thermal ring transformation of 4 (R=NO_2) (Eq. 3),[3] and the Friedlander reaction of 2-acyl-3-aminobenzofurans (Eq. 4).[5]

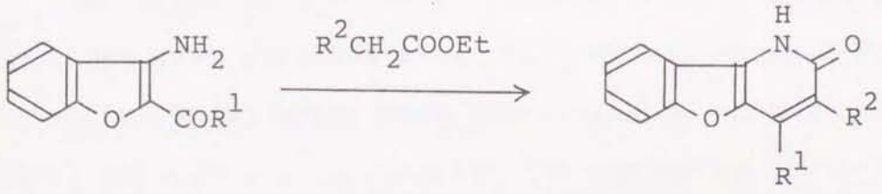


R=Me, Cl



(Eq. 2)

(Eq. 3)



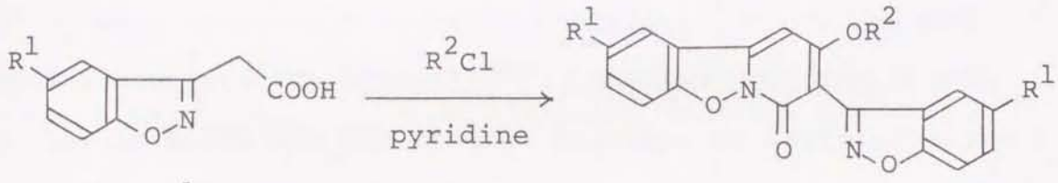
(Eq. 4)

Thus, this Chapter deals with the synthesis of the novel benzisoxazolo[2,3-a]pyridine ring system 2 and its photolytic ring transformation to the benzofuro[3,2-b]pyridine system 3.

Results and Discussion

4-Oxo-4H-benzisoxazolo[2,3-a]pyridines 2

Treatment of 1,2-benzisoxazole-3-acetic acids 1 with p-toluenesulfonyl (tosyl), acetyl, and benzoyl chlorides in pyridine afforded the corresponding 2-acyloxy-3-(1,2-benzisoxazol-3-yl)-4-oxo-4H-benzisoxazolo[2,3-a]pyridines 2 in 26-72% yields.



1a: R^1= H

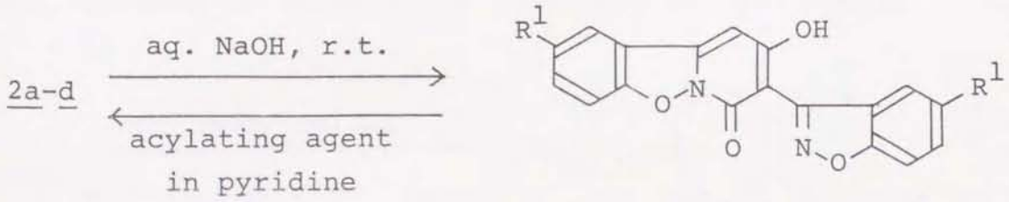
b: R^1= MeO

2a: R^1=H, R^2=Ts; b: R^1=H, R^2=Ac;

c: R^1=H, R^2=PhCO; d: R^1=MeO, R^2=Ts;

e: R^1=MeO, R^2=Ac

Hydrolyses of 2a-d with sodium hydroxide under mild conditions gave quantitatively the corresponding 2-hydroxyl derivatives 5a,b, which were reconvertable to the original acyloxy compounds 2 in quantitative yields by acylation.



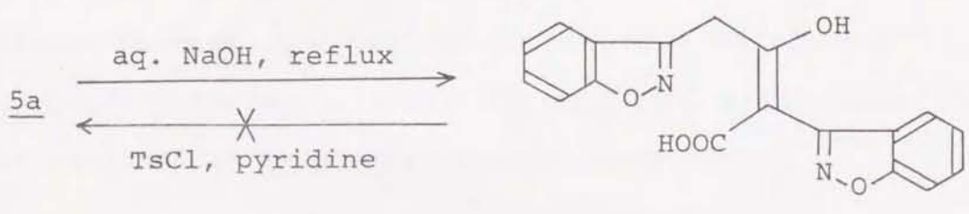
5a: R^1= H

b: R^1= MeO

The structures of the benzisoxazolo[2,3-a]pyridines 2 and 5 were deduced from elemental and spectral analyses. The IR spectra of 2 and 5 showed strong bands due to the amide carbonyls at 1650-1660 cm^{-1}: in the cases of the acetoxy and benzoyloxy derivatives 2b,c,e, other carbonyl bands due to the enol acylates appeared at 1760, 1730, and 1770 cm^{-1}, respectively. The NMR spectra (DMSO-d_6) of 2a,b,e and 5a,b showed characteristic singlet peaks of C_1-H at δ 7.38-7.62 and 6.86-6.93, respectively. In particular, all the protons of 2e were assignable by spin-decoupling, INDOR, and NOE techniques (see "Experimental"). The NMR spectrum (DMSO-d_6) of 5b, in which all the protons can also be assigned, showed a broad singlet at δ 11.2-11.5 corresponding to the enolic hydroxyl group. The data described above, together with elemental analyses and mass spectral data, were in good agreement with the proposed structures of the compounds 2 and 5.

In order to obtain further evidence of the structural assignments of 2 and 5, a series of the following chemical transformations have been examined.

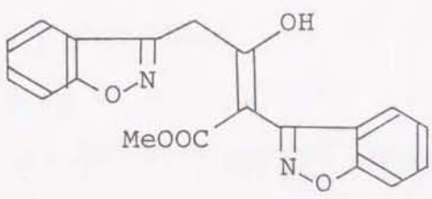
Under vigorous conditions, hydrolysis of 5a with sodium hydroxide gave an enol-carboxylic acid 6 in 14% yield. Under the same conditions, 5b underwent no hydrolysis.



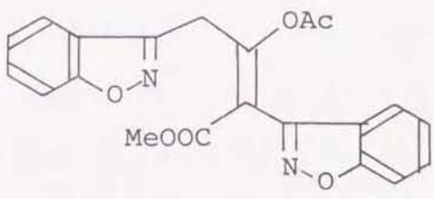
6

An attempt to reconvert 6 with tosyl chloride in pyridine to the original pyridine 5a was unsuccesful.

Esterification of 6 with methanol in the presence of a catalytic amount of conc. sulfuric acid gave a methyl ester 7. Its NMR spectrum showed a singlet peak at δ 4.00 due to the methyl ester group and the IR spectrum showed a strong carbonyl band at 1705 cm^{-1}, indicating the presence of a conjugated ester group. Treatment of 7 with acetic anhydride in pyridine gave an acetate 8. Its IR spectrum showed a strong carbonyl band at 1760 cm^{-1}, except for the carbonyl band of the methyl ester group at 1710 cm^{-1}, suggesting that the hydroxyl group of 7 is an enolic one.

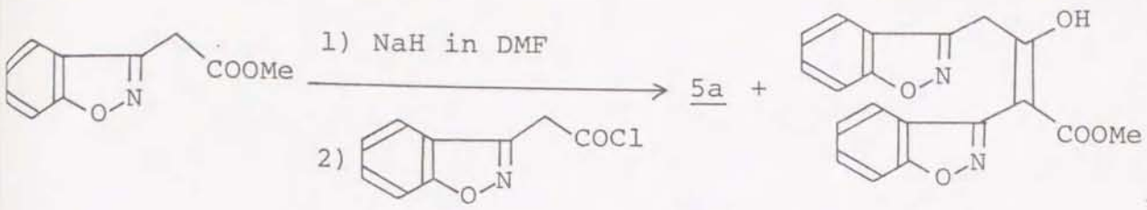


7



8

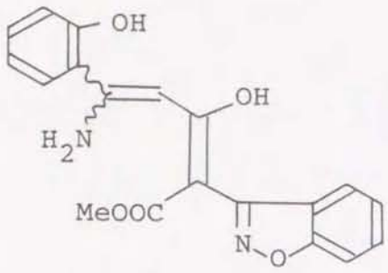
In order to confirm the structure of 7, an alternative synthesis of 7 was attempted by condensation of methyl 1,2-benzisoxazole-3-acetate with 1,2-benzisoxazole-3-acetyl chloride 9, prepared from 1a with phosphorus pentachloride, in the presence of sodium hydride in DMF. From the reaction mixture, however, the desired ester 7 was not obtained, but the pyridine 5a and an undesired ester 10, a (Z)-isomer of 7, were isolated in 5% yields, respectively.



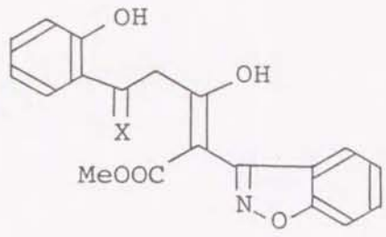
9 10

Since treatment of 7 with sodium hydride in DMF caused no cyclization, the pyridine 5a is considered to be produced via dimerization of the acetyl chloride 9. In fact, 9 underwent dimerization on treatment with sodium hydride in DMF to give 5a in 7% yield. The assignments of steric structures of the esters 7 and 10 were deduced from comparison of their NMR spectra in consideration of the anisotropic effect of the benzisoxazole ring: a singlet methylene signal of 10 appears at a higer field (δ 4.09) than that of 7 (δ 4.87), indicating that 10 is a (Z)-isomer. Alkaline hydrolysis of 10 gave 6 in 70% yield, accompanied by isomerization.

Catalytic hydrogenation of 7 on 5%Pd-C was stopped when one molar equivalent of hydrogen was absorbed, affording an enamine 11 in 45% yield as a mixture of (E)- and (Z)-isomers: the NMR spectrum showed two singlet peaks due to the vinyl proton at δ 5.80 and 6.18 in a ratio of 4:1. The N-O bond of 1,2-benzisoxazole ring has been reported to undergo catalytic hydrogenation with Pd-C to give an imine.[6] In the present case, 7 was considered to undergo at first reductive cleavage of the non-conjugated N-O bond followed by immediate isomerization of the resulting imine to give the stable conjugated enamine 11.



11



12: X=O

13: X= 

Treatment of the enamine 11 with 5% aq. HCl gave a ketone 12. Reduction of 12 with sodium borohydride gave an alcohol 13 whose NMR spectrum (DMSO-d_6) showed a typical A_2X system in keeping with the partial structure $-CH(OH)CH_2-$ (see "Experimental").

The results of a series of the reactions described above support the 1,2-benzisoxazolo[2,3-a]pyridine structure of the compounds 2 and 5.

In view of the fact that the enol-carboxylic acid 6 and its methyl ester 7 undergo no cyclization on treatment with tosyl chloride in pyridine and with sodium hydride in DMF, respectively, the dimerization reactions of 1,2-benzisoxazole-3-acetic acids 1 with acyl chlorides do appear not to involve 6 or its mixed anhydride as an intermediate; in other words, in these reactions the formation of C_2-C_3 bond of 2 does not precede the C_4-N_5 bond formation. Thus, a plausible mechanism of the formation of 2 may involve dimerization of the initially formed mixed anhydride (14) of 1 via the simultaneous formation of both the C_2-C_3 and C_4-N_5 bonds (Path A) or via the first C_4-N_5 bond formation followed by the C_2-C_3 bond formation (Path B), as shown in Chart 1.

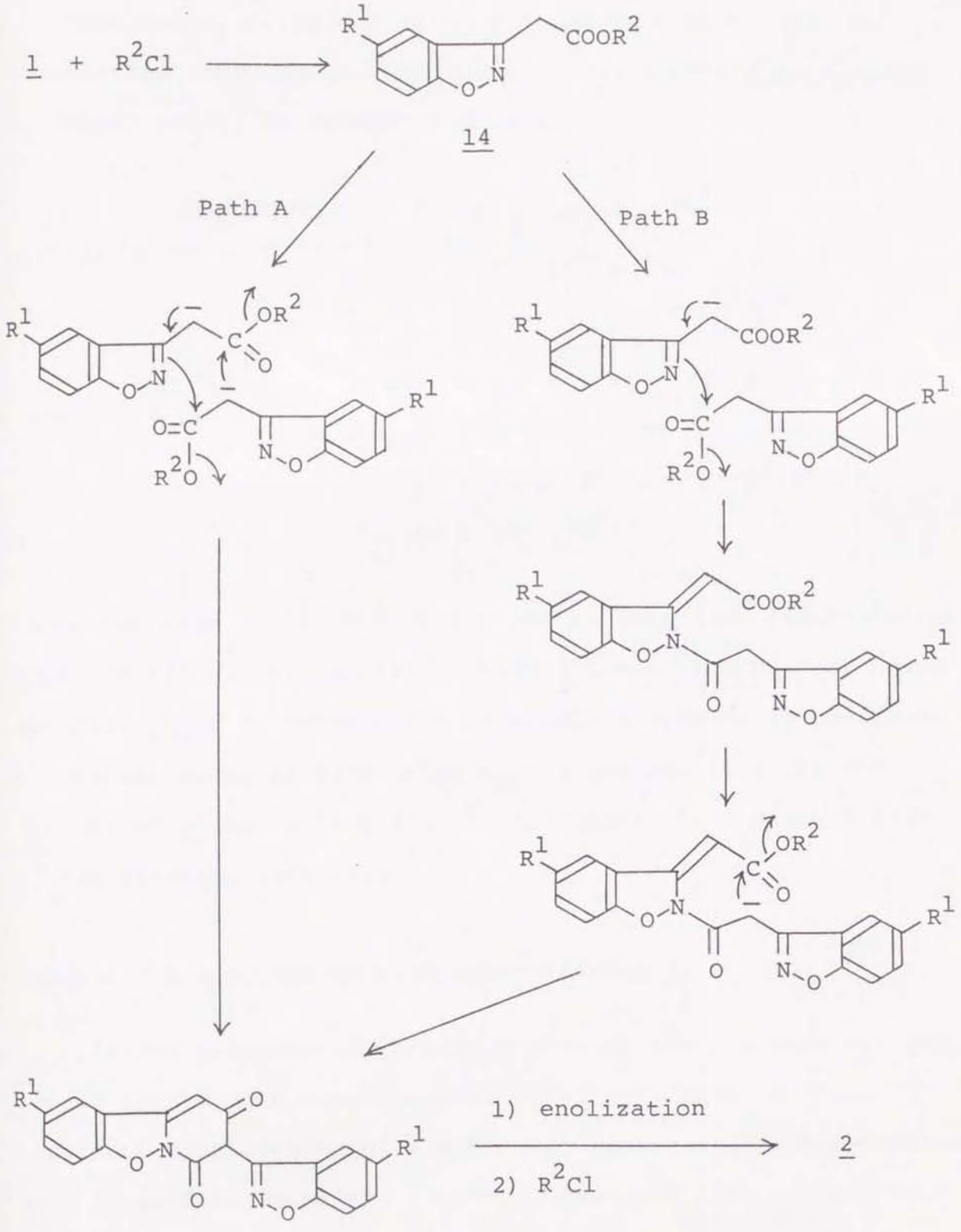
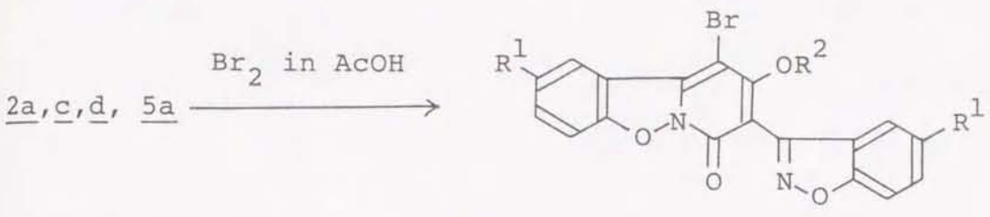


Chart 1

Meanwhile, treatment of 2a,c,d and 5a with bromine in acetic acid gave the corresponding mono-bromides 15a,c,d, and f, respectively, in excellent yields.

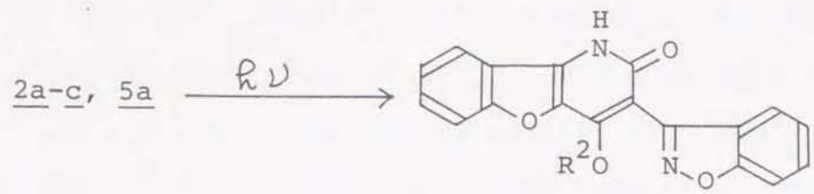


15a: R^1=H, R^2=Ts; b: R^1=H, R^2=Ac;
c: R^1=H, R^2=PhCO; d: R^1=MeO, R^2=Ts;
e: R^1=MeO, R^2=Ac; f: R^1=R^2=H;
g: R^1=MeO, R^2=H

Under the same conditions, the acetates 2b,e gave deacetylated bromides 15f,g, respectively, which afforded the corresponding acetates 15b,e on treatment with acetic anhydride in pyridine. The substitution of bromine at C_1 was deduced from the NMR spectra of 15 which lack the characteristic C_1-H singlet peak of the starting materials 2.

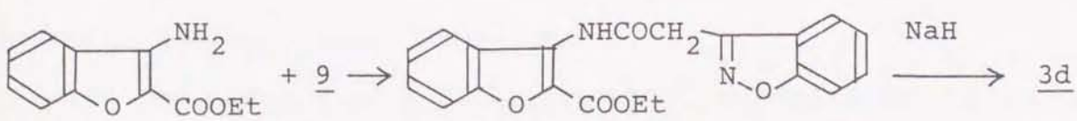
2-Oxo-1,2-dihydrobenzofuro[3,2-b]pyridines 3

In the presence of a light source (a low-pressure Hg-lamp or sun light), the benzisoxazolo[2,3-a]pyridines 2a-c and 5a underwent ring transformation to give benzofuro[3,2-b]pyridines 3a-d in good to excellent yields. Under the same conditions, however, the 9-methoxy derivatives 2d,e and 5b gave only dirty reaction mixtures from which no crystalline product could be isolated.



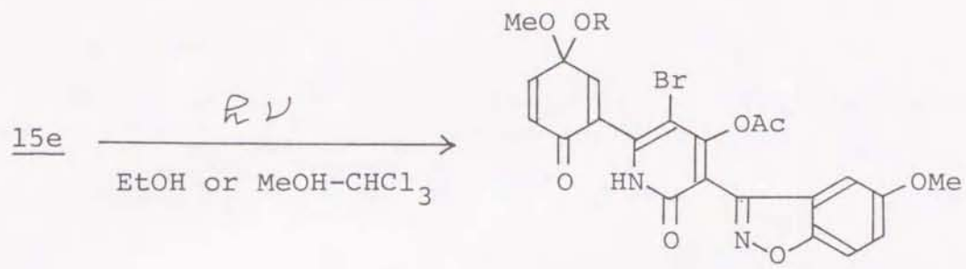
3a: R^2= Ts; b: R^2= Ac;
c: R^2= PhCO; d: R^2=H

The NMR spectrum of 3a does not have the characteristic singlet peak due to the C_1-H of 2a, but shows a new one proton signal at δ 12.8-13.4, exchangeable with D_2O. Its IR spectrum showed strong bands at 2600-2800 and 1635 cm^{-1}. Treatment of 3a with acetic anhydride in pyridine gave an acetate whose IR and NMR spectra suggested the presence of an enol acetate: IR, 1760 cm^{-1}; NMR, δ 2.06s(3H). These data suggest the partial 2-pyridone structure of 3a. The structure of 3 was comfirmed by direct comparison of 3d with a sample which was prepared alternatively from ethyl 3-aminobenzofuran-2-carboxylate[7] and the acetyl chloride 9 through the Friedlander reaction.[4]



Meanwhile, the bromopyridines 15a,c,f underwent a similar photo-induced isomerization to give the same ring transformation products 3a,c,d in good yields, whereas the acetyl derivative 15b underwent both isomerization and deacetylation simultaneously to give 3d in 90% yield: in these reactions, the liberation of bromine was observed.

Under the same conditions (in commercial chloroform), however, the 9-methoxy derivative 15e gave no ring transformation product but a quinone ethyl methyl ketal derivative 16a in 28% yield. The origin of the ethoxy group was considered



16a: R= Et

b: R= MeO

to be ethanol contained in commercial chloroform as a stabilizer. This assumption was confirmed by the following experiments. When photolysis of 15e was carried out in 5%EtOH-$CHCl_3$, 16a was obtained in 60% yield. Furthermore, photolysis of 15e in 5%MeOH-$CHCl_3$ was found to give a quinone dimethyl ketal 16b in 60% yield. The structure of 16 was deduced from elemental and spectral analyses (see "Experimental").

In the absence of a light source, the benzisoxazolo[2,3-a]-pyridines 2, 5, and 15 did not undergo the isomerizations described above and were recovered unchanged.

On the basis of these observations, possible mechanisms for the isomerizations of the pyridines 2, 5, and 15 are illustrated in Charts 2 and 3.

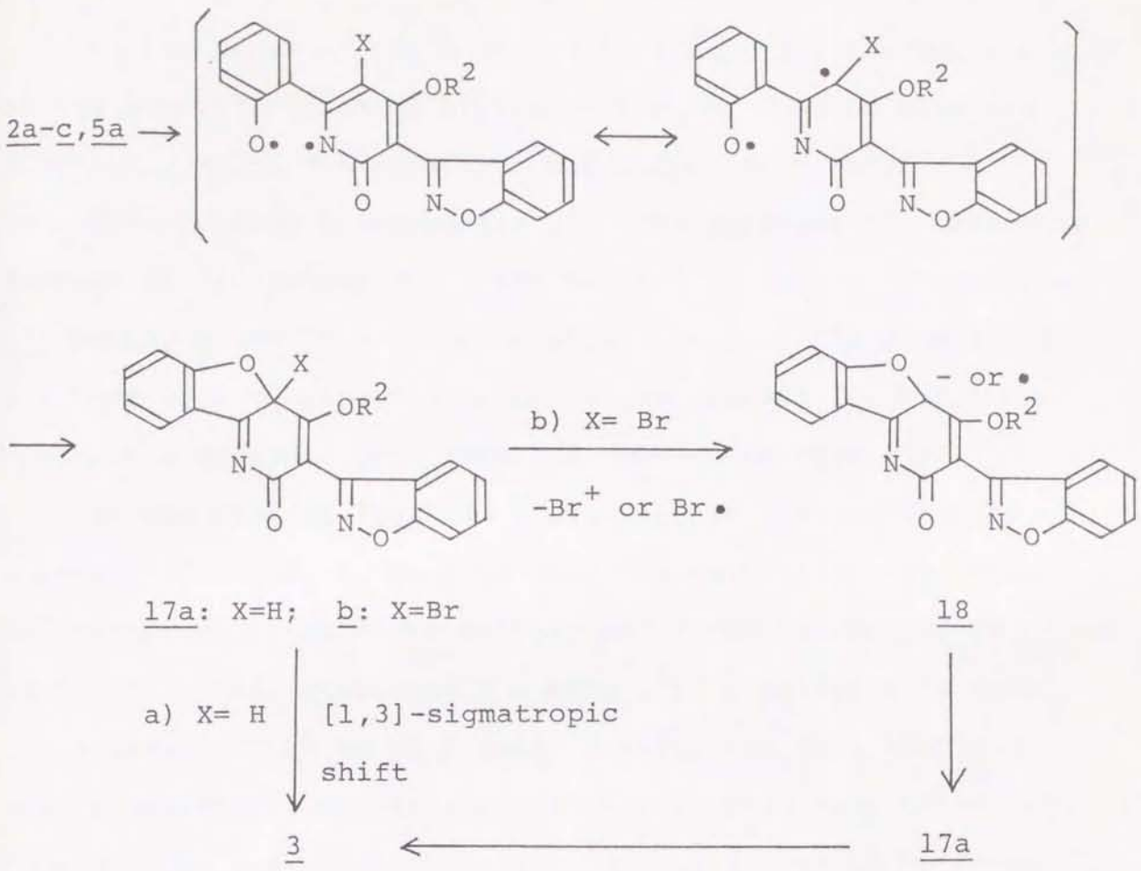


Chart 2

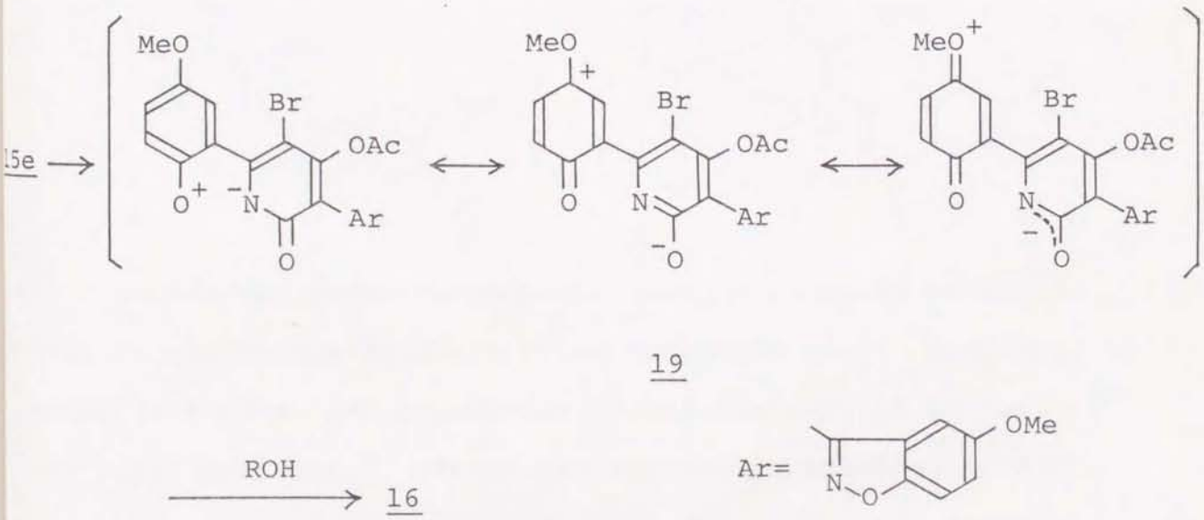
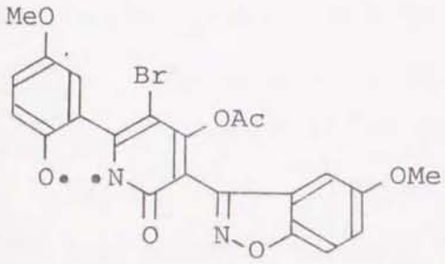


Chart 3

In the cases of 2(R^1= H) and 5a (Chart 2), the first step is the homolytic fission of the weak N_5-O_6 bond to give the diradical, which can isomerize and recyclize to give the benzofuropyridine intermediate 17. The pyridine 17a undergoes further [1,3]-sigmatropic shift to give 3. The bromopyridine 17b having no movable hydrogen atom undergoes the fission of the C-Br bond to give the carbanion or radical 18, which can abstract a hydrogen atom from the solvent to give 17a.

In the case of 15e, the first step is the heterolytic cleavage of the N_5-O_6 bond to give the zwitter ion 19, which is stabilized by both the methoxy and carbonyl groups, as shown in Chart 3; this stabilization effect is considered to enable the zwitter ion 19 to be formed, despite the fact that the electronegativity of nitrogen is lower than that of oxygen. However, the possibility for the zwitter ion 19 to be formed from the diradical 20 cannot be negligible.



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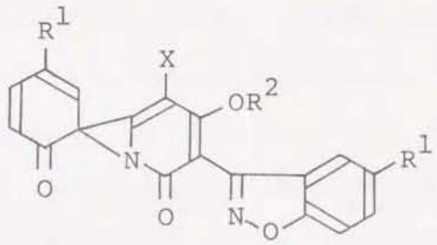

21

Beside the above mechanisms, another possible mechanism which involves the spiroaziridine intermediate 21, analogous to those in thermal and photolytic transformations of isoxazoles[8] and benzisoxazoles,[9] cannot be completely excluded; however, this mechanism seems to be difficult to explain the formation of the benzofuro[3,2-b]pyridines 3.

Experimental

The 2-Acyloxy- and 2-Hydroxy-4-oxo-4H-benzisoxazolo[2,3-a]-pyridines 2a-e and 5a,b

2a-e: After a mixture of 1a (30 g), tosyl chloride (97 g, 3 equiv.), and pyridine (300 ml) had been stirred for 1 hr at room temperature, the reaction mixture was concentrated in vacuo and ethanol was added to the residue. The resulting precipitates were collected by filtration and recrystallized from acetone-chloroform to give 28.7 g (72% yield) of 2a. Similarly, 2b-e were obtained from 1a,b by using acetyl chloride (1 equiv.) or benzoyl chloride (5 equiv.).

2a: mp 225-227°C. Anal. Calcd for $C_{25}H_{16}N_2O_6S$: C, 63.55; H, 3.41; N, 5.92; S, 6.79. Found: C, 63.60; H, 3.23; N, 5.98; S, 6.76. IR ν cm^{-1}: 1660, 1590, 1365, 1180. NMR (100 MHz, DMSO-d_6): δ 2.12s(3H, CH_3), 6.95d(J=9.0 Hz, 2H, arom), 7.33d(J= 9.0 Hz), 7.62s(C_1-H), 7.2-8.0m(10H), 8.50m(1H)(arom). Mass: m/z 472(M^+). 2b: mp 219-222°C. 26% yield. Anal. Calcd for $C_{20}H_{12}N_2O_5 \cdot 1/5H_2O$: C, 66.00; H, 3.38; N, 7.70. Found: C, 65.98; H, 3.12; N, 7.58. IR ν cm^{-1}: 1760, 1650, 1610. NMR (60 MHz, DMSO-d_6): δ 2.15s(3H, Ac), 7.47s(C_1-H), 7.3-8.5m(9H, arom). Mass: m/z 360(M^+). 2c: mp 223-231°C. 50% yield. Anal. Calcd for $C_{25}H_{14}N_2O_5$: C, 71.09; H, 3.34; N, 6.63. Found: C, 70.93; H, 3.49; N, 6.76. IR ν cm^{-1}: 1730, 1660, 1600. Mass: m/z 422(M^+). 2d: mp 231-233°C. 65% yield. Anal. Calcd for $C_{27}H_{20}N_2O_8S$: C, 60.90; H, 3.79; N, 5.26; S, 6.02. Found: C, 60.75; H, 3.73; N, 5.19; S, 5.97. IR ν cm^{-1}: 1660, 1590, 1380. NMR (100 MHz, DMSO-d_6): δ 2.10s(3H, $PhCH_3$), 3.72s, 3.92s(each

3H, 2 x OCH_3), 6.70d(J= 2.5 Hz, 1H), 6.95d(J= 8.5 Hz, 2H), 7.20dd(J= 2.5 and 9.0 Hz), 7.31d(J= 8.5 Hz)(3H), 7.48dd(J= 2.5 and 9.0 Hz), 7.58d(J= 9.0 Hz), 7.62s(C_1-H)(3H), 7.82d(J= 9.0 Hz, 1H), 8.10d(J= 2.5 Hz, 1H)(arom). Mass: m/z 532(M^+).

2e: mp 195-197°C. 28% yield. Anal. Calcd for $C_{22}H_{16}N_2O_7$: C, 62.86; H, 3.84; N, 6.66. Found: C, 62.85; H, 3.69; N, 6.55. IR ν cm^{-1}: 1770, 1650. NMR (100 MHz): in $CDCl_3$-- δ2.20s(3H, Ac), 3.82s(3H, C_9-OCH_3), 3.90s(3H, C_5,-OCH_3), 6.83s(1H, C_1-H), 7.17d(J= 2.5 Hz, C_4,-H), 7.17dd(J= 2.5 and 9.0 Hz, C_6,-H)(2H), 7.27dd(J= 1.2 and 2.5 Hz, C_{10}-H), 7.33dd(J= 2.5 and 9.0 Hz, C_8-H)(2H), 7.50d(J= 9.0 Hz, C_7,-H), 7.52dd(J= 1.2 and 9.0 Hz, C_7-H)(2H): there was an observable NOE of 12% at C_1-H (δ6.83) when C_{10}-H (δ7.27) was irradiated; in DMSO-d_6-- δ2.20s(3H, Ac), 3.78s(3H, C_5,-OCH_3), 3.91s(3H, C_9-OCH_3), 7.16dd(J= 0.5 and 2.5 Hz, 1H, C_4,-H), 7.30dd(J= 2.5 and 9.0 Hz, 1H, C_6,-H), 7.38s (1H, C_1-H), 7.47dd(J= 2.5 and 9.0 Hz, 1H, C_8-H), 7.73dd(J= 0.5 and 9.0 Hz, 1H, C_7,-H), 7.83d(J= 9.0 Hz, 1H, C_7-H), 7.89d(J= 2.5 Hz, 1H, C_{10}-H). The reasons for the solvent effect on the chemical shifts of the aromatic protons are not clear.

5a,b: After a mixture of 2a (1.0 g), NaOH (1.0 g), water (10 ml), dioxane (50 ml), and MeOH (50 ml) had been stirred for 10 min at 80°C, the reaction mixture was concentrated and the residue was dissolved in water and acidified with conc. HCl. The resulting precipitates were collected and washed with MeOH to give 5a in 94% yield. Similar treatments of 2b-e gave 5a,b in 92-95% yields.

5a: mp $>$ 280°C. Anal. Calcd for $C_{18}H_{10}N_2O_4$: C, 67.92; H, 3.17; N, 8.80. Found: C, 68.02; H, 2.89; N, 8.50. IR ν cm^{-1}: 1660,

1620. NMR (60 MHz, DMSO-d_6): δ6.93s(1H, C_1-H), 7.2-8.6m(7H, arom). Mass: m/z 318(M^+). 5b: mp 240-242°C. Anal. Calcd for $C_{20}H_{14}N_2O_6$: C, 63.49; H, 3.73; N, 7.40. Found: C, 62.80; H, 3.92; N, 7.11. IR ν cm^{-1}: 1655. NMR (100 MHz, DMSO-d_6): δ 3.78s(3H, C_9-OCH_3), 3.92s(3H, C_5,-OCH_3), 6.86s(1H, C_1-H), 7.09d (J= 2.5 Hz, 1H, C_{10}-H), 7.26dd(J= 2.5 and 9.0 Hz, 1H, C_8-H), 7.40dd(J= 2.5 and 9.0 Hz, 1H, C_6,-H), 7.69d(J= 9.0 Hz, C_7-H), 7.73d(J= 9.0 Hz, C_4,-H)(2H), 7.83d(J= 2.5 Hz, 1H, C_7,-H), 11.2-11.5br(1H, OH).

Acylation of 5a to 2a-c: After a solution of 5a (1.0 g), acetic anhydride (12 ml), and pyridine (12 ml) had been stirred for 1 hr at room temperature, the reaction mixture was concentrated and ether was added to the residue. The precipitates were collected and washed with ether and acetone to give 2b in 95% yield. A similar treatment of 5a with tosyl chloride (2 equiv.) or benzoyl chloride (3 equiv.) gave 2a or 2c nearly quantitatively.

The Enol-carboxylic Acid Derivatives 6-8

6: After a solution of 5a (1.0 g) and NaOH (20 g) in a mixture of dioxane (100 ml), EtOH (100 ml), and water (50 ml) had been refluxed for 5 hr, the reaction mixture was concentrated. The residue was dissolved in water and acidified with conc. HCl. The precipitates were collected and washed with MeOH to recover the starting material 5a (78%). The MeOH washings were concentrated and the residue was washed with acetone to give 6 in 14% yield. Mp 249-252°C (acetone- ether).

Anal. Calcd for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.60; N, 8.33. Found: C, 64.15; H, 3.43; N, 7.90. IR ν cm^{-1}: 3600-2400, 1705, 1680, 1625. NMR (60 MHz, DMSO-d_6): δ 4.92s(2H, CH_2), 6.8-8.1m(8H, arom), 10.6s(1H, COOH or OH). Mass: m/z 336(M^+).

7: A solution of 6 (100 mg) and a catalytic amount of conc. H_2SO_4 in MeOH (20 ml) was refluxed for 3 hr. After cooling, the precipitates were collected and washed with MeOH to give 86 mg (83% yield) of 7. Mp 167-168°C (MeOH). Anal. Calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 65.26; H, 4.12; N, 7.87. IR ν cm^{-1}: 1705, 1625. NMR (60 MHz, $CDCl_3$): δ 4.00s(3H, $COOCH_3$), 4.87s(2H, CH_2), 6.7-8.0m(8H, arom), 10.7br(1H, OH). Mass: m/z 350(M^+).

8: After a mixture of 7 (57 mg), acetic anhydride (2 ml), and pyridine (2 ml) had been stirred for 10 min at room temperature, the reaction mixture was concentrated and ether was added to the residue. The precipitates were collected and washed with ether to give 42 mg (66% yield) of 8. Mp 158-159°C (MeOH). Anal. Calcd for $C_{21}H_{16}N_2O_6$: C, 64.28; H, 4.11; N, 7.14. Found: C, 64.16; H, 4.07; N, 7.04. IR ν cm^{-1}: 1760, 1710, 1610.

1,2-Benzisoxazole-3-acetyl Chloride 9

A mixture of 1a (14.2 g) and PCl_5 (16.2 g) was stirred for 10 min at room temperature and then the resulting clear solution was heated at 40°C for 30 min. After the reaction mixture had been concentrated, the residue was extracted with hot hexane (200 ml). The hexane solution was concentrated to give 6.6 g

(43% yield) of the acetyl chloride 9 as a light-yellow oil, which solidified on cooling in an ice-water bath. IR (NaCl) ν cm^{-1}: 1780. NMR (60 MHz, $CDCl_3$): δ4.59s(2H, CH_2), 7.2-7.9m(4H, arom).

Reaction of Methyl 1,2-Benzisoxazole-3-acetate with 9

To a cooled solution of methyl 1,2-benzisoxazole-3-acetate (5.3 g) in DMF (30 ml) was added NaH (50% in oil, 2.0 g). After stirring for 10 min at 0°C, a solution of 9 (6.0 g) in DMF (30 ml) was added dropwise and the mixture was stirred for 1 hr at 0°C. The reaction mixture was poured onto ice-water and washed with $CHCl_3$. The $CHCl_3$ washings were concentrated and the residue was subjected to silica gel column chromatography to recover the starting ester (ca. 80%). The aq. layer was acidified (pH ca. 2) with aq. 10% HCl and extracted with $CHCl_3$. The extract was concentrated and washed with $CHCl_3$. Insoluble crystals were collected and washed with $CHCl_3$ to give 0.25 g (5% yield) of 5a. The $CHCl_3$ washings were concentrated and the residue was chromatographed on a silica gel column (three times) to give 0.6 g (5% yield) of the ester 10 as an oil. IR ν cm^{-1}: 1730, 1650, 1600. NMR (60 MHz, $CDCl_3$): δ3.74s(3H, $COOCH_3$), 4.09s(2H, CH_2), 7.15-8.0m(8H, arom). CI-Mass: m/z 351(MH^+).

The acetyl chloride 9 (1.4 g) alone was treated with NaH (1.5 equiv.) in DMF (30 ml) in a manner similar to that described above to give 5a in 7% yield.

The Enamine 11, the Ketone 12, and the Alcohol 13

11: A mixture of 7 (280 mg) and 5%Pd-C (100 mg) in dioxane (20 ml)- EtOH (30 ml) was submitted to the catalytic reduction at room temperature under an atmosphere of hydrogen. After ca. 18 ml of hydrogen had been absorbed, the catalyst was filtered off and the filtrate was concentrated in vacuo. The residue was washed with ether to give 127 mg (45% yield) of the enamine 11. Mp 250-260°C (EtOH-ether). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.20; H, 4.84; N, 7.73. IR ν cm^{-1}: 3360, 1675, 1620, 1590. NMR (100 MHz, DMSO-d_6): δ 3.79s(3H, $COOCH_3$), 5.80s(4/5H, vinyl-H), 6.18s(1/5H, vinyl-H), 6.80s(2H, NH_2), 6.5-7.5m(7H), 8.06dd(J= 7.0 and 1.5 Hz, 1H)(arom), 9.2-10.4br, 10.5-11.0br(each 1H, 2 x OH). Mass: m/z 352(M^+).

12: After a mixture of 11 (60 mg), EtOH (10 ml), and 5% aq. HCl (5 ml) had been stirred for 5 hr, the EtOH was evaporated. The precipitates were collected and washed with ether to give 37 mg (62% yield) of 12. Mp 160-162°C (ether-hexane). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.47; H, 4.49; N, 4.02. IR ν cm^{-1}: 1705, 1640, 1625, 1605. NMR (100 MHz, $CDCl_3$): δ 3.91s(3H, $COOCH_3$), 4.89s(2H, CH_2), 6.85-7.95m(8H, arom), 10.62s, 11.68s(each 1H, 2 x OH). Mass: m/z 353(M^+).

13: After a solution of 12 (50 mg) and $NaBH_4$ (100 mg) in MeOH (25 ml) had been stirred for 30 min at room temperature, the reaction mixture was concentrated, aq. HCl was added to the residue, and the precipitates were extracted with $CHCl_3$.

The extract was concentrated and washed with ether to give 27 mg (54% yield) of 13. Mp 161-162°C. Anal. Calcd for $C_{19}H_{17}NO_6 \cdot 1/2H_2O$: C, 62.63; H, 4.70; N, 3.84. Found: C, 62.83; H, 4.79; N, 3.68. IR ν cm^{-1}: 3550, 3320, 1705, 1625. NMR (100 MHz, DMSO-d_6): δ 3.43d(J= 7.0 Hz, 2H, CH_2), 3.78s(3H, $COOCH_3$), 5.33t(J= 7.0 Hz, 1H, CH), 6.7-7.8m(8H, arom), 4.0-4.9br, 9.34s, 10.66s(each 1H, 3 x OH).

The C_1-Bromopyridines 15a-g

After a solution of 2 or 5a (0.5- 1.0 g) and an equimolar amount of bromine in AcOH (20- 50 ml) had been stirred for 20 min at 60- 80°C, the reaction mixture was concentrated in vacuo. The residue was washed with acetone and recrystallized from acetone to give a pure product. Under these conditions, the acetates 2b,e gave the deacetylated 15f,g, respectively, which gave the corresponding acetates 15b,e on treatment with Ac_2O-pyridine in the usual way.

15a: mp 248-252°C. 93% yield. Anal. Calcd for $C_{25}H_{15}N_2O_6SBr$: C, 54.46; H, 2.74; N, 5.08; S, 5.82; Br, 14.49. Found: C, 54.58; H, 2.48; N, 5.04; S, 5.40; Br, 14.58. IR ν cm^{-1}: 1660, 1380, 1175. NMR (60 MHz, DMSO-d_6): δ 2.15s(3H, CH_3), 6.90d(J= 9.0 Hz, 2H), 7.1-8.3m, 7.32d(J= 9.0 Hz)(9H), 8.56d(J= 8.0 Hz, 1H) (arom). Mass: m/z 552, 550(M^+). 15b: mp 235-236°C. 91% over-all yield of bromination of 2b followed by acetylation. Anal. Calcd for $C_{20}H_{11}N_2O_5Br$: C, 54.69; H, 2.52; N, 6.38; Br, 18.19. Found: C, 55.13; H, 2.42; N, 6.33; Bs, 18.42. IR ν cm^{-1}: 1775, 1665. NMR (60 MHz, DMSO-d_6): δ 2.23s(3H, Ac), 7.2-8.1m(7H), 8.50d(J= 8.0 Hz, 1H)(arom). Mass: m/z 440, 438(M^+).

15c: mp 242-245°C. 93% yield. Anal. Calcd for $C_{25}H_{13}N_2O_5Br$: C, 59.90; H, 2.61; N, 5.59; Br, 15.94. Found: C, 59.86; H, 2.38; N, 5.34; Br, 16.10. IR ν cm^{-1}: 1750, 1655. Mass: m/z 502, 500(M^+). 15d: mp 248-252°C. 91% yield. Anal. Calcd for $C_{27}H_{19}N_2O_8SBr$: C, 53.04; H, 3.13; N, 4.58; S, 5.24; Br, 13.07. Found: C, 53.05; H, 3.16; N, 4.83; S, 5.41; Br, 12.82. IR ν cm^{-1}: 1660, 1380, 1175. NMR (100 MHz, DMSO-d_6): δ 2.18s (3H, CH_3), 3.78s, 3.96s(each 3H, 2 x OCH_3), 6.85-8.1m(10H, arom). Mass: m/z 612, 610(M^+). 15e: mp 235-236°C. 88% over-all yield of bromination of 2e followed by acetylation. Anal. Calcd for $C_{22}H_{15}N_2O_7Br$: C, 52.92; H, 3.00; N, 5.61; Br, 16.00. Found: C, 52.94; H, 3.09; N, 5.78; Br, 16.24. IR ν cm^{-1}: 1765, 1660. NMR (100 MHz, DMSO-d_6): δ 2.23s(3H, Ac), 3.78s, 3.95s (each 3H, 2 x OCH_3), 7.19dd(J= 0.8 and 2.5 Hz, 1H), 7.32dd(J= 2.5 and 9.0 Hz, 1H), 7.61dd(J= 2.5 and 9.0 Hz, 1H), 7.75dd(J= 0.8 and 9.0 Hz, 1H), 7.92d(J= 2.5 Hz), 7.94d(J= 9.0 Hz)(2H) (arom). Mass: m/z 500, 498(M^+). 15f: mp 244-246°C. 99% yield from 5a. Anal. Calcd for $C_{18}H_9N_2O_4Br$: C, 54.43; H, 2.28; N, 7.05; Br, 20.12. Found: C, 54.53; H, 2.18; N, 6.91; Br, 20.05. IR ν cm^{-1}: 1660. Mass: m/z 398, 396(M^+).

The 2-Oxo-1,2-dihydrobenzofuro[3,2-b]pyridines 3

From 2a-c and 5a: A solution of 2a-c (2.0 g) or 5a (0.2 g) in $CHCl_3$ (100- 200 ml) was exposed to sun light for 3-7 hr and then allowed to stand overnight. The precipitates were collected and washed with acetone to give the corresponding 3a-c or 3d.

3a: mp 266-269°C. 62% yield. Anal. Calcd for $C_{25}H_{16}N_2O_6S$:

C, 63.55; H, 3.41; N, 5.92; S, 6.76. Found: C, 63.60; H, 3.08; N, 6.14; S, 6.67. IR ν cm^{-1}: 2800-2600, 1635, 1390, 1340, 1170. NMR (100 MHz, DMSO-d_6): δ 2.14s(3H, CH_3), 7.00d(J= 8.5 Hz, 2H), 7.43d(J= 8.5 Hz), 7,2-7.9m(9H), 8.16m(1H)(arom), 12.8-13.4br (1H, NH). Mass: m/z 472(M^+). 3b: mp $>$ 300°C. 90% yield. Anal. Calcd for $C_{20}H_{12}N_2O_5$: C, 66.67; H, 3.36; N, 7.77. Found: C, 66.79; H, 3.19; N, 7.89. IR ν cm^{-1}: 2700-2600, 1785, 1650. NMR (100 MHz, DMSO-d_6): δ 2.30s(3H, Ac), 7.3-7.9m(7H), 8.17m (1H)(arom), 13.15s(1H, NH). Mass: m/z 360(M^+). 3c: mp 254-256°C. 47% yield. Anal. Calcd for $C_{25}H_{14}N_2O_5 \cdot 1/3H_2O$: C, 70.10; H, 3.37; N, 6.54. Found: C, 69.73; H, 3.06; N, 6.33. IR ν cm^{-1}: 2750, 1755, 1650. 3d: mp $>$ 290°C. 98% yield. Anal. Calcd for $C_{18}H_{10}N_2O_4$: C, 67.92; H, 3.17; N, 8.80. Found: C, 67.55; H, 3.17; N, 8.51. IR ν cm^{-1}: 2800-2700, 1650, 1625, 1605. NMR (100MHz, DMSO-d_6): δ 7.25-7.8m(7H), 8.10m(1H)(arom), 11.9-12.8br(2H, NH and OH). Mass: m/z 318(M^+).

From 15a-c,f: After a solution of 15a,b,c,or f (0.2 g) in $CHCl_3$ (30-60 ml) had been exposed to sun light for 3 hr, the $CHCl_3$ was evaporated off in vacuo. The residue was washed with acetone to give 3a,d,c, or d in 43%, 90%, 65%, or 74% yield, respectively.

The O-Acetate of 3a: Treatment of 3a (300 mg) with Ac_2O (10 ml)-pyridine (10 ml) in the usual way gave 195 mg (60% yield) of the O-acetate: mp 189-190°C (MeOH-acetone). Anal. Calcd for $C_{27}H_{18}N_2O_7S$: C, 63.03; H, 3.53; N, 5.44; S, 6.23. Found: C, 63.24; H, 3.34; N, 5.37; S, 6.18. IR ν cm^{-1}: 1760, 1380, 1365, 1185. NMR (100 MHz, $CDCl_3$): δ 2.06s(3H, Ac),

2.31s(3H, PhC$\underline{H}_3$), 6.94d(J= 8.5 Hz, 2H), 7.32d(J= 8.5 Hz), 7.2-7.8m(9H), 8.23m(1H)(arom). Mass: m/z 514(M^+).

Alternative Synthesis of 3d

A mixture of ethyl 3-aminobenzofuran-2-carboxylate[7] (0.5 g), 9 (2.0 g), and 10% aq. NaOH (10 ml) was vigorously stirred for 2 hr. The precipitates were collected, washed with water, dried, and subjected to silica gel column chromatography to give 0.15 g (20% yield) of ethyl 3-(1,2-benzisoxazol-3-yl)-acetylaminobenzofuran-2-carboxylate. Mp 193-195°C. IR ν cm^{-1}: 3260,1705, 1670, 1610. NMR (60 MHz, $CDCl_3$): δ 1.42t(J= 7.0 Hz, 3H, $CH_2C\underline{H}_3$), 4.28s(2H, $COCH_2$), 4.46q(J= 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 7.1-8.1m(7H), 8.2-8.5m(1H)(arom), 9.85s(1H, NH). Mass: m/z 364(M^+).

After a solution of the above amide (360 mg) and NaH (50% in oil, 100 mg) in DMF (10 ml) had been stirred for 3 hr at 50°C, the reaction mixture was poured onto ice-water and acidified with 5% aq. HCl. The precipitates were collected and washed with water, MeOH, and then dichloromethane to give 65 mg (20% yield) of 3d.

The Quinone Ketals 16

After a solution of 15e (500 mg) in commercial $CHCl_3$, 5%EtOH-$CHCl_3$, or 5%MeOH-$CHCl_3$ (50 ml) had been exposed to sun light for 1-2 hr, the solvent was evaporated off and the residue was subjected to silica gel column chromatography with 2% MeOH-$CHCl_3$ as an eluent to give the corresponding 16a or b.

16a: mp 190-194°C (ether-hexane). Anal. Calcd for $C_{24}H_{21}N_2O_8Br$: C, 52.86; H, 3.88; N, 5.14; Br, 14.65. Found: C, 53.06; H, 4.11; N, 5.26; Br, 14.14. IR ν cm^{-1}: 3200-2400, 1790, 1640. NMR (100 MHz, $CDCl_3$): quinone moiety-- δ 0.99t(J= 7.0 Hz, 3H, $OCH_2\underline{CH_3}$), 2.95s(3H, OCH_3), 3.0-3.6m(2H, $OC\underline{H_2}CH_3$), 6.02d(J= 10.5 Hz, 1H), 6.38dd(J= 3.0 and 10.5 Hz, 1H), 6.88d(J= 3.0 Hz, 1H) (vinyl-protons); pyridine moiety-- δ 2.19s(3H, Ac), 13.5-14.2br (1H, NH); benzisoxazole moiety-- δ 3.92s(3H, OCH_3), 7.01dd(J= 0.5 and 2.5 Hz, 1H), 7.18dd(J= 2.5 and 9.0 Hz, 1H), 7.48dd(J= 0.5 and 9.0 Hz, 1H). Mass: m/z 544(M^+). 16b: mp 202-204°C. IR ν cm^{-1}: 2920, 2810, 1780, 1635. NMR (60 MHz, $CDCl_3$): quinone moiety-- δ 2.94s(6H, 2 x OCH_3), 6.05d(J= 10.5 Hz, 1H), 6.41dd(J= 3.0 and 10.5 Hz, 1H), 6.89d(J= 3.0 Hz, 1H)(vinyl-protons); pyridine moiety-- δ 2.20s(3H, Ac); benzisoxazole moiety-- δ 3.91s(3H, OCH_3), 6.9-7.7m(3H). Mass: m/z 529(M^+).

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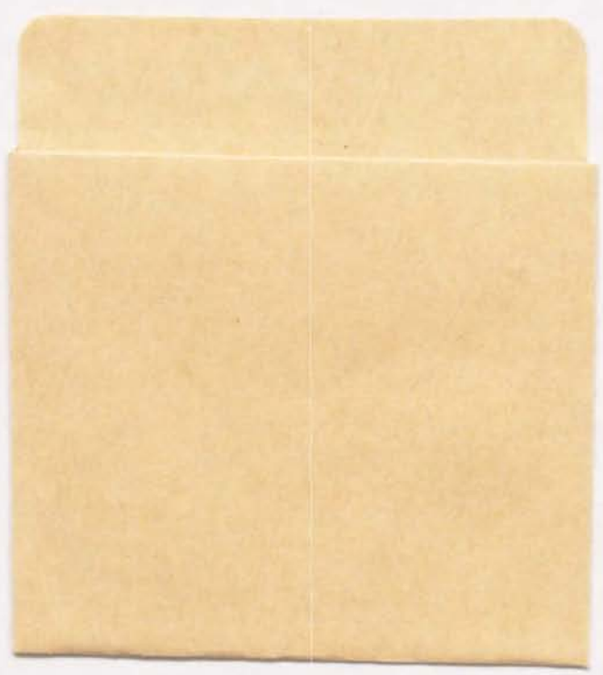
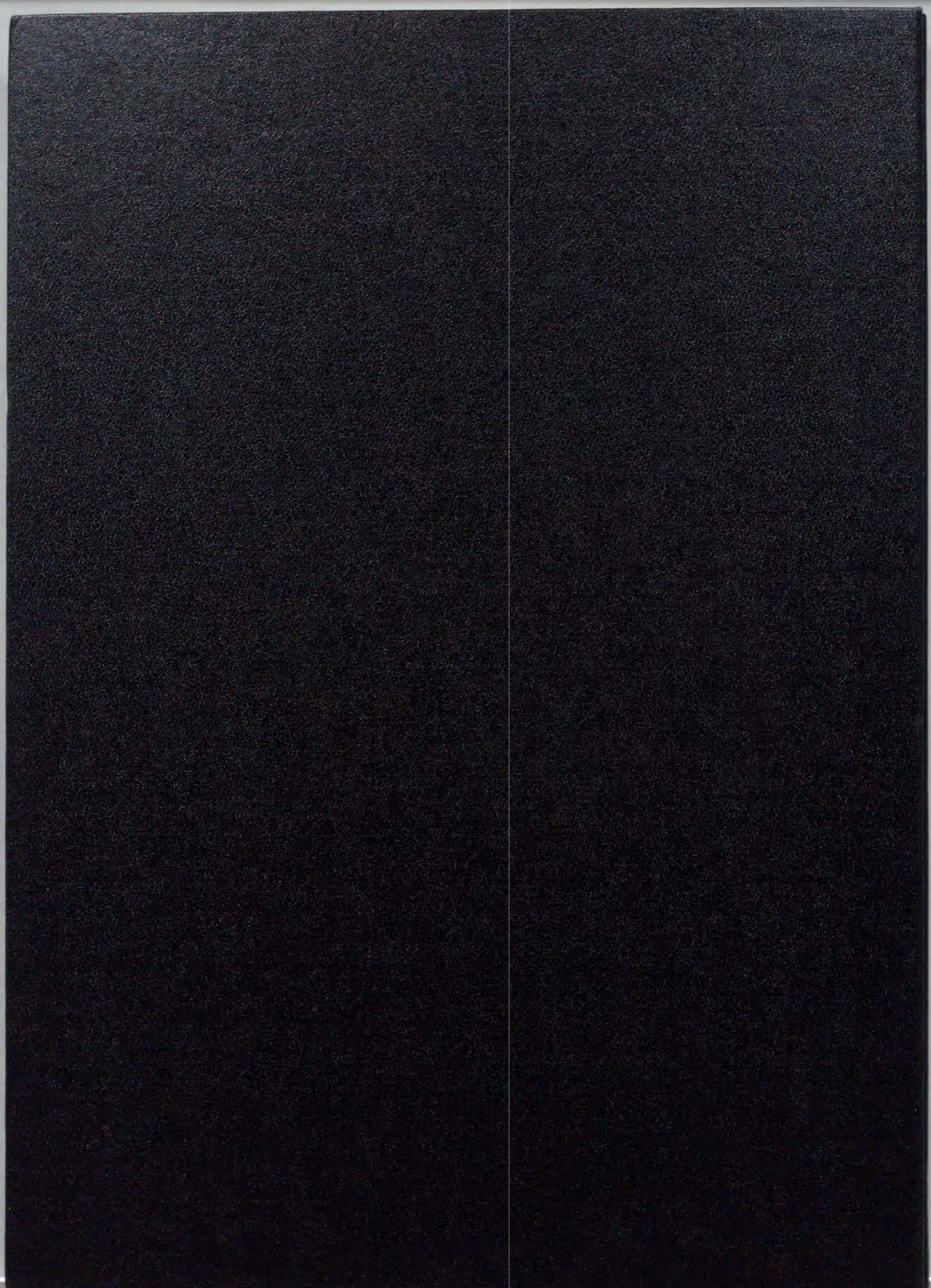
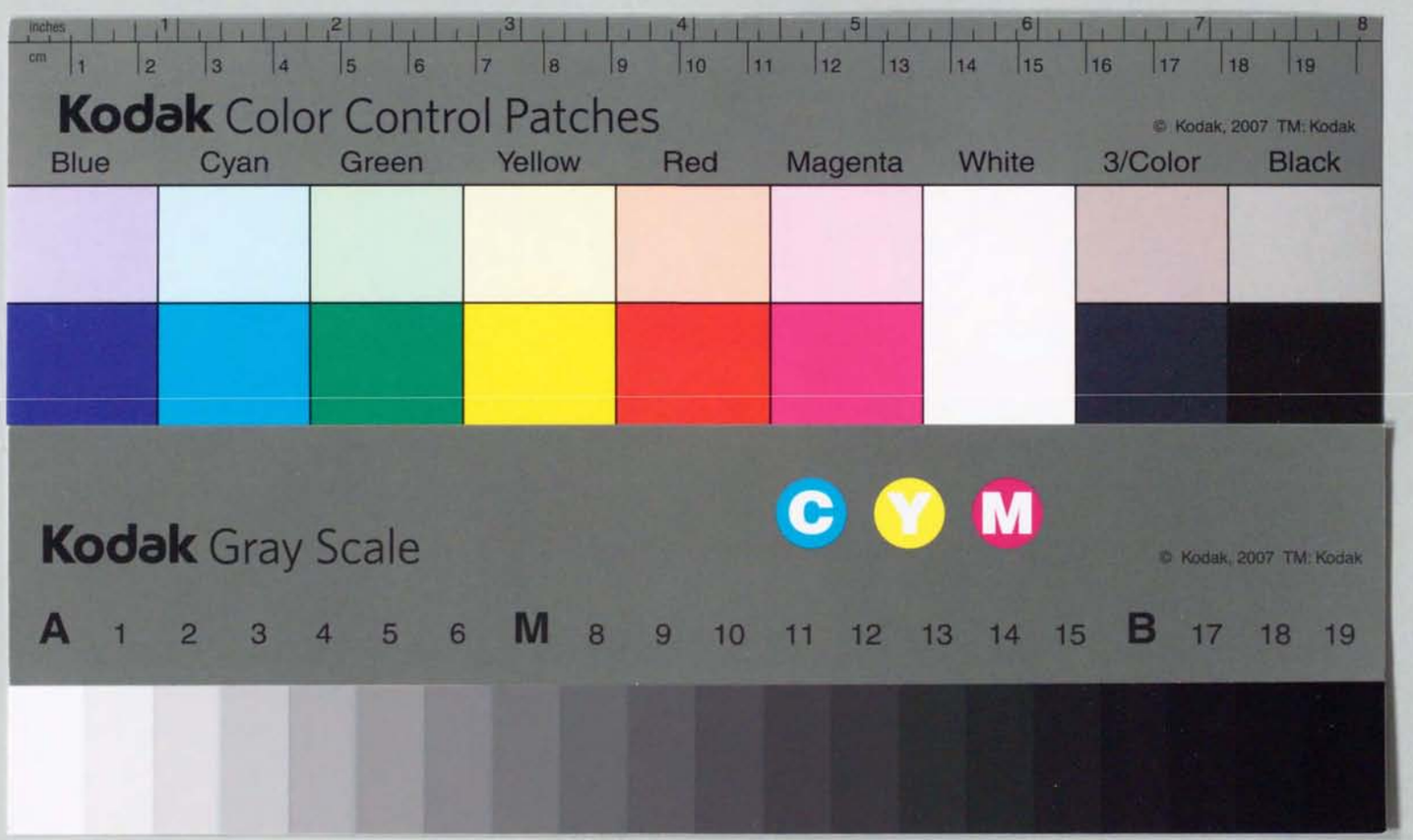
Toyokichi Yoshida



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