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Synthesis and Reactions of 1-Alkyl-2,1-benzisoxazolium Salts[1]

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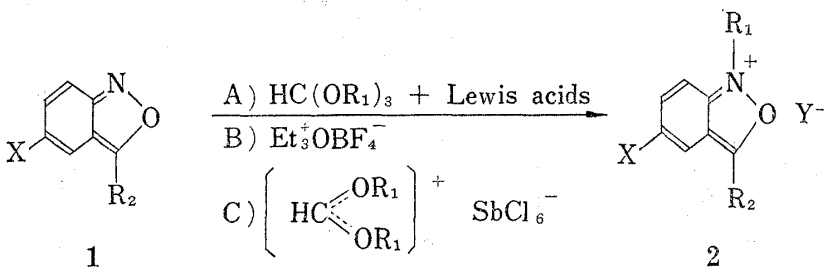
1-Alkyl-2,1-benzisoxazolium salts were prepared by the reaction of 2,1-benzisoxazoles with trialkyl orthoformates in the presence of Lewis acids as well as with Meerwein's reagents or dialkoxycarbonium hexachloroantimonates. Reactions of these quarternary salts with various nucleophilic reagents afforded 3-substituted 1-alkyl-2,1-benzisoxazoline derivatives.

Although the quarternary salts of isoxazoles have been extensively investigated,[3] no investigations have been done on the quarternary salts of 2,1-benzisoxazoles until recently.[4]

In this paper will be described a convenient preparation of quarternary salts of 2,1-benzisoxazoles with trialkyl orthoformates in the presence of Lewis acids, and reactions of these quarternary salts with various nucleophiles.

Preparation of 1-Alkyl-2,1-benzisoxazolium Salts

Although there have been several reports[5] on the quarternization of weak organic bases, there is no precedence, to our knowledge, of quarternization using trialkyl orthoformates in the presence of Lewis acids. We found the reaction of 2,1-benzisoxazoles (**1**) with trialkyl orthoformates in the presence of boron trifluoride etherate at room temperature to afford 1-alkyl-2,1-benzisoxazolium salts (**2**) in good yields as well as the reaction with Meerwein's reagent (trialkyloxonium fluoroborate) or dialkoxycarbonium hexachloroantimonate as shown in Chart 1 and Table I. The structure of **2** was established on the basis of the elemental analysis, spectroscopic evidence and chemical reactions summarized in Chart 2. The nuclear magnetic resonance (NMR) spectrum of 5-chloro-1-methyl-3-phenyl-



1
X=H,Cl,NO2
R2=H,CH3,C6H5

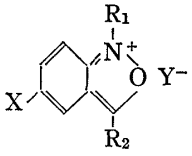
2
R1=CH3,C2H5
Y =BF4,SbCl6

Chart 1

1) A part of this paper was presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.
2) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
3) R.B. Woodward and R.A. Olofson, *Tetrahedron Suppl.*, **7**, 415 (1966); K.T. Buck and R.A. Olofson, *J. Org. Chem.*, **33**, 867 (1967).
4) R.V. Coombs and G.E. Hardtmann, *J. Org. Chem.*, **35**, 2440 (1970); R.A. Olofson, R.K. Vander Meer and S. Stournas, *J. Am. Chem. Soc.*, **93**, 1543 (1971).
5) T. Oishi, K. Kamata and Y. Ban, *Chem. Commun.*, **1970**, 777; S. Kabus, *Angew. Chem. Intern. Ed. Engl.*, **5**, 675 (1966); K. Dimroth and P. Heinrich, *ibid.*, **5**, 676 (1966).

2,1-benzisoxazolium tetrafluoroborate (**2**, X=Cl, R_1=Me, R_2=C_6H_5, Y=BF_4) exhibits the presence of low field resonance at 4.62 ppm which is attributable to the methyl protons attached to the quarternary nitrogen. The infrared (IR) spectra of these salts show a strong band at 1000—1100 cm^{-1} which is assigned to the antisymmetric stretching vibration of BF_4^-

Table I. 1-Alkyl-2,1-benzisoxazolium Salts



X	R_1	R_2	Y	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
H	Et	H	BF_4	78—79	86	$C_9H_{10}ONBF_4$	45.99	4.28	5.96	46.08	4.41	5.97
H	Me	Me	$SbCl_6$	174—175	89	$C_9H_{10}ONCl_6Sb$	22.39	2.09	2.90	22.57	2.33	2.85
H	Me	C_6H_5	BF_4	162—164	95	$C_{14}H_{12}ONBF_4$	56.60	4.07	4.72	56.69	3.96	4.76
Cl	Me	C_6H_5	BF_4	184—184.5	74	$C_{14}H_{11}ONBClF_4$	50.72	3.35	4.23	50.56	3.35	4.22
Cl	Me	C_6H_5	$SbCl_6$	180—181	94	$C_{14}H_{11}ONCl_7Sb$	29.03	1.91	2.42	28.92	2.22	2.24
Cl	$(CH_2)_2Cl$	C_6H_5	BF_4	164—165	29	$C_{15}H_{12}ONBCl_2F_4$	47.41	3.18	3.69	47.88	3.32	3.94
Cl	$(CH_2)_3Cl$	C_6H_5	BF_4	165—166	73	$C_{16}H_{14}ONBCl_2F_4$	48.77	3.58	3.56	49.33	4.00	3.65
Cl	Et	ClC_6H_4	BF_4	182—183	40	$C_{15}H_{12}ONBCl_2F_4$	47.41	3.18	3.69	47.70	3.42	3.80
NO_2	Me	C_6H_5	BF_4	213—214	76	$C_{14}H_{11}O_3N_2BF_4$	49.16	3.24	8.19	48.86	3.05	8.02

ion.[6] The quarternary salts (**2**) were converted to the known compounds **3**[7] on treatment with zinc in acetic acid or with $Na_2S_2O_4$ in aqueous methanol. Sodium borohydride, however, reduced the quarternary salts (**2**) in good yield to give 1-alkyl-2,1-benzisoxazoline derivatives (**4**) in aqueous tetrahydrofuran. These structures were established by the NMR, IR, and ultraviolet (UV) spectra given in experimental part. The salt **2** (X=Cl, R_1=Et, R_2=C_6H_5, Y=BF_4) was converted to the picrate (**5**) by neutralization with aqueous NaOH followed by the treatment with picric acid.

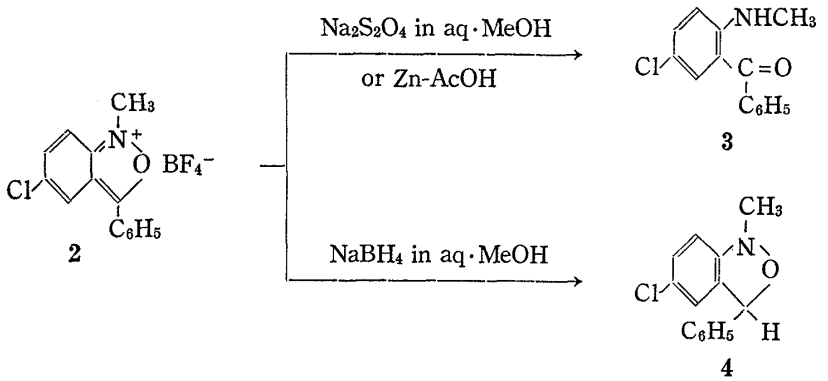


Chart 2

Reactions with Nucleophilic Reagents

1-Alkyl-2,1-benzisoxazolium tetrafluoroborates (**2**) were proved to be useful intermediates for the preparation of various 3-substituted 1-alkyl-2,1-benzisoxazoline derivatives as was expected from the chemical behavior of the quarternary salts of other N-heterocyclics.

6) N.N. Greenwood, *J. Chem. Soc.*, **1959**, 3811; D. Cook, S.G. Kuhn and G.A. Olah, *J. Chem. Phys.*, **33**, 1669 (1960).
7) L.H. Sternbach, R.I. Fryer, W. Metlesics, G. Sach and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

Treatment of **2** with Grignard reagents in tetrahydrofuran led to a number of 3-alkyl-substituted 1-alkyl-2,1-benzisoxazoline derivatives (**6**) in good yields. Reactions of **2** with various amines proceeded smoothly to give 3-aminosubstituted 1-alkyl-2,1-benzisoxazoline

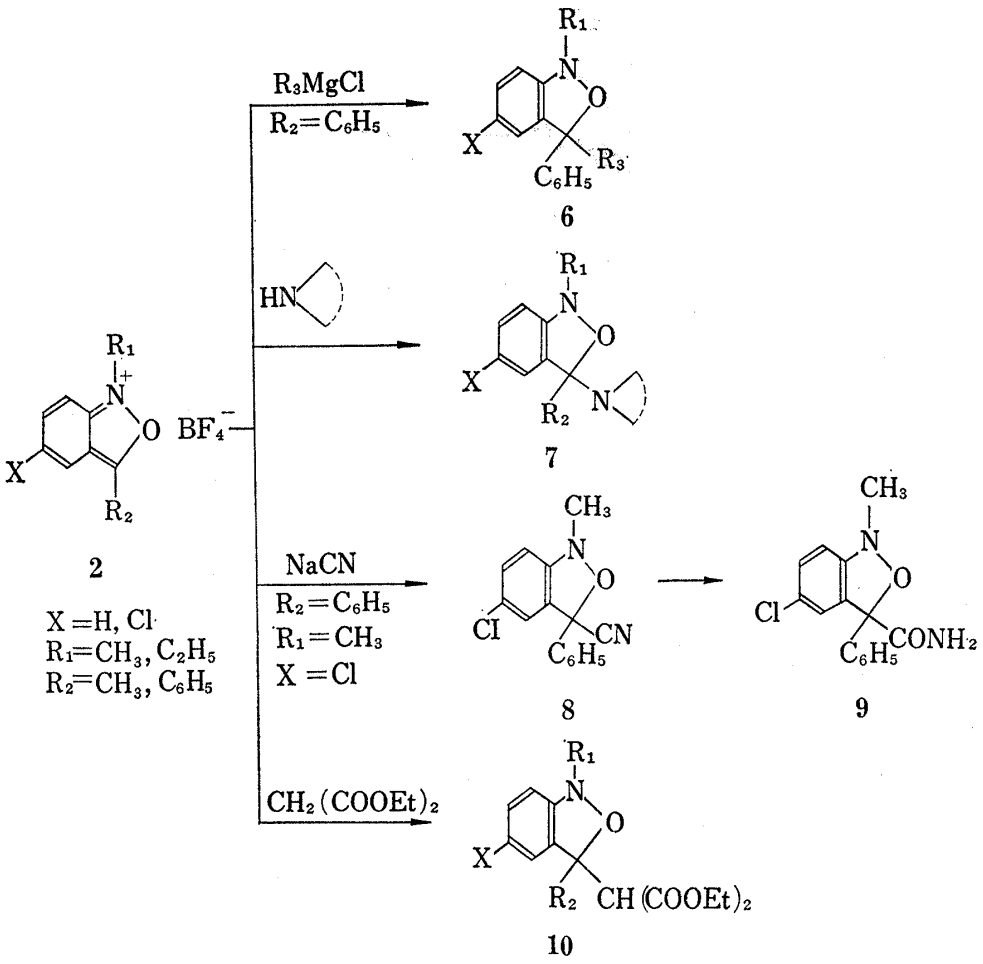
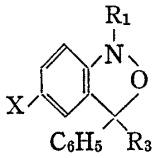


Chart 3

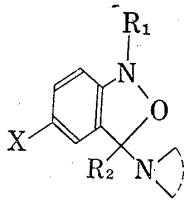
TABLE II. 1,3-Dialkyl-2,1-benzisoxazolines



R_1	R_3	X	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Me	$(CH_2)_3NMe_2$	H	122—123	35	$C_{21}H_{26}O_6N_2$ [a]	65.27	6.78	7.25	64.90	6.76	7.27
Me	$(CH_2)_3N\langle\rangle NMe$	H	185—186	18	$C_{26}H_{33}O_9N_3$ [b]	61.73	6.39	7.20	61.54	6.38	7.29
Me	Et	Cl	99—100	59	$C_{16}H_{16}ONCl$	70.20	5.89	5.12	70.32	5.99	4.84
Me	$C_6H_5CH_2$	Cl	90—91	33	$C_{21}H_{18}ONCl$	75.10	5.40	4.17	75.06	5.53	4.11
Me	$(CH_2)_3NMe_2$	Cl	123—124	16	$C_{21}H_{25}O_5N_2Cl$ [a]	59.92	5.99	6.66	59.42	6.29	6.44
$(CH_2)_2Cl$	Et	Cl	79—81	44	$C_{17}H_{17}ONCl_2$	63.36	5.32	4.35	63.18	5.21	4.19
$(CH_2)_3Cl$	Et	Cl	59—60	31	$C_{18}H_{19}ONCl_2$	64.29	5.69	4.17	64.24	5.75	4.31

a) hydrogenoxalate; *b*) maleate

Table III. 3-Aminosubstituted 1-Alkyl-2,1-benzisoxazolines

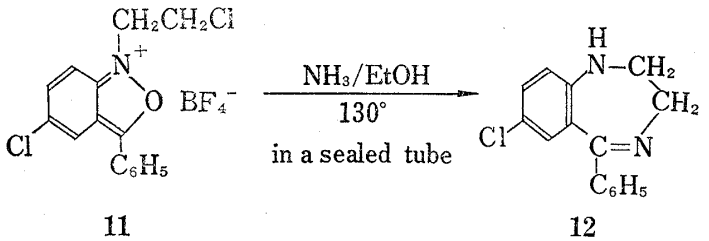


X	R_1	R_2	N⟨ ⟩	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
H	Me	H	N O	47—49	23	$C_{12}H_{16}O_2N_2$	65.43	7.32	12.72	65.24	7.27	12.61
H	Et	H	N O	55—56	63	$C_{13}H_{18}O_2N_2$	66.64	7.74	11.96	66.58	7.73	11.80
Cl	Me	C_6H_5	NHMe	95—96	89	$C_{15}H_{15}ON_2Cl$	65.53	5.50	10.20	65.38	5.46	10.42
Cl	Me	C_6H_5	NEt_2	83—84	72	$C_{16}H_{17}ON_2Cl$	66.54	5.93	9.70	66.57	5.88	9.70
Cl	Me	C_6H_5	N O	149—150	73	$C_{18}H_{19}ON_2Cl$	65.35	5.79	8.47	65.06	5.89	8.63
Cl	Me	C_6H_5	$NHCH_2CN$	78—79	42	$C_{16}H_{14}ON_3Cl$	64.70	4.70	14.01	64.78	4.70	13.88
Cl	Me	C_6H_5	$NHCH_2CO_2Et$	77—78	87	$C_{18}H_{19}O_3N_2Cl$	62.34	5.52	8.08	62.23	5.51	8.01
Cl	$(CH_2)_2Cl$	C_6H_5	N O	114—116	53	$C_{19}H_{20}O_2N_2Cl_2$	60.17	5.32	7.39	60.58	5.29	7.16
Cl	$(CH_2)_2$N O	C_6H_5	N O	150—151	47	$C_{23}H_{28}O_3N_3Cl$	64.25	6.56	9.77	64.15	6.60	9.56

derivatives (**7**). Treatment of **2** with sodium cyanide in dimethylsulfoxide afforded 3-cyano-2,1-benzisoxazoline (**8**), which was easily converted to 3-carbamoyl-2,1-benzisoxazoline (**9**) without ring-opening. Furthermore on treatment of **2** with diethylmalonate, 3-diethoxycarbonylmethyl-2,1-benzisoxazoline (**10**) was obtained in good yield. These reactions are summarized in Chart 3, and Tables II and III.

Preparation of 1,4-Benzodiazepine Derivative

The synthesis and biological properties of 1,4-benzodiazepine derivatives have been reported recently.[8] The present reaction of 2,1-benzisoxazolium salts provides an alternative synthesis of 1,2-dihydro-3H-1,4-benzodiazepine. Thus the treatment of 5-chloro-1-(2-chloroethyl)-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (**11**) with ethanolic ammonia in a sealed tube at 130° afforded 7-chloro-5-phenyl-1,2-dihydro-3H-1,4-benzo-diazepine (**12**) in 40% yield as shown in Chart 4. The reaction pathway still remained unresolved.



11 12

Chart 4

8) G.A. Archer and L.H. Sternbach, *Chem. Rev.*, **68**, 747 (1968); L.H. Sternbach, *Angew. Chem.*, **83**, 70 (1971) and references cited therein.

Experimental[9]

1-Alkyl-2,1-benzisoxazolium Salts——Typical Procedures are described: A) 5-Chloro-1-methyl-3-phenyl-2,1-benzisoxazolium Tetrafluoroborate (**2**, $R_1=CH_3$, $R_2=C_6H_5$, X=Cl, Y=BF_4): To a solution of 5-chloro-3-phenyl-2,1-benzisoxazole (22.9 g) and trimethyl orthoformate (21.2 g) in benzene (100 ml) was added boron trifluoride etherate (BF_3–ether, 28.4 g) in one portion. The reaction mixture was stirred for 1 hr at room temperature. The precipitated solid was collected and washed with AcOEt. Recrystallization from acetone gave 24.3 g (74%) of 5-chloro-1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate, mp 184—185° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}ONBClF_4$: C, 50.72; H, 3.35; N, 4.23. Found: C, 50.56; H, 3.35; N, 4.22. NMR (in d_6-DMSO): δ 4.62 (s, CH_3), 7.70—8.80 ppm (m, aromatic).

B) 5-Chloro-1-ethyl-3-phenyl-2,1-benzisoxazolium Tetrafluoroborate (**2**, $R_1=C_2H_5$, $R_2=C_6H_5$, X=Cl, Y=BF_4): Triethyloxonium tetrafluoroborate (3.2 g) was added in one portion to a solution of 5-chloro-3-phenyl-2,1-benzisoxazole (3.9 g) in CH_2Cl_2 (50 ml). The reaction mixture was stirred for 3 hr at room temperature. The precipitated solid was collected and recrystallized from CH_3CN–AcOEt to give 4.2 g (62%) of 5-chloro-1-ethyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate, mp 172—174.5° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}ONBClF_4$: C, 52.14; H, 3.79; N, 4.05. Found: C, 51.80; H, 3.48; N, 3.93. NMR (in d_6-DMSO): δ 1.68 (t, CH_3), 5.06 (q, CH_2), and 7.80—8.80 (m, aromatic).

C) 5-Chloro-1-ethyl-3-phenyl-2,1-benzisoxazolium Hexachloroantimonate (**2**, $R_1=C_2H_5$, $R_2=C_6H_5$, X=Cl, Y=$SbCl_6$): To a solution of diethoxycarbonium hexachloroantimonate[10] (8.8 g) in CH_2Cl_2 (50 ml) was added in one portion a solution of 5-chloro-3-phenyl-2,1-benzisoxazole (3.9 g) in CH_2Cl_2 (50 ml). The reaction mixture was stirred for 1 hr at room temperature. The precipitated solid was collected and washed with dry ether to give 4.0 g (41%) of 5-chloro-1-ethyl-3-phenyl-2,1-benzisoxazolium hexachloroantimonate, mp 173—174° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}ONCl_7Sb$: C, 30.37; H, 2.21; N, 2.36. Found: C, 30.40; H, 2.47; N, 2.30. Other 2,1-benzisoxazolium salts listed in Table I were prepared according to the method A.

5-Chloro-2-methylaminobenzophenone (**3**)——$Na_2S_2O_4$ (17.4 g) was added to a suspension of 5-chloro-1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (23 g) in 80% MeOH (30 ml) with stirring. The precipitated solid was collected and recrystallized from *n*-hexane to give 10.2 g (59%) of **3**, mp 92—93°, which was identical with an authentic sample.[7] Treatment of 5-chloro-1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (1.7 g) with zinc powder in AcOH at room temperature gave 0.8 g of **3**, which was identical with an authentic sample.

5-Chloro-1-methyl-3-phenyl-2,1-benzisoxazoline (**4**)——$NaBH_4$ (0.45 g) was added to a suspension of 5-chloro-1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (2.3 g) in MeOH (50 ml) with stirring. The methanol was removed under reduced pressure and the residue was extracted with ether (100 ml), washed with water and dried over $MgSO_4$. After removal of the ether *in vacuo*, the residue was recrystallized from *n*-hexane to give 1.0 g (59%) of **4**, mp 52—54°. *Anal.* Calcd. for $C_{14}H_{12}ONCl$: C, 68.43; H, 4.92; N, 5.70. Found: C, 68.38; H, 4.89; N, 5.28. NMR (in $CDCl_3$): δ 3.07 (s, CH_3), 6.13 (s, H), and 6.47—7.27 ppm (m, aromatic). UV λ_{max}^{EtOH} mμ(ε): 256 (6670), 299 (1990).

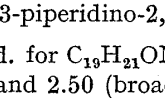
5-Chloro-1-ethyl-3-phenyl-2,1-benzisoxazolium Picrate (**5**)——To a suspension of 5-chloro-1-ethyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (0.7 g) in EtOH (20 ml) was added a solution of NaOH (0.4 g) in water (3 ml) with stirring at room temperature. After 30 min the ethanol was evaporated *in vacuo*, and the water layer was extracted with ether and dried over $MgSO_4$. To the ether extract was added a solution of picric acid (0.23 g) in EtOH (10 ml) and the precipitated solid was collected. Recrystallization from EtOH gave 0.5 g (51%) of **5**, mp 158—158.5°. *Anal.* Calcd. for $C_{21}H_{15}O_8N_4Cl$: C, 51.80; H, 3.10; N, 11.50. Found: C, 51.65; H, 3.06; N, 11.40.

1,3-Dialkyl-2,1-benzisoxazolines (**6**)——Typical Procedure is described: To a solution of 3-dimethylaminopropyl chloride (10.0 g) in dry ether (20 ml) was added activated magnesium (1.5 g), and the reaction mixture was heated under reflux with stirring for 2 hr. To the resulting Grignard reagent was added a suspension of 1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (4.5 g) in dry ether (100 ml). The mixture was heated under reflux for 1 hr. To the cooled reaction mixture was added dropwise a saturated aqueous solution of NH_4Cl (100 ml). The ether layer was washed with water and dried over $MgSO_4$. The ether solution was treated with anhydrous oxalic acid (1.0 g) to give 2.0 g (35%) of 3-(3-dimethylaminopropyl)-1-methyl-3-phenyl-2,1-benzisoxazoline hydrogenoxalate (**6**, $R_1=CH_3$, $R_3=(CH_2)_3N(CH_3)_2$, X=H), mp 122—123°. *Anal.* Calcd. for $C_{21}H_{26}O_5N_2$: C, 65.27; H, 6.78; N, 7.25. Found: C, 64.90; H, 6.76; N, 7.27. Other 1,3-dialkyl-2,1-benzisoxazolines (**6**) listed in Table II were prepared in a similar fashion.

1-Alkyl-3-amino-2,1-benzisoxazolines (**7**)——Typical procedure is described: A mixture of 5-chloro-1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (3.3 g) and piperidine (4.3 g) was heated at 80°

9) All melting points are uncorrected. IR spectra were obtained with a Hitachi-215 spectrophotometer and NMR spectra with a Varian A-60 spectrometer using TMS as internal standard. UV spectra were taken with a Perkin-Elmer 450 spectrophotometer.

10) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert and K. Wunderlich, *Ann. Chem.*, **632**, 38 (1960).

for 1 hr. The reaction mixture was extracted with ether (50 ml), washed with water and dried over $MgSO_4$. After removal of the ether, the residue was recrystallized from EtOH to give 2.0 g (61%) of 5-chloro-1-methyl-3-phenyl-3-piperidino-2,1-benzisoxazoline (**7**, $R_1=CH_3$, $R_2=C_6H_5$, X=Cl, ), mp 95—96°. *Anal.* Calcd. for $C_{19}H_{21}ON_2Cl$: C, 69.39; H, 6.44; N, 8.82. Found: C, 69.59; H, 6.61; N, 8.70. NMR (in CCl_4): δ 1.47 and 2.50 (broad, piperidine), 3.07 (s, CH_3), and 6.38—7.74 ppm (m, aromatic). UV λ_{max}^{MeOH} mμ(ε): 251.5 (8050), 299 (1960). Other 1-alkyl-3-amino-2,1-benzisoxazolines (**7**) listed in Table III were prepared in a similar fashion.

5-Chloro-3-cyano-1-methyl-3-phenyl-2,1-benzisoxazoline (**8**)——To a solution of NaCN (2.0 g) in DMSO (50 ml) was added 5-chloro-1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (6.6 g) and the mixture was stirred at room temperature for 2 hr. The precipitated solid was collected and recrystallized from benzene to give 4.1 g (76%) of **8**, mp 178—180°. *Anal.* Calcd. for $C_{15}H_{11}ON_2Cl$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.43; H, 4.09; N, 10.33.

3-Carbamoyl-5-chloro-1-methyl-3-phenyl-2,1-benzisoxazoline (**9**)——To a solution of **8** (4.1 g) in EtOH (80 ml) was added a solution of KOH (5.0 g) in water (20 ml) and then added portionwise 30% H_2O_2 (10 ml). The reaction mixture was heated with stirring at 50° for 1 hr. After removal of the ethanol *in vacuo*, the solution was diluted with water (50 ml). The precipitated solid was collected and recrystallized from 80% EtOH to give 3.3 g (76%) of **9**, mp 185—187°. *Anal.* Calcd. for $C_{15}H_{13}O_2N_2Cl$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.21; H, 4.54; N, 9.60.

5-Chloro-3-diethoxycarbonylmethyl-1-methyl-3-phenyl-2,1-benzisoxazoline (**10**)——To a solution of NaOEt prepared from sodium (0.5 g) and anhydrous EtOH (40 ml) were added diethylmalonate (3.2 g) and 5-chloro-1-methyl-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (4.5 g). The mixture was stirred for 1 hr. The solvent was evaporated to dryness and the residue was extracted with $CHCl_3$, washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was worked up with *n*-hexane to yield 4.5 g of **10**, mp 84—84.5°. *Anal.* Calcd. for $C_{21}H_{22}O_5NCl$: C, 62.45; H, 5.49; N, 3.47. Found: C, 62.36; H, 5.20; N, 3.47.

7-Chloro-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepine (**12**)——5-Chloro-1-(2-chloroethyl)-3-phenyl-2,1-benzisoxazolium tetrafluoroborate (**11**, 3.8 g) was dissolved in 16% ethanolic ammonia solution (70 ml), and the mixture was heated at 130° in a sealed tube for 2 hr. After cooling the solution was extracted with AcOEt (200 ml). The AcOEt layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The oily residue was chromatographed over 100 g of silica gel (Kiesel gel 0.05—0.2 mm) using benzene–acetone (10:1) as eluent. Separation and recrystallization of the product from pet-ether gave 1.0 g (40%) of **12**, mp 170—171°, which was identical with the authentic sample.[11]

Acknowledgement The authors are grateful to Dr. K. Morita for the encouragement throughout this work.

11) L.H. Sternbach, E. Reeder and G.A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).