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Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. I

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3-Amidinomethyl- (**8**), 3-imidazolinylmethyl- (**9**) and 3-tetrahydropyrimidinylmethyl-1,2-benzisoxazole (**10**) were synthesized from 1,2-benzisoxazole-3-acetonitrile (**4**) *via* iminoether (**7**). 3-Tetrazolylmethyl-1,2-benzisoxazole (**5**) and 1,2-benzisoxazole-3-acetamide oxime (**11**) were also prepared from **4**. 3-Aminoethyl-1,2-benzisoxazole (**25**), a tryptamine analogue of 1,2-benzisoxazole, was synthesized from 3-chloroethyl-1,2-benzisoxazole (**20**).

The bromination of 1,2-benzisoxazole-3-acetic acid (**1**) with one molar equivalent of bromine afforded α-bromo-1,2-benzisoxazole-3-acetic acid (**27**), which was decarboxylated to give 3-bromomethyl-1,2-benzisoxazole (**30**). The amination of **30** afforded 3-aminomethyl-1,2-benzisoxazole (**31**). The bromination of **1** with excess of bromine gave 3-tribromomethyl-1,2-benzisoxazole (**28**). N-Substituted 1,2-benzisoxazolylglycine ester (**32**) was synthesized from methyl α-bromo-1,2-benzisoxazole-3-acetate (**29**) which was obtained by the bromination of methyl 1,2-benzisoxazole-3-acetate (**2**).

Benzisoxazole bears a close structural resemblance to indole. Ginnella, *et al.*[2] reported that 1,2-benzisoxazole nucleus can substitute indole nucleus as far as auxine like activity concerns, in the course of their studies on isosters of naturally occurring plant regulator indole-3-acetic acid.

Since many derivatives of indole are biologically important, it appeared to be of biological interest to study the properties of derivatives of 1,2-benzisoxazole which are analogous to indole derivatives. In this paper, the syntheses of several 3-substituted 1,2-benzisoxazole derivatives were described.

The Posner reaction[2,3] between 4-hydroxycoumarine and hydroxylamine, afforded an excellent route to the starting material, 1,2-benzisoxazole-3-acetic acid[4-6] (**1**). With hydrogen chloride in methanol, methyl ester[5] (**2**) of **1** was prepared and converted into the corresponding amide[5] (**3**) by the treatment with ammonia in methanol. 1,2-Benzisoxazole-3-acetonitrile (**4**) was obtained by heating **3** in phosphorous oxychloride. When **4** was heated with sodium-azide in dimethylformamide (DMF), 3-(tetrazol-5-yl)methyl-1,2-benzisoxazole (**5**) was obtained, and **5** was alkylated with N,N-dimethylaminoalkyl chloride to give **6a, b**. When **4** was heated with anhydrous ethanol saturated with hydrogen chloride, hydrochloride of corresponding iminoether (**7**) was obtained. Reactions of **7** with ammonia, ethylenediamine or 1,3-diaminopropane gave amidine (**8a**), imidazoline derivatives (**9**) or tetrahydropyrimidine derivatives (**10**), respectively. Several N-substituted amidines (**8b-t**) were also obtained by the reactions of **7** and primary or secondary amines.

The reaction of **4** with hydroxylamine gave amide oxime (**11**), which was acylated by acetyl chloride, benzoyl chloride, ethyl chloroformate, 3,4,5-trimethoxybenzoyl chloride or cinnamyl chloride to give O-acylated amide oximes (**12a-e**). On infrared (IR) spectrum, **12b**

1) Location: *33-94, Enoki-cho, Suita, Osaka.*
2) T. Posner, *Chem. Ber.*, **42**, 2523 (1909).
3) T. Posner and R. Hess, *Chem. Ber.*, **46**, 3816 (1913).
4) M. Ginnella, F. Gualtieri, and C. Melchiorre, *Phytochemistry*, **10**, 539 (1971).
5) G. Casini, F. Gualtieri, and M.L. Stein, *J. Heterocyclic Chem.*, **6**, 279 (1969).
6) M. Ginnella, F. Gualtieri, and M.L. Stein, *J. Heterocyclic Chem.*, **8**, 397 (1971).

showed absorption band due to the carbonyl group at 1724 cm^{-1} and gave phenyl-1,2,4-oxadiazole (**13**) by heating. From these facts **12** was assigned to be O-acylamide oximes. The reaction of **11a** and phenylisothiocyanate gave anilinothiadiazole derivative (**14**). By the treatment with primary amines, **11** gave N-substituted acetoamide oximes (**15**). Hydroxamic

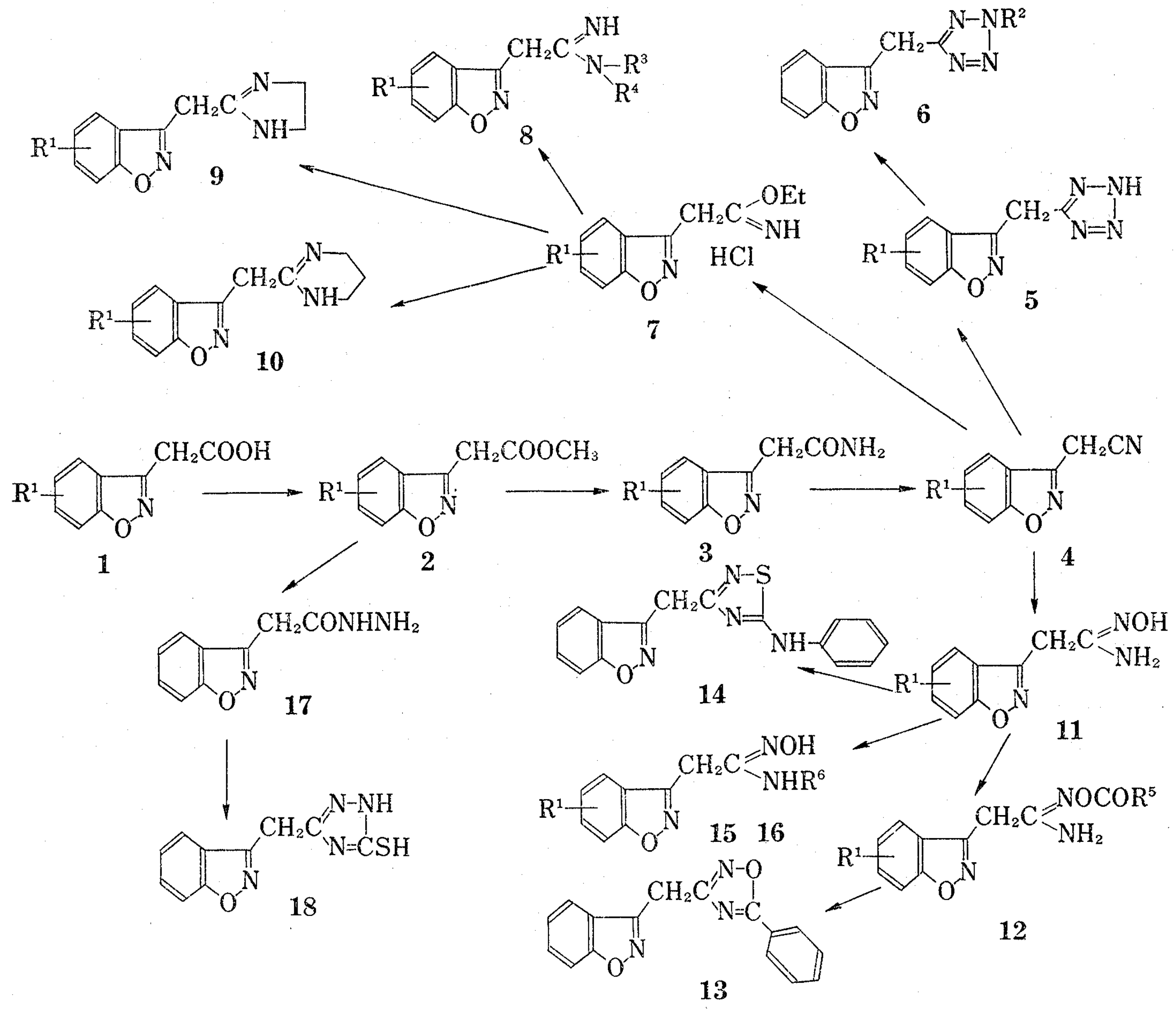


Chart 1

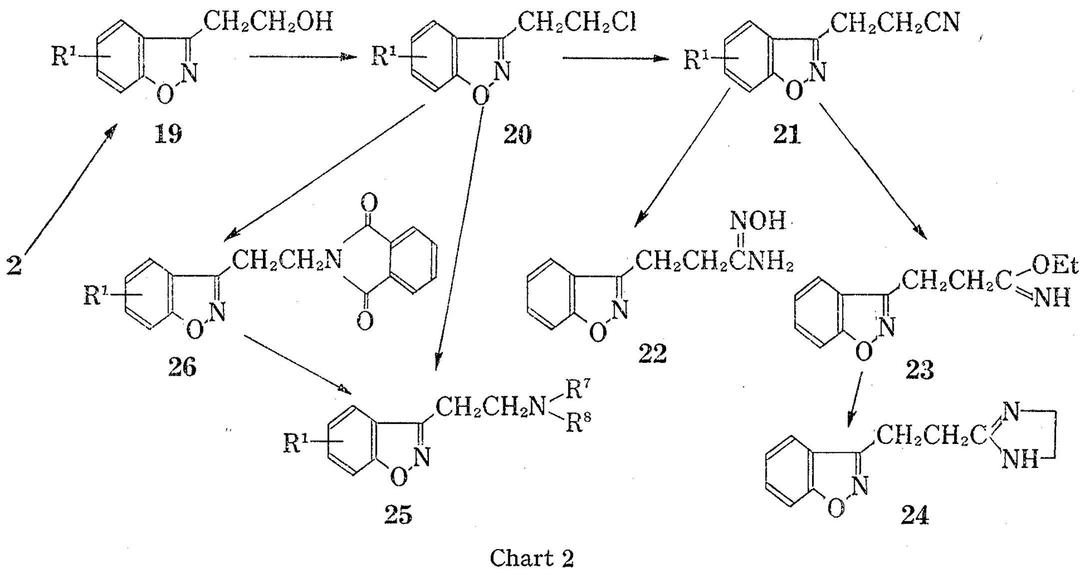


Chart 2

acid oxime derivatives (**16**) were obtained from **11** by the reaction with hydroxylamine. By the treatment with hydrazine, **2** gave hydrazide[6] (**17**) which was converted to mercaptotriazole (**18**) by the reaction with ammoniumthiocyanate.

The reduction of **2** with lithium aluminium hydride gave corresponding alcohol derivative (**19**). Chlorination of **19** with thionyl chloride afforded chloroethyl derivative (**20**). The reaction of **20** with sodium cyanide in dimethyl sulfoxide (DMSO) gave 3-cyanoethyl-1,2-benzisoxazole (**21**) which gave amide oxime (**22**) by the treatment with hydroxylamine. With hydrogen chloride in ethanol, **21** was converted to iminoether hydrochloride (**23**), which gave imidazoline derivative (**24**) by the treatment with ethylenediamine.

Reactions of **20** with several amines gave N-substituted β-aminoethyl-1,2-benzisoxazole derivatives (**25**). When heated with ammonia in a sealed tube, **20** gave β-aminoethyl-1,2-benzisoxazole (**25a**), an analogue of tryptamine or serotonin. Compound **25a**, **g**, **l** were also obtained by the hydrolysis of β-phthalimidoethyl-1,2-benzisoxazole (**26**), which was obtained by the reaction of **20** and potassium phthalimide.

The bromination of **1** with one molar equivalent of bromine in acetic acid afforded α-bromo-1,2-benzisoxazole-3-acetic acid[7] (**27**). By treatment with more than three molar equivalent of bromine, **1** gave 3-tribromomethyl-1,2-benzisoxazole[7] (**28**), which was also obtained by Ginnella, *et al.*[7] by the bromination of **1** with one molar equivalent of bromine at elevated temperature. The bromination of **2** with excess of bromine did not gave α,α-dibrome ester but α-monobromo ester (**29**).

Generally halogenation of α-methylene to a free carboxyl group is not so easy. Usually the halogenation is carried out in acid chloride or anhydride form, or using catalytic amount of phosphorous or iodine, while ester is halogenated more easily than free acid. But in the case of 1,2-benzisoxazole-3-acetic acid (**1**), free acid seemed to be halogenated more easily than its ester. These facts suggested that α-methylene of **1** is unusually activated. Further studies on the reactions of this activated methylene of **1** are now under investigation in this laboratory, and results will be reported in successive papers.

On the other hand, 3-methyl-1,2-benzisoxazole was not brominated in the same condition and 3-bromomethyl-1,2-benzisoxazole (**30**), which was obtained by decarboxylation of **27**, was no more brominated with excess of bromine. When brominated with one mole of N-bromo succin-

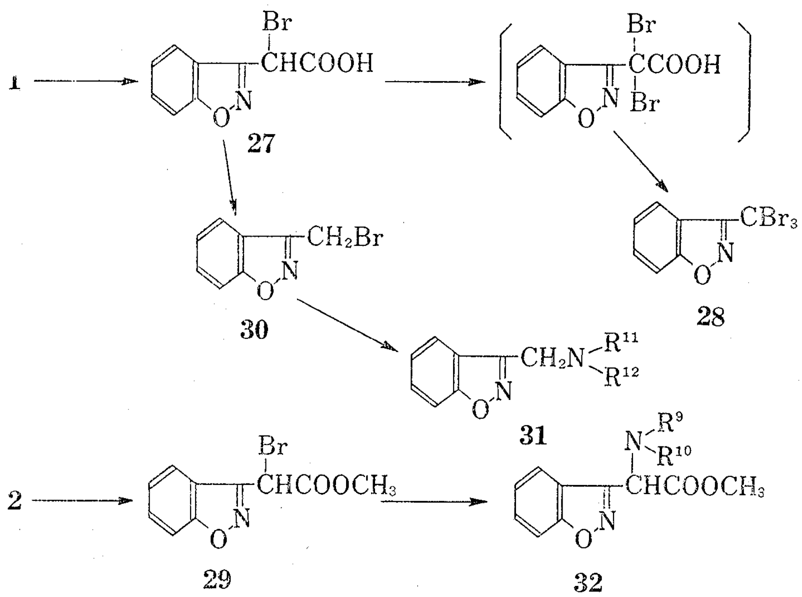
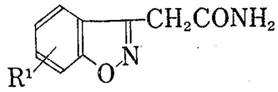
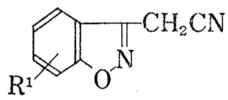


Chart 3

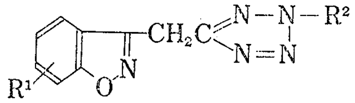
7) M. Ginnella, F. Gualtieri, C. Melchiorre, and A. Orlandoni, *Chimie Therapeutique*, 1972, 127.

TABLE I. 

No.	R^1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Hal.	Found C	H	N	Hal.
3a[6]	H	147—149	96	$C_9H_8O_2N_2$	61.36	4.58	15.90	—	61.17	4.78	15.79	—
3b	4–OCH_3	193—195	82.3	$C_{10}H_{10}O_3N_2$	58.25	4.86	13.59	—	58.32	4.81	13.77	—
3c	5–OCH_3	170—173	85.1	$C_{10}H_{10}O_3N_2$	58.25	4.86	13.59	—	58.08	4.93	13.75	—
3d	6–OCH_3	158—162	63.2	$C_{10}H_{10}O_3N_2$	58.25	4.86	13.59	—	57.98	4.83	13.74	—
3e	5–F	161—162	89	$C_9H_7O_2N_2F$	55.67	3.63	14.42	9.79	55.37	3.47	14.32	9.32
3f	5–Cl	211—211.5	74.5	$C_9H_7O_2N_2Cl$	51.32	3.35	13.30	16.83	51.10	3.43	13.33	17.11
3g	7–CH_3	173—175	100	$C_{10}H_{10}O_2N_2$	63.15	5.30	14.73	—	63.11	5.19	14.50	—
3h	6,7–$(OH)_2$	221—223	71.8	$C_9H_8O_4N_2$	51.92	3.87	13.46	—	51.65	3.76	13.35	—
3i	6,7–$(OCH_3)_2$	152—158	75.4	$C_{11}H_{12}O_4N_2$	55.93	5.12	11.86	—	56.16	5.00	11.75	—

TABLE II. 

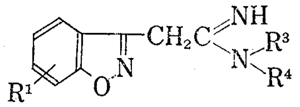
No.	R^1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Hal.	Found C	H	N	Hal.
4a	H	77— 78	93	$C_9H_6ON_2$	68.35	3.82	17.71	—	68.27	4.07	17.60	—
4b	4–OCH_3	108—109	47	$C_{10}H_8O_2N_2$	63.83	4.29	14.89	—	63.69	4.42	14.88	—
4c	5–OCH_3	122—124	95.2	$C_{10}H_8O_2N_2$	63.83	4.29	14.89	—	63.77	4.36	14.90	—
4d	6–OCH_3	102	61.3	$C_{10}H_8O_2N_2$	63.83	4.29	14.89	—	64.16	4.31	14.72	—
4e	5–F	79— 81	83	$C_9H_5ON_2F$	61.37	2.86	15.90	10.79	61.15	2.86	15.82	10.54
4f	5–Cl	76— 78	83.2	$C_9H_5ON_2Cl$	56.13	2.62	14.54	18.41	56.02	2.84	14.56	18.61
4g	7–CH_3	116—118	85	$C_{10}H_8ON_2$	69.75	4.68	16.10	—	69.66	4.75	16.10	—
4h	6,7–$(OH)_2$	219—222	32.9	$C_9H_6O_3N_2$	56.84	3.18	14.73	—	56.71	3.48	14.70	—
4i	6,7–$(OCH_3)_2$	118—121	91.9	$C_{11}H_{10}O_3N_2$	60.54	4.62	12.84	—	60.36	4.34	12.72	—
4j	5–OH	156—159	85.7	$C_9H_6O_2N_2$	62.07	3.47	16.09	—	61.76	3.76	16.31	—
4k	6–OH	154—156	64.4	$C_9H_6O_2N_2$	62.07	3.47	16.09	—	62.31	3.57	15.90	—

TABLE III. 

No.	R^1	R^2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Hal.	Found C	H	N	Hal.
5a	H	H	141—145	$C_9H_7ON_5$	53.73	3.51	34.81	—	53.82	3.62	34.83	—
5b	5-F	H	134—136	$C_9H_6ON_5F$	49.32	2.76	31.96	8.67	49.02	2.71	31.70	8.50
6a	H	$CH_2CH_2N(CH_3)_2$	156—159	$C_{13}H_{16}ON_6 \cdot HCl$	50.57	5.55	27.22	11.48	51.02	5.74	27.02	11.63
6b	H	$(CH_2)_3N(CH_3)_2$	146—148	$C_{14}H_{18}ON_6 \cdot HCl$	52.09	5.93	26.03	10.98	52.21	6.11	26.06	11.05

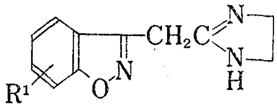
imide(NBS) carefully, **1** gave a mixture of **1**, **27**, **28** and a trace amount of α,α-dibromo acid. The mixture was treated with diazomethane and the products were separated by chromatography on silica gel column. A mixture of α-monobromoester and α,α-dibromoester, thus obtained, was hydrolyzed with dil NaOH in ethanol. The decarboxylation of the resulting mixture gave α,α-dibromomethyl-1,2-benzisoxazole which was separated from monobromo derivative on thin-layer chromatography (silica gel plate, developed with benzene–hexane 30: 70). By treatment with excess of bromine in acetic acid, α,α-dibromomethyl-1,2-benzisoxazole did not give **28** and starting material was recovered. Therefore, the bromination of **1** might have proceeded as follows: at first α-bromo acid (**27**) was formed and then α-hydrogen was replaced

TABLE IV.



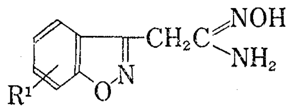
No.	R^1	$N(R^3)(R^4)$	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Hal.
8a	H	NH_2	209—212	86	$C_9H_9ON_3\cdot HCl$	51.07 (50.99)	4.76 (4.76)	19.85 (19.84)	16.75 (17.04)
8b	5-F	NH_2	224—227 (decomp.)	—	$C_9H_8ON_3F\cdot HCl$	47.07 (46.95)	3.95 (3.82)	18.30 (18.12)	15.44[a] (16.11)[a]
8c	H	$NHCH_3$	194—197 (decomp.)	64	$C_{10}H_{11}ON_3\cdot HCl$	53.22 (53.33)	5.36 (5.11)	18.62 (18.67)	15.71 (15.99)
8d	H	$NHNH_2$	205—210	53	$C_9H_{10}ON_4\cdot HCl$	47.69 (47.97)	4.89 (5.08)	24.72 (24.56)	15.14 (15.37)
8e	H	$NHCH_2CH_2OH$	147—149	49	$C_{11}H_{13}O_2N_3\cdot HCl$	51.67 (51.78)	5.52 (5.44)	16.43 (16.19)	13.86 (13.83)
8f	H	$NH(CH_2)_3$-$N(CH_3)_2$	219—222 (decomp.)	75	$C_{14}H_{20}ON_4\cdot 2HCl$	50.46 (50.25)	6.65 (6.62)	16.81 (16.75)	21.28 (21.11)
8g	H	$N(CH_3)_2$	220—233 (decomp.)	76	$C_{11}H_{13}ON_3\cdot HCl$	55.12 (54.82)	5.89 (5.69)	17.53 (17.48)	14.79 (14.52)
8h	H	$N(CH_3)(CH_2C_6H_5)$	205—207 (decomp.)	79	$C_{17}H_{18}ON_4\cdot HCl$	61.72 (61.78)	5.79 (5.67)	16.94 (17.06)	10.72 (10.76)
8i	H	N (ring)	233—235 (decomp.)	75	$C_{14}H_{17}ON_3\cdot HCl$	60.10 (59.95)	6.48 (6.41)	15.02 (14.88)	12.67 (12.84)
8j	H	N O (ring)	230—235 (decomp.)	82	$C_{13}H_{15}ON_3\cdot HCl$	55.42 (55.08)	5.72 (5.54)	14.91 (14.71)	12.57 (12.70)
8k	H	N NCH$_3$ (ring)	151—153	71	$C_{14}H_{18}ON_4\cdot HCl$	57.04 (57.10)	6.50 (6.21)	19.01 (18.88)	12.01 (11.72)
8l	H	H NCH$_2$Ph (ring)	204—206 (decomp.)	68	$C_{20}H_{20}ON_4\cdot HCl$	64.77 (64.99)	6.25 (6.04)	15.11 (15.06)	9.56 (9.55)
8m	H	N NPh (ring)	245—250 (decomp.)	89	$C_{19}H_{20}ON_4\cdot HCl$	63.95 (64.08)	5.93 (6.08)	15.70 (15.59)	9.93 (10.16)
8n	H	N N-(Cl-phenyl) (ring)	214—217 (decomp.)	64	$C_{19}H_{19}ON_4Cl\cdot HCl$	58.32 (58.34)	5.15 (5.04)	14.32 (14.13)	18.12 (18.05)
8o	6,7-$(OCH_3)_2$	$NH(CH_2)_3CH_3$	77— 80	—	$C_{15}H_{21}O_3N_3\cdot HCl$	54.96 (54.87)	6.77 (6.54)	12.82 (12.72)	10.82 (10.70)
8p	6,7-$(OH)_2$	$NHCH_2Ph$	167—170	—	$C_{18}H_{19}O_3N_3\cdot HCl$	59.75 (59.74)	5.57 (5.40)	11.61 (11.73)	9.80 (10.11)
8q	5-F	$NHCH_3$	255—260 (decomp.)	—	$C_{10}H_{10}ON_3F\cdot HCl$	49.29 (49.26)	4.55 (4.83)	17.25 (17.52)	14.55[a] (14.80)[a]
8r	5-F	NHC_2H_5	247—255 (decomp.)	—	$C_{11}H_{12}ON_3F\cdot HCl$	51.27 (51.59)	5.08 (4.90)	16.31 (16.44)	13.76[a] (13.97)[a]
8s	5-F	$NHCH_2Ph$	189—192	—	$C_{16}H_{14}ON_3F\cdot HCl$	60.10 (60.39)	4.73 (5.04)	13.14 (13.14)	11.09[a] (11.26)[a]
8t	5-F	N (ring)	244—247 (decomp.)	—	$C_{14}H_{16}ON_3F\cdot HCl$	56.47 (56.80)	5.76 (5.84)	14.11 (14.44)	11.91[a] (12.16)[a]

a) values for chlorine

Table V. 

No.	R^1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Hal.
9a	H	223—228 (decomp.)	83	$C_{11}H_{11}ON_3 \cdot HCl$	55.60 (55.51)	5.09 (5.26)	17.68 (17.53)	14.92 (14.96)
9b	4-OCH_3	248—258 (decomp.)	59	$C_{12}H_{13}O_2N_3 \cdot HCl$	53.83 (53.92)	5.27 (5.13)	15.70 (15.66)	13.25 (13.33)
9c	5-OCH_3	240—252 (decomp.)	22.8	$C_{12}H_{13}O_2N_3 \cdot HCl$	53.83 (53.68)	5.27 (5.19)	15.70 (15.46)	13.25 (13.47)
9d	6-OCH_3	225—230 (decomp.)	59.7	$C_{12}H_{13}O_2N_3 \cdot HCl$	53.83 (54.12)	5.27 (5.03)	15.70 (15.73)	13.25 (13.27)
9e	5-F	270—290 (decomp.)	82	$C_{11}H_{10}ON_3F \cdot HCl$	51.67 (51.63)	4.34 (4.24)	16.43 (16.57)	13.87[a] (14.23)[a]
9f	5-Cl	255—260 (decomp.)	30.4	$C_{11}H_{10}ON_3Cl \cdot HCl$	48.55 (48.38)	4.08 (3.99)	15.44 (15.24)	26.06 (26.35)
9g	7-CH_3	235—240 (decomp.)	61	$C_{12}H_{13}ON_3 \cdot HCl$	57.26 (57.44)	5.61 (5.60)	16.69 (16.42)	14.09 (14.10)
9h	6,7-$(OH)_2$	244—248 (decomp.)	38.8	$C_{11}H_{11}O_3N_3 \cdot HCl$	48.99 (48.63)	4.99 (4.47)	15.58 (15.13)	13.15 (13.13)
9i	6,7-$(OCH_3)_2$	211—216	47.4	$C_{13}H_{15}O_3N_3 \cdot HCl$	52.44 (52.51)	5.42 (5.15)	14.11 (14.05)	11.91 (11.92)
9j	5-OH	254—260 (decomp.)	75.5	$C_{11}H_{11}O_2N_3 \cdot HCl$	52.08 (52.41)	4.77 (4.82)	16.56 (16.52)	13.98 (14.13)
9k	6-OH	235—255	61.5	$C_{11}H_{11}O_2N_3 \cdot HCl$	52.08 (52.06)	4.77 (4.58)	16.56 (16.33)	13.98 (14.06)

a) value for chlorine

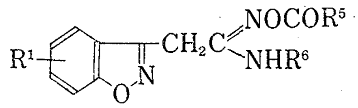
Table VI. 

No.	R^1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Hal.
11a	H	161—168	85	$C_9H_9O_2N_3 \cdot HCl$	47.49 (47.84)	4.42 (4.65)	18.46 (18.22)	15.57 (15.70)
11b	4-OCH_3	197—201	43	$C_{10}H_{11}O_3N_3 \cdot HCl$	46.61 (46.62)	4.69 (4.66)	16.31 (16.45)	13.76 (14.05)
11c	5-OCH_3	205—215	75	$C_{10}H_{11}O_3N_3 \cdot HCl$	46.61 (46.82)	4.69 (4.61)	16.31 (16.47)	13.76 (13.96)
11d	6-OCH_3	185—187	58.4	$C_{10}H_{11}O_3N_3 \cdot HCl$	46.61 (46.45)	4.69 (4.44)	16.31 (16.22)	13.76 (13.66)
11e	5-F	182—190	82	$C_9H_8O_2N_3F \cdot HCl$	44.03 (44.24)	3.69 (3.62)	17.11 (17.23)	14.44[a] (15.11)[a]
11f	5-Cl	181.5—182.5	46.5	$C_9H_8O_2N_3Cl \cdot HCl$	41.24 (41.01)	3.46 (3.46)	16.03 (16.19)	27.05 (27.26)
11g	7-CH_3	190—201	90	$C_{10}H_{11}O_2N_3 \cdot HCl$	49.69 (49.70)	5.01 (4.81)	17.39 (17.36)	14.67 (14.57)
11h	6,7-$(OH)_2$	226—228	47	$C_9H_9O_4N_3$	48.43 (48.54)	4.06 (3.93)	18.83 (19.03)	— —
11i	6,7-$(OCH_3)_2$	195—200	80	$C_{11}H_{13}O_4N_3 \cdot HCl$	45.92 (46.15)	4.90 (4.76)	14.61 (14.42)	12.33 (12.45)

No.	R^1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	Hal.
11j	5-OH	195—199 (decomp.)	58	$C_9H_9O_3N_3\cdot HCl$	44.36 (44.14)	4.14 (4.21)	17.25 (16.91)	14.55 (14.50)
11k	6-OH	213—218	66.5	$C_9H_9O_3N_3\cdot HCl$	44.36 (44.63)	4.14 (3.91)	17.25 (17.02)	14.55 (14.43)
11l	6-F	171—177	—	$C_9H_8O_2N_3F\cdot HCl$	44.03 (43.72)	3.69 (3.49)	17.11 (16.79)	14.44[a] (14.51)[a]
11m	5-NO_2	183—185	—	$C_9H_8O_4N_4$	45.76 (45.70)	3.41 (3.22)	23.72 (23.67)	— —

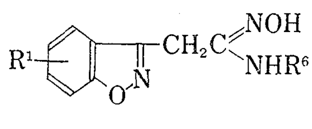
a) value for chlorine

TABLE VII.

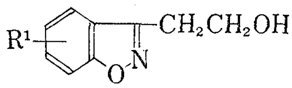


No.	R^1	COR^5	R^6	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	F
12a	H	$COCH_3$	H	173—176 (decomp.)	$C_{11}H_{11}O_3N_3$	56.59 (56.59)	4.75 (4.63)	18.02 (18.20)	— —
12b	5-F	$COCH_3$	H	181—183	$C_{11}H_{10}O_3N_3F$	52.59 (52.61)	4.01 (3.91)	16.73 (16.68)	7.56 (7.39)
12c	H	COC_2H_5	H	113—114	$C_{12}H_{13}O_4N_3$	54.75 (54.87)	4.98 (4.68)	15.96 (16.07)	— —
12d	H	COC_6H_6	H	169—171	$C_{16}H_{13}O_3N_3$	65.08 (65.24)	4.44 (4.24)	14.23 (14.13)	— —
12e	H	CO-C_6H_2-3,4,5-$(OCH_3)_3$	H	127—129	$C_{19}H_{19}O_6N_3$	59.21 (59.15)	4.97 (4.99)	10.90 (10.70)	— —
12f	H	$CH=CHC_6H_5$	H	171—173	$C_{18}H_{15}O_3N_3$	67.28 (67.41)	4.71 (4.53)	13.08 (12.86)	— —

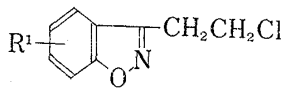
TABLE VIII.



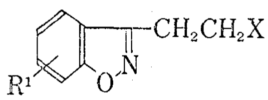
No.	R^1	R^6	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	F	Found C	H	N	F
15a	H	CH_2CH_2OH	108—111	$C_{11}H_{13}O_3N_3$	56.16	5.57	17.86	—	56.33	5.33	18.06	—
15b	H	C_6H_6	160—163	$C_{15}H_{13}O_2N_3$	67.40	4.90	15.72	—	67.58	5.12	15.70	—
16a	H	OH	134—136 (decomp.)	$C_9H_9O_3N_3$	52.17	4.38	20.28	—	52.74	4.27	20.12	—
16b	5-F	OH	152—154 (decomp.)	$C_9H_8O_3N_3F$	48.00	3.58	18.66	8.44	48.22	3.35	18.83	8.80

TABLE IX. 

No.	R^1	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	F	Found C	H	N	F
19a	H	oil	$C_9H_9O_2N$	66.24	5.56	8.58	—	65.51	5.52	8.50	—
19b	5-F	49— 52	$C_9H_8O_2NF$	59.67	4.45	7.73	10.49	59.41	4.58	7.68	10.31
19c	5-OCH_3	66— 67	$C_{10}H_{11}O_3N$	62.16	5.74	7.25	—	61.96	5.78	7.18	—
19d	5-OH	113—116	$C_9H_9O_3N$	60.33	5.06	7.82	—	60.36	5.05	7.51	—

TABLE X. 

No.	R^1	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
20a	H	oil	C_9H_8ONCl	59.52	4.44	7.11	19.52	56.40	4.23	6.58	21.73
20b	5-F	63—65	C_9H_7ONClF	54.15	3.54	7.02	17.76	54.42	3.48	7.12	18.04
20c	6-F	39—40	C_9H_7ONClF	54.15	3.54	7.02	17.76	54.13	3.59	7.01	17.60
20d	5-OCH_3	76—77	$C_{10}H_{10}O_2NCl$	56.74	4.76	6.61	16.75	56.81	4.87	6.84	16.91
20e	5-OH	96—97	$C_9H_8O_2NCl$	54.69	4.07	7.08	17.94	54.80	4.02	7.04	17.86
20f	6-OCH_3	53—54	$C_{10}H_{10}O_2NCl$	56.75	4.76	6.52	16.75	56.92	4.69	6.60	16.99

TABLE XI. 

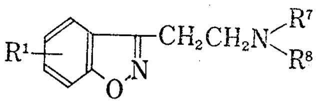
No.	R^1	X	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Hal.	Found C	H	N	Hal.
21a	H	CN	75— 77	$C_{10}H_8ON_2$	69.75	4.68	16.27	—	69.83	4.58	16.17	—
21b	5-F	CN	95— 97	$C_{10}H_7ON_2F$	63.15	3.71	14.73	9.99	63.10	3.56	14.90	9.68
22a	H	$C(=NOH)NH_2$	135—138	$C_{10}H_{11}O_2N_3$	58.53	5.40	20.48	—	58.77	5.19	20.36	—
22b	5-F	$C(=NOH)NH_2$	134—136	$C_{10}H_{10}O_2N_3F$	53.81	4.52	18.83	8.51	54.03	4.55	18.87	8.68
22c	6-F	$C(=NOH)NH_2$	135—138	$C_{10}H_{10}O_2N_3F$	53.81	4.52	18.83	8.51	53.82	4.73	18.94	8.28
24	H	C(=N–CH₂CH₂–NH) (imidazolinyl)	210—213[a]	$C_{12}H_{13}ON_3$	57.26	5.61	16.69	14.09[b]	57.19	5.41	16.86	14.33[b]

a) hydrochloride *b*) value for chlorine by another bromine. Resulting α,α-dibromo acid was rapidly brominated and could not be isolated. The decarboxylation of α,α-dibromo acid and the third bromination seemed to occur concertedly.

Reactions of **30** with amines gave 3-aminomethyl-1,2-benzisoxazole derivatives (**31**). Similarly, reactions of **29** with amines gave N-substituted glycine methylester derivatives (**32**).

Synthesized compounds were summarized in Tables. Of these compounds, **8b**, **9e**, **9j**, **11e**, **16a**, **16b** and **25l** showed strong hypotensive activities in animals, and **9a**, **11a**, **11d**, **12a** and **12d** showed anti-reserpinic activities. The pharmacological profile of **11a** was already reported by M. Shimizu, *et al.*[8] of this laboratory. Details of biological studies of these compounds will be reported elsewhere.

TABLE XII.

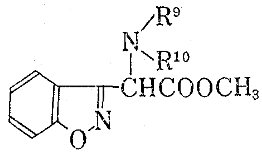


No.	R^1	$N<^{R^7}_{R^8}$	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	Cl
25a	H	NH_2	191—194	$C_9H_{10}ON_2 \cdot HCl$	54.42 (54.35)	5.58 (5.57)	14.10 (14.08)	17.85 (18.14)
25b	H	$NHCH_3$	153—163	$C_{10}H_{12}ON_2 \cdot HCl$	56.47 (56.59)	6.16 (6.08)	13.17 (13.13)	16.68 (16.97)
25c	H	$NHCH_2CH_2OH$	147—154	$C_{11}H_{14}O_2N_2 \cdot HCl$	54.44 (54.42)	6.23 (6.24)	11.54 (11.49)	14.61 (14.88)
25d	H	N⟨ ⟩ (piperidino ring)	209—212	$C_{14}H_{15}ON_2 \cdot HCl$	63.06 (62.94)	7.18 (7.28)	10.50 (10.33)	13.29 (13.80)
25e	H	N O (ring)	205—209	$C_{13}H_{16}ON_2 \cdot HCl$	58.10 (57.80)	6.38 (6.41)	10.42 (10.33)	13.19 (13.80)
25f	H	N NCH_3 (ring)	193—196	$C_{14}H_{19}ON_3 \cdot 2HCl$	52.83 (52.45)	6.65 (6.82)	13.20 (13.00)	22.38 (22.20)
25g	5-F	NH_2	217—220	$C_9H_9ON_2F \cdot HCl$	49.89 (49.63)	4.65 (4.50)	12.93 (13.00)	16.37 (16.67)
25h	5-F	$NHCH_2CH_2OH$	143—153	$C_{11}H_{13}O_2N_2F \cdot HCl$	50.68 (50.68)	5.41 (5.38)	10.75 (10.76)	13.60 (13.66)
25i	5-F	$NH(CH_2)_3$-$N(CH_3)_2$	187—190	$C_{14}H_{20}ON_3F \cdot 2HCl$	49.71 (50.08)	6.65 (6.78)	12.41 (12.45)	20.96 (20.83)
25j	5-F	N NPh (ring)	215—219	$C_{19}H_{20}ON_3F \cdot 2HCl$	57.29 (57.41)	5.57 (5.61)	10.55 (10.71)	17.80 (17.83)
25k	5-F	$NHCH_3$	170—180	$C_{10}H_{11}ON_2F \cdot HCl$	52.06 (51.88)	5.25 (5.02)	12.15 (12.12)	15.37 (15.57)
25l	5-OCH_3	NH_2	172—175	$C_{10}H_{12}O_2N_2 \cdot HCl$	52.52 (52.35)	5.73 (5.73)	12.25 (12.55)	15.51 (15.67)
25m	5-OCH_3	N NPh (ring)	200—203	$C_{20}H_{23}O_2N_3 \cdot 2HCl$	58.54 (58.52)	6.14 (5.96)	10.24 (10.10)	17.28 (17.20)
25n	H	N NPh (ring)	203—206	$C_{19}H_{21}ON_3 \cdot 2HCl$	60.00 (60.37)	6.10 (6.32)	11.04 (11.06)	18.65 (18.32)
25o	6-OCH_3	N NPh (ring)	162—164	$C_{20}H_{23}O_2N_3 \cdot HCl \cdot 1/2H_2O$	62.74 (63.23)	6.58 (6.20)	10.98 (10.60)	9.26 (9.60)
25p	6-OCH_3	N⟨ ⟩⟨O O⟩ (ring)	289—290	$C_{17}H_{22}O_4N_2 \cdot HCl$	57.54 (57.71)	6.45 (6.45)	7.89 (7.91)	9.99 (10.00)
25q	5-OH	NH_2	210—213[a]	$C_9H_{10}O_2N_2 \cdot HBr$	41.71 (41.60)	4.28 (4.16)	10.81 (10.70)	30.84[b] (30.86)[b]
25r	5-OH	N NPh (ring)	210—230[a]	$C_{19}H_{21}O_2N_3 \cdot 2HBr$	47.03 (46.76)	4.87 (4.69)	8.66 (8.39)	32.94[b] (32.78)[b]
25s	5-F	$NHCH_2Ph$	209—212	$C_{16}H_{15}ON_2F \cdot HCl$	62.64 (62.62)	5.26 (5.08)	9.13 (9.10)	11.66 (11.66)

a) hydrobromide, *b*) value for bromine.

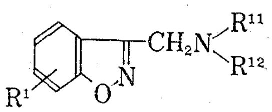
8) M. Shimizu, K. Yoshida, T. Karasawa, M. Masuda, M. Oka, T. Ito, C. Kamei, M. Hori, Y. Sohji, and K. Furukawa, *Experientia*, 30, 405 (1974).

TABLE XIII.



No.	$N\langle^{R^9}_{R^{10}}$	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
32a	N	133—142 (decomp.)	$C_{15}H_{18}O_3N_2 \cdot HCl$	57.97	6.16	9.02	11.41	57.74	6.32	9.05	11.37
32b	N O	160—170 (decomp.)	$C_{14}H_{16}O_4N_2 \cdot HCl$	53.76	5.48	8.96	11.34	53.74	5.43	8.79	11.35
32c	N NCH$_3$	145—155 (decomp.)	$C_{15}H_{19}O_3N_3 \cdot 2HCl$	49.73	5.84	11.60	19.73	49.73	5.73	11.61	19.31

TABLE XIV.



No.	R^1	$N\langle^{R^{11}}_{R^{12}}$	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	Cl
31a	H	NH_2	220—247 (decomp.)	$C_8H_8ON_2 \cdot HCl$	52.04 (52.25)	5.09 (4.71)	15.18 (15.19)	19.21 (19.33)
31b	H	N O	195—200 (decomp.)	$C_{12}H_{14}O_2N_2 \cdot HCl$	56.58 (56.35)	5.94 (5.80)	11.00 (10.85)	13.92 (14.05)
31c	H	N	225—228 (decomp.)	$C_{13}H_{16}ON_2 \cdot HCl$	61.78 (61.92)	6.78 (6.73)	11.09 (11.02)	14.03 (14.12)
31d	H	N NCH$_3$	200—205 (decomp.)	$C_{13}H_{17}ON_3 \cdot 2HCl$	51.32 (51.00)	6.29 (6.42)	13.81 (13.50)	23.31 (23.06)
31e	H	N NPh	188—191 (decomp.)	$C_{18}H_{19}ON_3 \cdot 2HCl$	59.02 (59.18)	5.78 (5.67)	11.47 (11.37)	19.36 (19.35)
31f	H	$NHCH_2CH_2OH$	167—170	$C_{10}H_{12}O_2N_2 \cdot HCl$	52.52 (52.47)	5.73 (5.70)	12.25 (12.27)	15.51 (15.78)
31g	5-F	NH_2	220—225	$C_8H_7ON_2F \cdot HCl$	47.42 (47.28)	3.98 (4.15)	13.83 (13.96)	17.50 (17.54)

Experimental[9)]

General Procedure for the Preparation of 1,2-Benzisoxazole-3-acetonitrile (4)——To 250 ml of $POCl_3$ was added **3** (0.28 mole) and the mixture was refluxed for 1.5 hr. The excess of $POCl_3$ was removed under reduced pressure and the residue was poured onto ice–H_2O. The resulting solid was collected, washed with H_2O and dissolved into ether. Insoluble material was removed and the solution was concentrated. The residue was crystallized from benzene–hexane.

General Procedure for the Preparations of 3-(Tetrazol-5-yl)methyl-1,2-benzisoxazole (5)——To 15 ml of DMF were added **4** (0.025 mole), NaN_3 (0.028 mole) and NH_4Cl (0.028 mole) and the mixture was heated for 12 hr at 120°. After cooled, the mixture was added to H_2O and the resulting solid was collected and recrystallized from EtOH and H_2O.

Alkylation of 5——In 40 ml of EtOH was dissolved **5** (0.02 mole) and $NaOCH_3$ (0.044 mole) and N,N-dimethylaminoalkyl chloride hydrochloride (0.02 mole) were added to the solution. The mixture was heated for 6 hr at 80—90° and then evaporated *in vacuo*. The oily residue was dissolved in $CHCl_3$ and the solution

9) All melting points are uncorrected.

was washed with H_2O and dried over Na_2SO_4. After the evaporation of solvent, the oily residue was converted to hydrochloride with HCl in MeOH. The hydrochloride was recrystallized from EtOH–ether.

General Procedure for the Preparation of Iminoether (7 and 23)——In 30 ml of EtOH was dissolved **4** or **21** (63 mmole). Under cooling on an ice-bath, dry HCl was passed into the solution. The mixture was kept at 5° overnight, and then filtered. To the filtrate was added ether and resulting crystals were collected, washed with ether and dried.

General Procedure for the Preparation of Amidine (8a,b)——In 10 ml of EtOH was dissolved **7** (2 mmole) and under cooling dry NH_3 was saturated into the solution. The mixture was kept at 5° overnight. The solvent was evaporated *in vacuo* and the residue was recrystallized from EtOH.

General Procedure for the Preparation of Imidazoline (9,24) and Tetrahydropyrimidine (10)——In 10 ml of EtOH was dissolved **7** or **23** (8 mmole) and under cooling on an ice-bath ethylenediamine or propylenediamine (10 mmole) was added to the solution. The mixture was kept at 5° overnight. To the mixture was added HCl saturated in EtOH and resulting crystals were collected and recrystallized from EtOH.

General Procedure for the Preparation of N-Substituted Amidine (8c—t)——In 10 ml of EtOH was dissolved **7** (2 mmole) and under cooling amine (2.2 mmole) was added to the solution. The mixture was kept at 5° overnight and resulting precipitates were collected and recrystallized from EtOH. Hydrochlorides of **8c-t** were obtained.

General Procedure for the Preparation of Amide Oxime (11, 22)——In 45 ml of a mixture of EtOH and H_2O (2: 1) was dissolved **4** or **21** (20 mmole), and Na_2CO_3 (11 mmole) and NH_2OH HCl (22 mmole) were added to the solution. The mixture was heated at 70° for 4 hr. To the mixture was added H_2O (15 ml) and the mixture was cooled. Resulting crystals were collected, washed with H_2O and recrystallized from EtOH. With HCl in EtOH, amide oxime was converted to its hydrochloride.

Acylation of 11——In 130 ml of acetone was dissolved **11** (15 mmole). To the solution was added Na_2CO_3 (15 mmole) and under cooling acyl chloride (15 mmole) was added to the mixture. The mixture was heated at 80° for 30 min. The resulting solid material was filtered off and the filtrate was concentrated *in vacuo*. The resulting crystals were collected and recrystallized from acetone.

3-(Phenyl-1,2,4-oxadiazole-3-yl)methyl-1,2-benzisoxazole (13)——Compound **12d** (1.5 g) was heated at 180° for 3 min. The resulting solid was dissolved in benzene and chromatographed on silica gel column. The $CHCl_3$ eluate was concentrated and the residue was crystallized from ether to give 1.2 g of **13**, mp 93—95°. *Anal.* Calcd. for $C_{16}H_{11}O_2N_3$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.54; H, 4.11; N, 15.15.

3-(5-Anilinothiadiazol-3-yl)methyl-1,2-benzisoxazole (14)——Phenylisothiocyanate (5.4 g) and **11a** (3.8 g) were added to 20 ml of $CHCl_3$ and the mixture was heated at 70° for 20 hr. After the solvent was removed, the residue was dissolved in $CHCl_3$ and passed onto silica gel column. The product was eluted with $CHCl_3$. The solvent was removed and the residue was recrystallized from $CHCl_3$–ether to give **14**, mp 157—159°, 1.6 g. *Anal.* Calcd. for $C_{16}H_{12}ON_4S$: C, 62.32; H, 3.92; N, 18.17; S, 10.40. Found: C, 62.22; H, 3.88; N, 17.91; S, 10.51.

5-Fluoro-1,2-benzisoxazole-3-acetohydroxamic Acid Oxime (16b)——In 50 ml of MeOH were added **11e** (2.1 g) and NH_2OH HCl (0.8 g). The mixture was refluxed for 24 hr and MeOH was removed *in vacuo*. The residue was dissolved in ether and insoluble material was filtered off. The filtrate was evaporated to dryness and the residue was dissolved in $CHCl_3$ (50 ml) under heating. After cooling resulting precipitates were collected and recrystallized from EtOH to give **14b**, mp 152—154° (decomp.), 1.7 g. *Anal.* Calcd. for $C_9H_8O_3N_3F$: C, 48.00; H, 3.58; N, 18.66; F, 8.44. Found: C, 48.22; H, 3.35; N, 18.83; F, 8.80.

3-(5-Mercapto-1,2,4-triazol-3-yl)methyl-1,2-benzisoxazole (18)——Ammoniumthiocyanate (1.4 g) and **17**[6] (1.0 g) were mixed and heated at 180—190° for 20 min. After cooled, 5 ml of H_2O was added to the mixture and insoluble material was collected, washed with H_2O and recrystallized from EtOH to give **18**, mp 253—257° (decomp.), 0.6 g. *Anal.* Calcd. for $C_{10}H_8ON_4S$: C, 51.71; H, 3.47; N, 24.12; S, 13.80. Found: C, 51.68; H, 3.61; N, 23.98; S, 14.12.

3-Hydroxyethyl-1,2-benzisoxazole (19)——In 50 ml of dried ether was dissolved **2** (0.05 mole) and the solution was added to a solution of $LiAlH_4$ (0.1 mole) under cooling in nitrogen atmosphere. After stirred for 5 min, dioxane–H_2O (1: 1) was added to the mixture and ether layer was separated. The solvent was removed and the residue was chromatographed on silicagel column. The product was eluted with benzene.

Chlorination of 19——To 100 ml of $SOCl_2$ was added **19** (0.1 mole) and the mixture was refluxed for 2 hr. The excess of $SOCl_2$ was removed *in vacuo* and the residue was dissolved in 100 ml of toluene. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel column. The product was eluted with $CHCl_3$.

General Procedure for the Preparation of 3-cyanoethyl-1,2-benzisoxazole (21)——A solution of **20** (0.04 mole) in 10 ml of DMSO was mixed with a solution of NaCN (0.12 mole) in 15 ml of DMSO. The mixture was heated 1 hr at 80° and then poured into H_2O. The aq. solution was extracted with benzene. The benzene layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was chromatographed on silica gel column. The product was eluted with $CHCl_3$. Recrystallization from benzene and *n*-hexane gave **21**.

General Procedure for the Preparation of N-Substituted 3-β-Aminoethyl (or methyl)-1,2-benzisoxazole (25 and 31)——In 100 ml of xylene was dissolved **20** (or **30**) (1 mole). To the solution was added amine (2 mole) and the mixture was heated on an oil-bath (150°) for 3 hr. The mixture was poured into H_2O and the product was extracted with benzene. The organic layer was washed with H_2O and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was dissolved in $CHCl_3$ and chromatographed on silica gel column. The product was eluted with $CHCl_3$ containing 3% MeOH. After the evaporation of the solvent, the product was converted into its hydrochloride with ethanolic HCl.

General Procedure for the Preparation of 3-Aminoethyl (or methyl)-1,2-benzisoxazole (25a, g, 1, 31a, g)——In 10 ml of DMF were added **20** (or **30**) (0.01 mole) and potassium phthalimide (0.01 mole) and the mixture was heated at 60° for 3 hr and then kept at room temperature overnight. The addition of H_2O to the mixture resulted in the precipitation of phthalimide derivative. In 25 ml of MeOH were dissolved the precipitate and hydrazine hydrate (1.2 ml) and the mixture was heated under reflux for 2 hr. The mixture was concentrated *in vacuo* and the residue was added to 40 ml of concd. HCl. Insoluble material was filtered off and the filtrate was made alkaline with NaOH and then extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4 and evaporated *in vacuo*. The residue (free base) was converted to hydrochloride with ethanolic HCl. The hydrochloride was recrystallized from EtOH.

Methyl α-Bromo-1,2-benzisoxazole-3-acetate (29)——To the solution of **2** (3.8 g) in 50 ml of AcOH was added a solution of bromine (3.2 g) in 50 ml of AcOH and the mixture was kept overnight at room temperature. The mixture was poured into H_2O and the aqueous solution was extracted with benzene. The benzene extract was washed with H_2O and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residue was chromatographed on silicagel column. The product was eluted with benzene–*n*–hexane (2: 8). The solvent was removed and the residue was recrystallized from MeOH to give 1.0 g of **29**, mp 49—50°. *Anal.* Calcd. for $C_{10}H_8N_3Br$: C, 44.47; H, 2.98; N, 5.18; Br, 29.59. Found: C, 44.28; H, 2.69; N, 5.17; Br, 29.96.

3-Tribromomethyl-1,2-benzisoxazole[7] (28)——To the solution of **1** (1.77 g) in 7 ml of AcOH was added a solution of bromine (6.4 g) in 5 ml of AcOH. The mixture was heated at 70° for 6 hr and then poured into H_2O. The aqueous solution was extracted with benzene. The benzene extract was washed with H_2O, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was recrystallized from ether to give 3.25 g of **28**, mp 116—118°. *Anal.* Calcd. for $C_8H_4ONBr_3$: C, 25.98; H, 1.09; N, 3.79; Br, 64.82. Found: C, 26.05; H, 1.03; N, 3.92; Br 65.02.

General Procedure for the Preparation of N-Substituted Methyl α-Amino-1,2-benzisoxazole-3-acetate (32)——To the solution of **29** (3.7 mmole) in 20 ml of benzene was added amine (23 mmole) and the mixture was kept at room temperature for 2 days. The solvent was removed *in vacuo* and the residue was chromatographed on silicagel column. The product was eluted with $CHCl_3$. The solvent was evaporated off and the residue was treated with ethanolic HCl and hydrochloride of **32** was obtained.

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