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Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. IV.[1] Rearrangement of N-Substituted 2H-1,2-Benzisoxazolin-3-one to 2-Substituted 2H-1,3-Benzoxazin-4-one

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The base catalyzed ring expansion of 2-substituted 2H-1,2-benzisoxazolin-3-one (**3**) to 2-substituted 2H-1,3-benzoxazin-4-one (**4**) was observed during the alkylation of 3-hydroxy-1,2-benzisoxazole (**1**).

Keywords——base catalyzed rearrangement; 3-substituted 1,2-benzisoxazole; 2H-1,3-benzoxazin-4-one; ring expansion; mechanism

King, *et al.*[3] have reported that a quaternary salt of 3-phenyl-1,2-benzisoxazole (I) underwent a base catalyzed ring expansion to give 1,3-benzoxazine (II). Recently Grivas[4] has reported the formation of 1,3-benzothiazine (IV) from N-phenacyl-1,2-benzisothiazolin-3-one (III). He suggested that this reaction must be initiated by abstraction of an α-hydrogen from III to form a carbanion which may rearrange to IV.

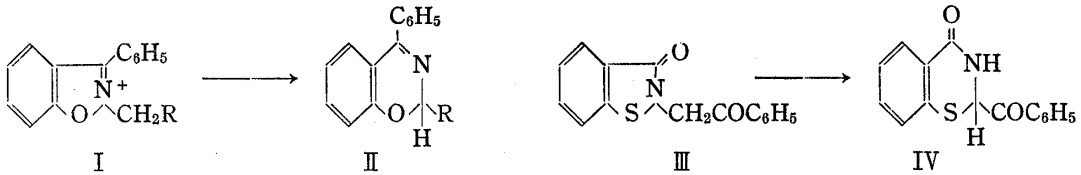


Chart 1

In the course of our studies on 3-substituted 1,2-benzisoxazole derivatives, it was found that N-alkylated 2H-1,2-benzisoxazolin-3-one derivatives also underwent the base catalyzed ring expansion to give 2-substituted 2H-1,3-benzoxazin-4-ones.

The rearrangement was first observed during the reaction of 3-hydroxy-1,2-benzisoxazole (**1**) with benzyl bromide. This reaction gave a mixture of three products (**2a**, **3a** and **4a**). Compound **2a**, which was obtained as an oil, revealed the M^+ ion peak at *m/e* 225 in the mass (MS) spectrum. The nuclear magnetic resonance (NMR) spectrum of **2a** in $CDCl_2$ revealed a signal of benzyl protons at δ 5.48 ppm and the infra red (IR) spectrum did not show any absorption bands due to a carbonyl group. The ultraviolet (UV) spectrum of **2a** resembled to that of **1**, as were shown in Fig. 1. From these data, **2a** was assigned to 3-benzyloxy-1,2-benzisoxazole. Compound **3a** was analysed to $C_{14}H_{11}NO_2$. The NMR spectrum of **3a** in $CDCl_3$ revealed a signal of benzyl protons at δ 4.99 ppm and the IR spectrum gave absorption bands due to a carbonyl group at 1670 cm^{-1}. The UV spectrum showed λ_{max} at 290 and 298 nm. Thus, **3a** was assigned to 2-benzyl-2H-1,2-benzisoxazolin-3-one. The third product **4a**, $C_{14}H_{11}NO_2$, was not reduced on a catalytic hydrogenation. By the treatment with diluted potassium hydroxide solution, **4a** gave salicylamide. The NMR spectrum of **4a** in dimethyl-

1) Part III: H. Uno and M. Kurokawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 312 (1978).
2) Location: *33–94, Enokicho, Suita, Osaka.*
3) J.F. King and T. Durst, *Can. J. Chem.*, **40**, 882 (1962).
4) J.C. Grivas, *J. Org. Chem.*, **41**, 1325 (1976).

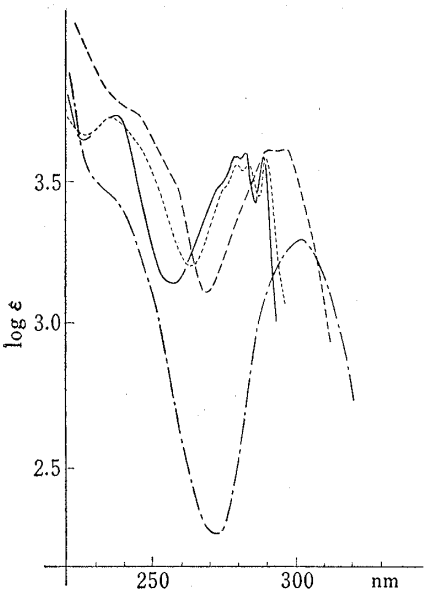


Fig. 1. UV Spectra of **1**, **2a**, **3a** and **4a**

----------: **1**, ———: **2a**,
----------: **3a**, ———: **4a**.

sulfoxide-d_6 revealed signals at δ 6.38 ppm (1H, doublet, J=1.8 Hz, $C_2\underline{H}$) and 8.93 ppm (1H, doublet, J=1.8 Hz, =N$\underline{H}$). The IR spectrum showed absorption bands due to a carbonyl group at 1680 cm^{-1}. The UV spectrum showed λ_{max} at 302 nm. From these data the structure of **4a** was determined to be 2-phenyl-2H-1,3-benzoxazin-4-one. Finally, **4a** was identified with the sample prepared from benzaldehyde and salicylamide (**5**) according to the method of Titherly *et al.*[5] The treatment of **3a** with potassium carbonate in dimethylformamide (DMF) afforded **4a**.

It was suggested that in this reaction N-substituted derivative (**3**) was formed at first, and then a hydrogen of the methylene group was abstracted to form the carbanion. The phenyl group may attract electrons and facilitate the formation of the carbanion. Therefore, reaction of **1** with several halide which have an electron attracting group adjacent to the methylene group, such as chloroacetone, benzoylmethyl bromide and so on, might afford 2-substituted 2H-1,3-benzoxazine derivatives.

Results of reactions of **1** with several halides were summerized in Table I. With methyl bromoacetate, benzoylmethyl bromide, chloroacetone, diphenylmethyl bromide, methyl α-bromopropionate or propargyl bromide, **1** gave O-substituted 3-hydroxy-1,2-benzisoxazole derivatives (**2b—g**) and 2-substituted 2H-1,3-benzoxazin-4-one derivatives (**4b—g**), expectedly.

The catalytic reduction of **4g** gave 2-ethyl-2H-1,3-benzoxazin-4-one (**6**), which was identified with the sample prepared from **5** and propanal by a reported method.[6]

A reaction of **1** with allyl bromide did not afford 1,3-benzoxazine derivative, but a mixture of **2h** and **3h** was obtained.

Thus, a substituent which attracts electrons makes the formation of the carbanion easy and facilitates the ring expansion reaction.

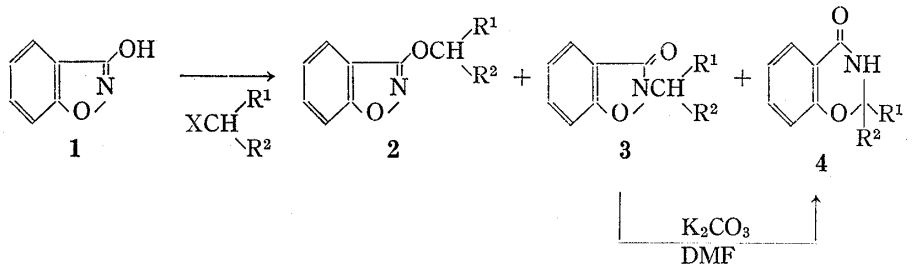


Chart 2

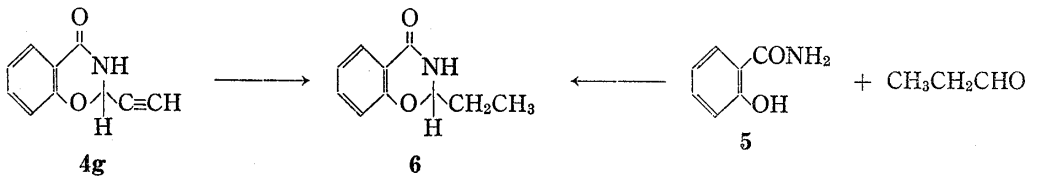
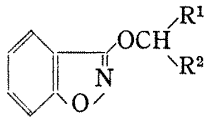
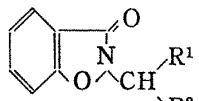


Chart 3

5) A.W. Titherley and W.L. Hicks, *J. Chem. Soc.*, **95**, 908 (1909).
6) W.L. Hicks, *J. Chem. Soc.*, **97**, 1032 (1910).

TABLE I. Results of Reactions of 2H-1,2-Benzisoxazolin-3-one (1) and Several Halides

Halide	Products					
	Compound No.	Yield (%)	Compound No.	Yield (%)	Compound No.	Yield (%)
$BrCH_2C_6H_5$	**2a**	54	**3a**	31	**4a**	2
$BrCH_2COOCH_3$	**2b**	41	—	—	**4b**	25
$BrCH_2COC_6H_5$	**2c**	36	—	—	**4c**	16
$ClCH_2COCH_3$	**2d**	51	—	—	**4d**	10
$BrCH(C_6H_5)_2$	**2e**	9	—	—	**4e**	14
Br-CH(CH$_3$)COOCH$_3$	**2f**	75	—	—	**4f**	17
$BrCH_2C{\equiv}CH$	**2g**	45	—	—	**4g**	15
$BrCH_2CH{=}CH_2$	**2h**	51	**3h**	45	—	—

TABLE II.  and 

2 **3**

Compound No.	$-CH(R^1)R_2$	mp, °C (Solvent)	MS (M^+)	Formula	Analysis (%) Calcd. C	H	N	(Found) C	H	N
2a	$-CH_2C_6H_5$	Oil	225	$C_{14}H_{11}NO_2$	74.65	4.92	6.22	74.37	5.09	6.51
2b	$-CH_2COOCH_3$	70—72 (EtOH–H_2O)	—	$C_{10}H_9NO_4$	57.97	4·38	6.76	57.74	4.35	6.63
2c	$-CH_2COC_6H_5$	120—122 (Benzene)	—	$C_{15}H_{11}NO_3$	71.14	4.38	5.53	71.31	4.14	5.63
2d	$-CH_2COCH_3$	Oil	191	$C_{10}H_9NO_3$						
2e	$-CH(C_6H_5)_2$	126—129 (MeOH)	—	$C_{20}H_{15}NO_4$	79.71	5.02	4.65	79.85	4.88	4.56
2f	$-CH(COOC_2H_5)CH_3$	Oil	235	$C_{12}H_{13}NO_4$						
2g	$-CH_2C{\equiv}CH$	39—40 (MeOH)	—	$C_{10}H_7NO_2$	69.35	4.08	8.09	69.35	3.96	8.12
2h	$-CH_2CH{=}CH_2$	Oil	175	$C_{10}H_9NO_2$	68.56	5.18	8.00	68.60	5.19	7.93
3a	$-CH_2C_6H_5$	99—101 (Benzene–hexane)	—	$C_{14}H_{11}NO_2$	74.65	4.92	6.22	74.87	4.91	6.16
3h	$-CH_2CH{=}CH_2$	Oil	175	$C_{10}H_9NO_2$	68.56	5.18	8.00	68.57	5.19	7.92

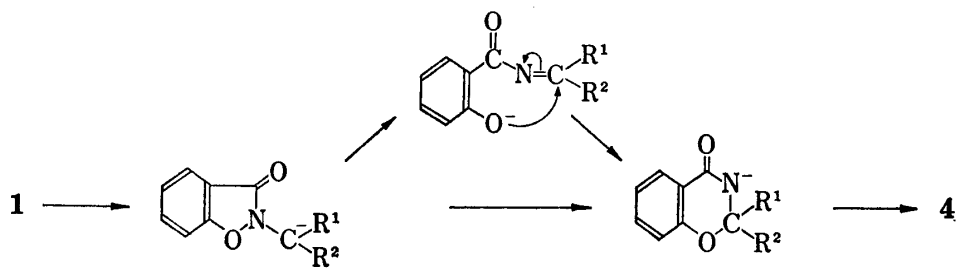
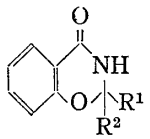


Chart 4

To investigate the effect of the substituent on the phenyl ring of 1,2-benzisoxazole, reactions of several substituted 3-hydroxy-1,2-benzisoxazole with propargyl bromide were carried out. Results were summerized in Table IV. It was suggested that an electron attracting group at 5- (or 7-) position of 1,2-benzisoxazole might facilitate the cleavage of the N–O bond and accelerate the rearrangement.

The reaction of 3-hydroxy-1,2-benzisothiazoline (**7**) with propargyl bromide afforded a mixture of 3-propargyloxy-1,2-benzisothiazole (**8**) and 2-propargyl-2H-1,2-benzisothiazolin-3-one (**9**), and 2-ethyl-2H-1,3-benzthiazin-4-one was not obtained. Generally, an N–S bond

Table III.

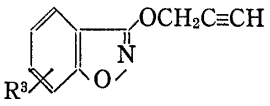


Compound No.	R^1	R^2	mp., °C (Solvent)	Formula	Analysis (%) Calcd. C	H	N	(Found) C	H	N
4a	$-C_6H_5$	-H	168—171 (Benzene)	$C_{14}H_{11}NO_2$	74.65	4.92	6.22	74.91	5.11	6.31
4b	$-COOCH_3$	-H	161—163 (AcOEt)	$C_{10}H_9NO_4$	57.97	4.38	6.76	57.63	4.28	6.68
4c	$-COC_6H_5$	-H	153—156 (Benzene)	$C_{15}H_{11}NO_3$	71.14	4.38	5.53	71.23	4.33	5.72
4d	$-COCH_3$	-H	116—118 (Benzene)	$C_{10}H_9NO_3$	62.82	4.74	7.33	63.01	4.54	7.31
4e	$-C_6H_5$	$-C_6H_5$	255—258 (AcOEt)	$C_{20}H_{15}NO_2$	79.71	5.02	4.65	79.74	4.85	4.51
4f	$-COOC_2H_5$	$-CH_3$	135—138 (AcOEt)	$C_{12}H_{13}NO_4$	61.27	5.57	5.96	61.56	5.52	5.88
4g	$-C\equiv CH$	-H	180—183 (Benzene)	$C_{10}H_7NO_2$	69.35	4.08	8.09	69.19	3.81	7.83

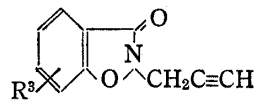
Table IV. Results of Reactions of Substituted 2H-1,2-Benzisoxazolin-3-one and Propargyl Bromide

Substituent	Compound No.	Yield (%)	Products compound No.	Yield (%)	Compound No.	Yield (%)
-H	**2f**	45	—	—	**4f**	15
5-Cl	**2i**	47	—	—	**4i**	18
5-Br	**2j**	49	—	—	**4j**	18
$5\text{-}OCH_3$	**2k**	39	**3k**	7	**4k**	5
$5\text{-}CH_3$	**2l**	46	**3l**	20	**4l**	6
$6\text{-}CH_3$	**2m**	43	**3m**	Trace	**4m**	3
$7\text{-}CH_3$	**2n**	55	**3n**	19	**4n**	6
$5,7\text{-}Cl_2$	**2o**	48	—	—	**4o**	2
$5,7\text{-}Br_2$	**2p**	44	—	—	**4p**	7
$5,7\text{-}I_2$	**2q**	43	—	—	**4q**	10
$7\text{-}C_6H_5$	**2r**	50	**3r**	25	**4r**	6

is more stable than an N–O bond to an alkali, therefore, this finding might support the proposed mechanism of the rearrangement (Chart 4).

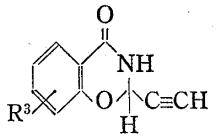
Table V. 

Compound No.	R^3	mp, C° (Solvent)	Formula	Analysis (%) Calcd. C	H	N	Halogen	(Found) C	H	N	Halogen
2i	5-Cl	108—109 (MeOH)	$C_{10}H_6ClNO_2$	57.85	2.91	6.75	17.08	57.92	2.59	6.88	16.89
2j	5-Br	143—144 (MeOH)	$C_{10}H_6BrNO_2$	47.64	2.40	5.56	31.70	47.55	2.27	5.51	31.39
3k	5-OCH_3	77—78 (MeOH)	$C_{11}H_9NO_3$	65.02	4.46	6.90		65.07	4.32	6.72	
2l	5-CH_3	94—96 (MeOH)	$C_{11}H_9NO_2$	70.58	4.85	7.48		70.72	4.66	7.25	
2m	6-CH_3	59—60 (MeOH)	$C_{11}H_9NO_2$	70.58	4.85	7.48		70.53	4.55	7.29	
2n	7-CH_3	61—63 (MeOH)	$C_{11}H_9NO_2$	70.58	4.85	7.48		70.34	4.55	7.29	
2o	5,7-Cl_2	78—80 (MeOH)	$C_{10}H_5Cl_2NO_2$	49.62	2.08	5.71	29.29	49.73	1.79	5.68	29.53
2p	5,7-Br_2	100—102 (MeOH)	$C_{10}H_5Br_2NO_2$	36.29	1.52	4.23	48.29	36.39	1.22	4.07	48.23
2q	5,7-I_2	144—147 (MeOH)	$C_{10}H_5I_2NO_2$	28.26	1.19	3.30	59.73	28.20	0.95	3.17	59.73
2r	7-C_6H_5	71—73 (MeOH)	$C_{16}H_{11}NO_2$	77.09	4.45	5.62		77.20	4.26	5.40	

Table VI. 

Compound No.	R^3	mp, °C (Solvent)	Formula	Analysis (%) Calcd. C	H	N	(Found) C	H	N
3k	5-OCH_3	132—133 (AcOEt)	$C_{11}H_9NO_3$	65.02	4.46	6.90	65.11	4.37	6.78
3l	5-CH_3	86—87 (MeOH)	$C_{11}H_9NO_2$	70.58	4.85	7.48	70.72	4.64	7.28
3n	7-CH_3	109—111 (AcOEt)	$C_{11}H_9NO_2$	70.58	4.85	7.48	70.55	4.60	7.25
3r	7-C_6H_5	125—128 (AcOEt)	$C_{16}H_{11}NO_2$	77.09	4.45	5.62	76.91	4.11	5.23

Table VII.



Compound No.	R^3	mp, °C (Solvent)	Formula	Analysis (%) Calcd. C	H	N	Halogen	(Found) C	H	N	Halogen
4i	5-Cl	188—191 (AcOEt)	$C_{10}H_6ClNO_2$	57.85	2.91	6.75	17.08	57.66	2.65	6.48	17.28
4j	5-Br	201—204 (AcOEt)	$C_{10}H_6BrNO_2$	47.64	2.40	5.56	31.38	47.45	2.10	5.40	31.38
4k	5-OCH_3	194—196 (AcOEt)	$C_{11}H_9NO_3$	65.02	4.46	6.90		65.00	4.27	6.58	
4l	5-CH_3	183—186 (AcOEt)	$C_{11}H_9NO_2$	70.58	4.85	7.48		70.62	4.56	7.08	
4m	6-CH_3	197—199 (AcOEt)	$C_{11}H_9NO_2$	70.58	4.85	7.48		70.80	4.87	7.55	
4n	7-CH_3	179—182 (AcOEt)	$C_{11}H_9NO_2$	70.58	4.85	7.48		70.81	4.65	7.17	
4o	5,7-Cl_2	164—166 (AcOEt)	$C_{10}H_5Cl_2NO_2$	49.62	2.08	5.71	29.29	49.04	2.65	5.73	29.40
4p	5,7-Br_2	188—190 (AcOEt)	$C_{10}H_5Br_2NO_2$	36.29	1.51	4.23	48.29	36.14	1.82	4.16	47.46
4q	5,7-I_2	242—245 (AcOEt)	$C_{10}H_5I_2NO_2$	28.06	1.19	3.30	59.73	28.29	1.00	3.20	59.73
4r	7-C_6H_5	197—199 (AcOEt)	$C_{16}H_{11}NO_2$	77.09	4.45	5.62		76.91	4.11	5.63	

Experimental[7]

Reaction of 3-Hydroxy-1,2-benzisoxazole (1) with Halides——In 40 ml of DMF were added **1** (0.037 mol), K_2CO_3 (0.037 mol) and appropriate halide (0.037 mol). The mixture was stirred at room temperature for 48 hr and then poured into H_2O. The aqueous solution was extracted with AcOEt. The AcOEt solution was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column. From the fraction eluted with benzene–hexane (1: 1), **2** was obtained. The fraction eluted with benzene gave **3**, and **4** was isolated from the fraction eluted with $CHCl_3$. Melting points, yields and analytical data were summerized in Table I, II and III.

2-Phenyl-2H-1,3-benzoxazin-4-one (4a) from 2-Benzyl-1,2-benzisoxazolin-3-one (3a)——In a solution of **3a** (0.8 g) in DMF (15 ml) was added K_2CO_3 (0.48 g). The mixture was stirred af 50° for 4 hr and poured into H_2O. The solution was extracted with AcOEt. The AcOEt solution was washed with H_2O, dried and evaporated. The residue was chromatographed on a silica gel column. The fraction eluted with $CHCl_3$ gave 0.23 g of **4a**, mp 168—171°. Spectral data and mp were identical with those of the sample prepared from salicylamide and benzaldehyde.[5]

Catalytic Reduction of 2-Ethynyl-2H-1,3-benzoxazin-4-one (4g)——In a solution of **4g** (0.5 g) in EtOH (15 ml) was added 5% Pd–C (0.5 g). The mixture was shaken under hydrogen atomosphere. The catalyst was removed and the solvent was evaporated. The residue was recrystallized from AcOEt to give 0.45 g of 2-ethyl-2H-1,3-benzoxazin-4-one (**6**), mp 115—117°.

Reaction of Salicylamide (5) and Propanal——Propanal (5.8 g) and **5** (13.7 g) were added fo 50 ml of ether. To the mixture was added EtOH (2 ml) saturated with HCl. The mixture was refluxed for 4 hr. The solvent was removed and to the residue was added 1 N NaOH (50 ml). The mixture was stirred for 1.5 hr. The precipitafe was collected and recrystallized from EtOH to give 6 g of **6**, mp 112—115°. *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.08; H, 6.06; N, 7.76.

Reaction of 3-Hydroty-1,2-benzisothiazole (7) and Propargyl Bromide——To the mixture of **7** (5.0 g), K_2CO_3 (4.6 g) and DMF (40 ml) was added propargyl bromide (3.9 g). The mixture was stirred at room

7) All melting points are uncorrected. NMR spectra were taken with Varian A-60 spectrometer using TMS as an internal standard, mass spectra with Hitachi RMU-6L mass spectrometer, IR with Hitachi Grating Infrared Spectrophotometer 215 and UV with Shimadzu MPS-5000.

temperature for 16 hr, poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was triturated with warm hexane. The solid was collected and recrystallized from benzene to give 2.1 g of **9**, mp 140—143°. *Anal.* Calcd. for $C_{10}H_7NOS$: C, 63.46; H, 3.73; N, 7.52; S, 16.95. Found: C, 63.11; H, 3.49; N, 7.52; S, 16.69. NMR (in DMSO-d_6) δ: 4.72 (2H, doublet, J=2.5 Hz, -C$\underline{H}_2$-), 3.50 (1H, triplet, J=2.5 Hz, -C≡CH). MS *m/e*: 189 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3180, 2100 (-C≡CH), 1670 (=CO).

The hexane solution was evaporated and the residue was chromatographed on a silica gel column. The fraction eluted with 20% benzene–hexane gave **8** (2.0 g) as an oil. NMR (in $CDCl_3$) δ: 5.17 (2H, doublet, J=2 Hz, -C$\underline{H}_2$-), 2.56 (1H, triplef, J=2 Hz, -C≡C$\underline{H}$). MS *m/e*: 189 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3280, 2520 (-C≡CH).

Acknowledgement The author are grateful to Dr. H. Takamatsu, the director of these laboratories, Drs. S. Minami and H. Nishimura for their encouragement throughout the course of this work. Thanks are also due to the staffs of analytical section of these laboratories for their spectral measurement and elemental analyses.