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Synthesis and Adrenergic β-Blocking Activity of Some Propanolamine Derivatives

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Some propanolamine derivatives were synthesized and their β-adrenergic blocking activities were determined. Among the compounds tested, all compounds with benzothiazole nucleus were found to have potent β-adrenergic blocking activity, and those with other nuclei failed to produce substantial β-blocking activity with one exception. Three compounds with benzothiazole nucleus were more potent than sotalol in their β-blocking activity, and the other two were equipotent to sotalol. One with benzotriazole nucleus had about the same β-blocking activity as sotalol.

Keywords——adrenergic beta-blocking activity; hypotensive activity; benzothiazole; benzotriazole; structure-activity relationship; propanolamines

In a series of experiments in an attempt to find new β-adrenoceptor blocking agents, we have synthesized some 1,3-benzodioxole derivatives and examined their β-blocking and hypotensive activities.[2] In the present report, we will describe the syntheses and biological activities of some propanolamine derivatives. Out of twelve compounds we synthesized and tested in the present study, three had stronger β-adrenergic blocking activity than sotalol and the other three had about the same potency as sotalol.

The compounds listed in Table I were usually prepared by the reaction of epoxypropane intermediate listed in Table II with the appropriate amine.

$$ROCH_2CH\text{–}CH_2 \xrightarrow{R'NH_2} ROCH_2CHOHCH_2NHR'$$
(O)

N-Methyl derivatives (**1, 5**) and N-isopropyl derivative (**6**) were synthesized by catalytic hydrogenolysis of the corresponding N-alkyl-N-benzylaminopropanol derivatives.

$$ROCH_2CHOHCH_2N(CH_2Ph)R' \xrightarrow{Pd\text{–}H_2} ROCH_2CHOHCH_2NHR'$$

The ring opening reaction of epoxypropane derivatives by amines gave exclusively the desired secondary alcohols as in the propranolol series.[3]

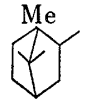
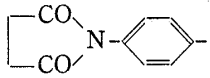
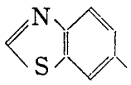
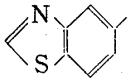
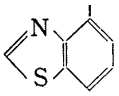
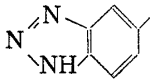
The epoxypropane derivatives (**16—20**) listed in Table II were obtained easily from the corresponding phenols and epichlorohydrin by using K_2CO_3 or CH_3ONa as a condensing agent. However the standard procedure for the etherification using K_2CO_3, $NaNH_2$ or NaH as a condensing agent in various solvents failed to produce epoxypropane derivatives (**13**—

1) Location: *a) 3-6-6, Asahimachi, Machida-shi, Tokyo; b) Bunkyo-ku, Tokyo; c) 1-1-53, Takasu-cho, Sakai-shi, Osaka.*

2) H. Tatsuno, K. Goto, K. Shigenobu, Y. Kasuya, H. Obase, Y. Yamada, and S. Kudo, *J. Med. Chem.*, **20**, 394 (1977).

3) A.F. Crowther and L.H. Smith, *J. Med. Chem.*, **11**, 1009 (1968).

Table I

Compd.	$ROCH_2CHOHCH_2NHR_1$ R[a]	R_1	Form	Crystn. solvent	mp (C°)	Formula[b]
1[d]		CH_3	HCl	iso-PrOH	135—136	$C_{14}H_{27}NO_2 \cdot HCl$
2		$CH(CH_3)_2$	HCl	iso-PrOH	195—196	$C_{16}H_{31}NO_2 \cdot HCl$
3	$(C_6H_5)_2CH-$	$CH(CH_3)_2$	HCl	*n*-BuOH–EtOH	199—200	$C_{19}H_{25}NO_2 \cdot HCl$
4	$C_6H_5CH(CH_3)-$	$CH(CH_3)_2$	Oxalate	iso-PrOH	145—146	$C_{14}H_{23}NO_2 \cdot 0.5C_2H_2O_4$
5[c]		CH_3	HCl	iso-PrOH–EtOH	153—155	$C_{14}H_{18}N_2O_4 \cdot HCl$
6		$CH(CH_3)_2$	HCl	EtOH	216—217	$C_{16}H_{23}N_2O_4 \cdot HCl$
7		$CH(CH_3)_2$	Succinate	iso-PrOH	149.5—150.5	$C_{13}H_{18}N_2O_2S \cdot 0.5C_4H_6O_4$
8		$C(CH_3)_3$	Succinate	iso-PrOH	159.5—160	$C_{14}H_{20}N_2O_2S \cdot 0.5C_4H_6O_4$
9		$CH(CH_3)_2$	Succinate	iso-PrOH	141—143	$C_{13}H_{18}N_2O_2S \cdot 0.5C_4H_6O_4$
10		$C(CH_3)_3$	Succinate	iso-PrOH	176—177	$C_{14}H_{20}N_2O_2S \cdot 0.5C_4H_6O_4$
11		$CH(CH_3)_2$	Succinate	iso-PrOH	165—166	$C_{13}H_{18}N_2O_2S \cdot 0.5C_4H_6O_4$
12[e]		$CH(CH_3)_2$	2HCl	iso-PrOH	180—181	$C_{12}H_{18}N_4O_2 \cdot 2HCl$

a) Where there is a blank space in this column, the R group is the preceding structure.
b) All compounds analyzed for C,H, and N.
c) Intermediate 1-(N-benzyl-N-methylamino)-3-[4-(2,5-dioxo-pyrrolidin-1-yl)-phenoxy]-propan-2-ol, mp 85—86° (from EtOH).
d) Intermediate 1-(N-benzyl-N-methylamino)-3-(bornan-2-yloxy)-propan-2-ol·HCl, mp 169—170° (from iso-PrOH).
e) Intermediate 1-isopropylamino-3-(4-acetoamino-3-nitrophenoxy)-propan-2-ol, mp 148—149.5° (from EtOH). Intermediate 1-isopropylamino-3-(4-acetoamino-3-aminopheoxy)-propan-2-ol (**24**), mp 139—140° (from EtOH).

15) and the starting materials were recovered unchanged. So, starting aliphatic and alicyclic alcohols were converted to allylethers, which were then oxidized with H_2O_2[4] or NBS-NaOH[5] to epoxypropane derivatives.

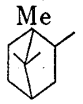
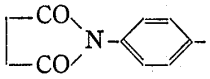
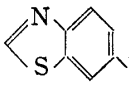
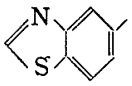
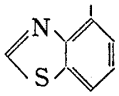
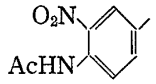
Most of the epoxypropane intermediates were purified. However, in the cases of compounds **17**—**19**, purification was not attained and the crude materials were directly used in the following reactions.

For the synthesis of **12**, 1-acyl protected 5-hydroxybenzotriazole *i.e.* **21** has been chosen as starting material.

The synthesis of **21** through the partial hydrolysis of O,N-diacetyl-5-hydroxybenzotriazole[6] was unsuccessful because the hydrolysis of N-acetyl group proceeded the hydrolysis

4) G.B. Payne and P.H. Williams, *J. Org. Chem.*, **26**, 651 (1961); G.P. Payne, P.H. Deming, and P.H. Williams, *ibid.*, **26**, 659 (1965).
5) W.S. Johnson, T.J.B.P. Loew, D.H. Rich, L.W.R.A. Arnold, T. Li, and J. Faulker, *J. Am. Chem. Soc.*, **92**, 4464 (1970); D.R. Dalton and D.G. Jones, *Tetrahedron Lett.*, **1967**, 2875.
6) The synthesis of O,N-diacetyl-5-hydroxybenzotriazole has been reported by Fieser, *et al.* (L.F. Fieser and E.L. Martin *J. Am. Chem. Soc.*, **57**, 1835, (1935)). They stated that cyclization of 1-acetylamino-2-amino-4-acetoxybenzene gave a compound with a mp 125—126° which was identified as O,N-diacetyl derivative. We repeated their procedure and obtained the compound with the same mp reported by above authors. However, we found that the compound (mp 125—126°) was not a O,N-diacetyl derivative but a O-acetyl derivative (*cf.* IR 1755 cm^{-1}, NMR δ 2.4 for $OCOCH_3$ in DMSO-d_6). Recrystallization of the crude product which was obtained according to the procedure reported by above authors, from benzene-ligroin gave a compound with mp 118—119° which was a O,N-diacetyl derivative (*cf.* IR 1763, 1745 cm^{-1}, NMR δ 2.33 for $OCOCH_3$, δ 2.92 for $NCOCH_3$ in DMSO-d_6).

Table II

Compd.	R	Crystn. solvent[a]	mp (°C) or bp (°C/mmHg)	Formula	Analyses
13		—	103—104/4	$C_{13}H_{22}O_2$	C, H
14[b]	$(C_6H_5)_2CH-$	P (40)	47— 48, 160/3	$C_{16}H_{16}O_2$	C, H
15[c]	$C_6H_5CH(CH_3)-$	—	131—132/18	$C_{11}H_{14}O_2$	C, H
16[d]		EtOH	164—165	$C_{13}H_{13}NO_4$	C, H, N
17		—		$C_{10}H_9NO_2S$	C, H, N
18		—		$C_{10}H_9NO_2S$	C, H, N
19		—		$C_{10}H_9NO_2S$	C, H, N
20[e]		Ligroine	110—113	$C_{11}H_{12}N_2O_5$	C, H, N

a) P (40), petroleum ether (bp 40—60°).
b) Starting material, benzohydrol, mp 69° (lit.[7] mp 69°). Intermediate 3-(diphenylmethoxy)-propen-1, bp 130—132° (4 mmHg).
c) Starting material, α-phenylethanol, bp 100° (18 mmHg) (lit.[8] bp 100° (18 mmHg)). Intermediate 3-(1-phenylethoxy)-propen-1, bp 93—94° (18 mmHg).
d) Starting material, N-(4-hydroxyphenyl)-succinimide.
e) Starting material, 3-nitro-4-acetoaminophenol, mp 219° (lit.[9] mp 218°).

of O-acetyl group. The synthesis of **21** was accomplished in 80.5% yield by the reaction of 4-acetoamino-3-aminophenol with $NaNO_2$.

Condensation of **21** with epichlorohydrin in acetone using K_2CO_3 as a condensing agent gave a mixture of three products. One of these products was easily separated and identified as 5-hydroxybenzotriazole. The other two products (A and B) were separated by preparative thin-layer chromatography (TLC). Proton magnetic resonance (PMR) and TLC analyses of the crude product indicate that the ratio of A: B was about 1: 1.7. A and B had a same molecular formula of $C_{13}H_{14}N_3O_4Cl$, with *m/e* 311 (M^+). The physical properties of compound A and B were summerized in Table III.

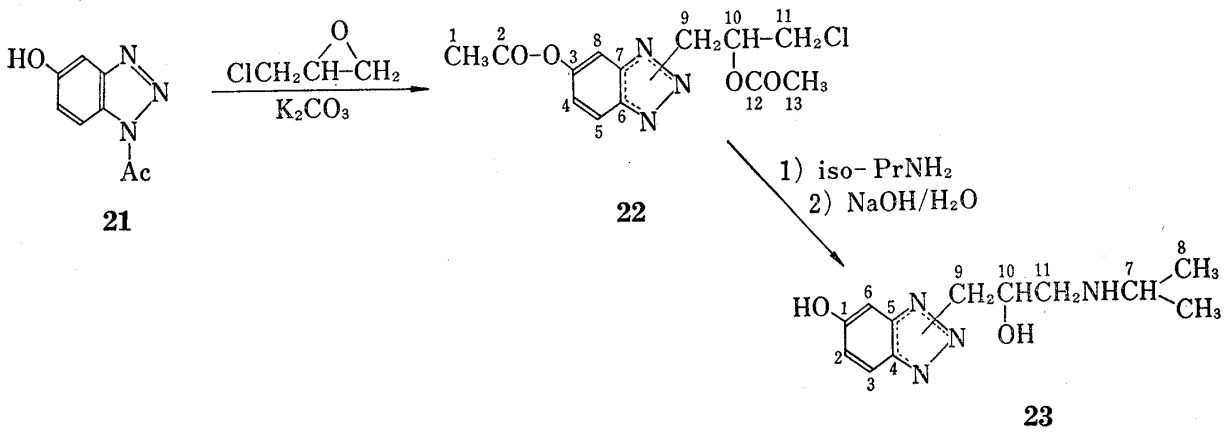
In view of the coupling patterns and chemical shifts of PMR and CMR spectra given in Table III we could conclude that C-9 methylene group linked with nitrogen atom rather than with oxygen atom (*cf*, proton at δ 3.4—4.0 and carbon at δ 55.99 for compound A and proton at δ 3.4—4.0 and carbon at δ 48.04 for compound B). Further support that the compounds A and B are N-alkylation products **22** was obtained from the following facts.

7) F.Y. Wiselogle and H. Sonneborn, "Organic Syntheses," Collect, Vol. I, Wiley, New York N.Y., 1941, p. 90.
8) V. Braun and Kochendorfer, *Ber.*, **56**, 2174 (1923).
9) M.H. Broyles and W.K. Easley, *J. Org. Chem.*, **25**, 2233 (1960).

Table III. Physical properties of Compound A and B

	Compound A	Compound B
Mass	311(M^+), 269(M–Ac) 209(269–OAc), 174(209–Cl)	311(M^+), 269(M–Ac) 209(269–OAc), 174(209–Cl)
PMR[a]	2.05[b] ($CHOCHC\underline{H}_3$), 2.34($ArOCOC\underline{H}_3$) 3.4—4.0($NC\underline{H}_2CHOAc$), 4.8—5.05 ($C\underline{H}_2Cl$), 5.4—5.8($NCH_2C\underline{H}OAc$)	1.95($CHOCHC\underline{H}_3$), 2.34($ArOCOC\underline{H}_3$) 3.4—4.0($NC\underline{H}_2CHOAc$), 4.7—5.1 ($C\underline{H}_2Cl$), 5.2—5.7($NCH_2C\underline{H}OAc$)
CMR[c]	20.68, 21.12(C-1, C-13), 42.77 (C-11), 55.99(C-9), 70.56(C-10), 109.34(C-4), 119.05(C-5), 123.05(C-8), 142.66, 144.51 (C-6, C-7), 149.14(C-3), 169.38, 169.67(C-2, C-12)	20.73, 21.07(C-1, C-13), 42.58 (C-11), 48.04(C-9), 71.16(C-10), 109.73(C-4), 119.49(C-5) 123.34(C-8), 146.11(C-6, C-7), 150.46(C-3), 169.82, 169.72 (C-2, C-12)
UV[d]	λ_{max} nm (ε): 281(8.97×10^3) $\lambda_{sh.}$ nm (ε): 286(8.19×10^3)	λ_{max} nm (ε): 258(5.28×10^3) λ_{max} nm (ε): 264(5.39×10^3) λ_{max} nm (ε): 283(4.44×10^3)
IR (film)	1760 cm^{-1} (Broad), 1220 cm^{-1} (Broad)	1760 cm^{-1} (Broad), 1220 cm^{-1} (Broad)
R*f*	0.80(Benzene–MeOH, 6:1)	0.61(Benzene–MeOH, 6:1)

a) Measured in $CDCl_3$.
b) Chemical shift (60 Mc) ppm.
c) Chemical shifts were obtained in $CDCl_3$ and are expressed downfield from Me_4Si. The assignment of each signals was based on chemical shift and multiplicity in off-resonance decoupled spectrum: C-1, C-13 (q), C-9 (t), C-11 (t), C-10 (d), C-4 (d), C-5 (d), C-8 (d), C-6 (s), C-7 (s), C-3 (s), C-2 (s) (s=singlet, d=doublet, t=triplet, q=quartet).
d) Measured in EtOH.



In a CMR spectrum the C-9 signal of compound **23**, which was obtained by the treatment of **22** with iso-$PrNH_2$ and subsequent alkaline hydrolysis, appeared at 50.09 ppm, while that of **12** which was obtained by alternative method descrived later appeared at 70.42 ppm.

The spectral data of compound A and B closely resemble except C-9 signals in CMR. The facts indicate that compound A and B would be position isomers. The ultraviolet (UV) spectrum provides some informations on the position of alkylation. 1-Substituted benzotriazoles have UV absorptions around 255 and 283 nm (some compounds have two peaks in former region) and the intensity of the former (ε_{255}) is stronger than that of the later (ε_{283}). The 2 substituted benzotriazoles absorb at *ca.* 275 nm.[10]

10) D. Dal Monte, A. Mangini, and R. Passerini, *Bull. Sci. facolta Chim. ind. Bologna* **12**, 168 (1954) [*Chem. Abstr.*, **49**, 10739^f (1955)]; R.H. Wiley and K.H. Hussung, *J. Am. Chem. Soc.*, **79**, 4395 (1957); J,H, Boger, "Heterocyclic Compounds," Vol. 7, Ch. 5, ed. by R.C. Elderfield, Wiley, New York, 1961, p. 422; V. Mozolis and S. Jokubaityte, *Liet. T. S. R. Mokslu Akad. Darb.*, Ser. B, **1970**, 129.

From the UV spectra of compound A and B in Table III, we can deduce that compound A and B would be the benzotriazole derivatives substituted at 2- and 1- position respectively.

The confirmation of the position of alkylation and reaction mechanisms are under investigation.

Since the synthesis of **12** from acyl protected benzotriazole such as **21** proved to be unsuccessful because rapid migration occured in preference to a O-etherification, the alternative approach to **12** was undertaken. 4-Acetoamino-3-nitrophenol was used as starting material and the final product **12** was obtained by another synthetic route shown in Chart 1.

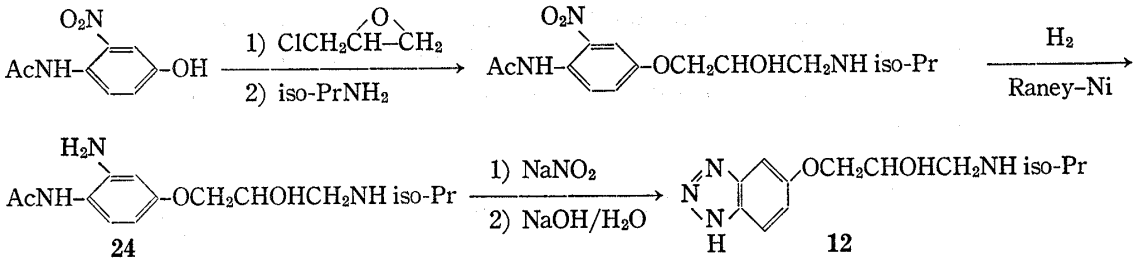


Chart 1

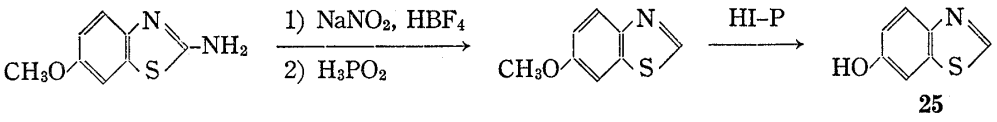
The reaction of **24** with $NaNO_2$ was accomplished without protecting isopropylamino side chain and pure **12** was obtained after column chromatography on silicagel.

Most of the starting phenols and alcohols were easily obtained but the known methods to synthesize phenols fused with thiazole nucleus were not satisfactory because of the low yield.

6-Hydroxybenzothiazole (**25**), which is the starting material of **7** and **8**, has been reported by Boggust, *et al.*[11]

Their process for obtaining **25** starting from benzothiazole has several disadvantages; 5-nitro derivative formed as a by-product during nitration of benzothiazole and **25** was often contaminated with 5-hydroxy derivative and the yield was only 3.7% from benzothiazole. We synthesized **25** *via* an alternative route.[12]

2-Amino-6-methoxybenzothiazole, which was commercially available, was diazotized with $NaNO_2$ in dil. H_2SO_4 and the diazotized compound was isolated as HBF_4 salt. Subsequent reduction of the resulting 2-diazotized derivative with H_3PO_2 or iso-PrOH afforded 6-methoxybenzothiazole, which could be converted into **25** on further hydrolysis (HI–P). Compound (**25**) was obtained in comparatively good yield (29.9%).

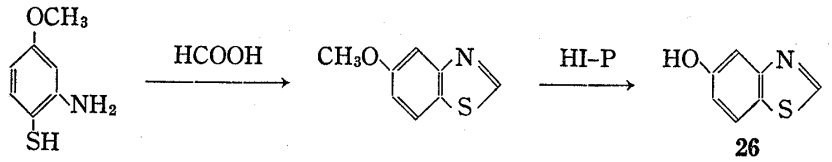


The starting material of **11**, 4-hydroxybenzothiazole was also obtained by the same procedure described above.[13]

The synthesis of 5-hydroxybenzothiazole (**26**) which is the starting material of **9** and **10** has been reported by Davies, *et al.*[14] Neverthless, according to their process 5-hydroxybenzothiadiazole was formed as a by-product during diazotization of 5-aminobenzothiazole.[14]

11) W.A. Boggust and W. Cocker, *J. Chem. Soc.*, **1949**, 355.
12) The process for obtaining 6-methoxybenzothiazole was unknown at the beginning of our investigation, but has been described by Friedman, *et al.* in a paper published (M.D. Friedman, P.T. Stotter, T.H. Porter and K. Folkers, *J. Med. Chem.*, **16**, 1314 (1973)) since the completion of this part of our work. Diazotization and reduction process was essentially the same as their process but there is a little difference in detailed experimental conditions.
13) H. Erlenmeyer and H. Ueberwasser, *Helv. Chim. Acta*, **25**, 515 (1942).
14) J.H. Davies and P. Kirby, *J. Chem. Soc.* (*C*), **1967**, 321.

We synthesized 26 from 2-amino-4-methoxythiophenol[15]; 2-amino-4-methoxythiophenol was converted to the benzothiazole derivative by using HCOOH and subsequent acid hydrolysis of the resulting 5-methoxybenzothiazole gave **26** in 70.3% yield.



26

We were interested in the pharmacology of **7**, especially in the relation of its β-blocking activity with its antiarrhythmic activity. We attempted to resolve **7** to its optical active forms but attempted resolution of **7** was unsuccessful because **7** did not form crystalline salt with various reagents for resolution.

Biological Results

β-Adrenergic blocking activity was determined with guinea-pig atrial preparations. Isolated guinea-pig atria were suspended in physiological salt solution maintained at 37° and oxygenated with 95% O_2 and 5% CO_2. Composition of the physiological salt solution used was as follows (in mM): NaCl 135, KCl 5, $CaCl_2$ 2, $MgCl_2$ 1, $NaHCO_3$ 15 and glucose 5.5. Isometric contractions were measured with a force displacement transducer (Nihon Kohden, Model SB 1T) and recorded on an ink-writing oscillograph (Nihon Kohden, Model RM-150); rate of contractions was electrically measured (Nihon Kohden, RT-2).

In the first step of the screening, the compounds were tested for the activities to inhibit the increases in rate and force of the contractions produced by a single dose of isoproterenol (3×10^{-8} M, a concentration producing approximately 80% of the maximum effect); two atria were used for each compound. As a result of this step of the experiments, six of the

Table IV. β-Adrenergic Blocking Actions of the Compounds tested in the Guinea-pig Atria

Compd.	β-Blocking action in guinea-pig atria	
	pA_2	N
1	*a*)	
2	*a*)	
3	*a*)	
4	*a*)	
5	*a*)	
6	*a*)	
7	7.55±0.12*b*)	6
8	6.69±0.10	5
9	6.61±0.06	4
10	6.90±0.21	6
11	7.32±0.06	4
12	6.25±0.05	4
Propranolol	8.20±0.1	5
Sotalol	6.80±0.1	4

a) Compounds were substantially inactive. The highest dose tested was 5×10^{-5} M.
b) Values are mean±SE.

15) R.L. Dannley and D.A. Zazaris, *Can. J. Chem.*, **43**, 2610 (1965).

compounds tested (**7**—**12**, in Table I) were found to be considerably potent, while the rest of the compounds were very weak in the β-adrenergic blocking activity when compared with sotalol. Therefore, pA_2 values for these compounds were determined on the basis of the shift of dose-response curve to isoproterenol. As shown in Table IV, pA_2 values for these compounds were higher than 6; 7.6 for compound **7**, 6.7 for compound **8**, 6.6 for compound **9**, 6.9 for compound **10**, 7.3 for compound **11** and 6.3 for compound **12**. Since pA_2 value for sotalol determined in the present series of experiments was 6.8, compounds **7**, **10** and **11** were more potent in the β-adrenergic blocking activity than sotalol. Compounds **8**, **9** and **12** were almost equipotent to sotalol.

The compounds were also tested on their hypotensive activities. Male rats (150—180 g) were anesthetized and a cannula was fixed in the carotid artery of each rat. After the operation (3—4 days), blood pressure was led to the pressure transducer through the cannula and recorded on an ink-writing oscillograph. Animals were unanesthetized and freely movable during the blood pressure measurement. As a result, compound **8** was found to have a relatively strong hypotensive action. In the experiments with twelve animals, the mean control blood pressure was 117.8±1.8 mmHg before the drug administration. The blood pressure reduced to 110.5±2.0, 104.3±2.5 and 99.2±2.9 mmHg, 1, 3 and 5 hours after the oral administration of 50 mg/kg of compound **8**, respectively. In the present series of experiments, the control blood pressure (122±2.7 mmHg) reduced to 83±1.6, 89±2.3 and 94±1.7 mmHg, 1, 3 and 5 hours after the oral administration of 5 mg/kg of hydralazine (number of the experiments were 16), respectively. Therefore, 50 mg/kg of compound **8** showed about the same degree of hypotensive action as that of 5 mg/kg of hydralazine at 5 hours after the oral administration.

Discussion

Since only a limited number of the compounds were examined in the present study, detailed discussions on the structure-activity relationships are impossible. However, the following may be pointed out. Among the compounds with various nuclei tested in the present study, all compounds with benzothiazole nucleus showed significant β-adrenergic blocking activity, and the rest of the compounds were free from substantial β-blocking activity with one exception (compound **12**). With respect to the side chain, isopropyl group is better for producing β-blocking activity than tertially butyl group, when the side chain is attached to six position of benzothiazole structure. On the contrary, it is interesting that tertially butyl substituent is better than isopropyl substituent for the β-blocking action, when the side chain is connected to five position of the benzothiazole ring. A compound with a side chain at four position of benzothiazole nucleus compound **11** also showed a potent β-blocking action.

Direct cardiac depressant action was found with the compounds **1**, **3**, and **9**—**12**. Compound **5** produced a slight cardiac acceleration. Rest of the compounds tested were free from direct cardiac action. No structural correlation could be found with respect to the direct cardiac actions of the compounds tested.

Compound **7** was reported elsewhere in more detail on its general pharmacology[16] and its antiarrhythmic action.[17] The antiarryhythmic activities of the rest of the compounds tested were weaker than those of compound **7** in the first screening. Compound **7** antagonized ouabain-induced arrhythmias in normal and bilaterally vagotomized guinea pigs: its antagonistic activity was equal to that of propranolol. The antiarrhythmic activity of compound **7** paralleled its β-blocking activity in the isolated preparations but not in the intact animals.

16) Y. Kasuya, Y.F.-Chiu-Wei, K. Goto, and M. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **25**, 2105 (1977).
17) H. Tatsuno, K. Goto, K. Shigenobu, and Y. Kasuya, *Europ. J. Pharm.*, **40**, 145 (1976).

Experimental

Melting points and recrystallizing solvents given in the tables are usually not reported in the text. Hydrogenations were carried out at room temperature and atmospheric pressure unless stated otherwise. The melting points for the samples were determined with a Mitamura hot-stage apparatus and were not corrected. Infrared spectra were recorded on a Hitachi-215 Grating Infrared spectrophotometer and Ultraviolet spectra on a Hitachi EPS-3 spectrophotometer. Proton magnetic resonance (PMR) spectra were determined on a Varian T-60 spectrometer. Chemical shifts were reported in δ values relative to Me_4Si as external standard (in D_2O) and as internal standard (in $CDCl_3$ and CCl_4). Carbon magnetic resonance (CMR) spectra were obtained at 25.1 MHz on a JEOL-JNM-PS-100 spectrometer, operating in a Fourier transform mode with dioxane (in D_2O) or Me_4Si (in $CDCl_3$) as internal standard. Low resolution mass spectra were obtained on a JEOL-JMS-OISG-2 mass spectrometer. Thin-layer chromatography was carried out on silica gel plates (Silica gel 60, F_{254}, Merck).

1-Isopropylamino-3-(bornan-2-yloxy)-propan-2-ol (2)——Powdered $NaNH_2$ (39.2 g, 1 mol) was added to a stirred solution of borneol (144.6 g, 1 mol) in toluene (200 ml). The mixture was heated to reflux for 3 hr and then allylchloride (306 g, 4 mol) was added dropwise to the mixture. The heating at reflux was continued further for 1 hr and cooled. The precipitates were removed by filtration and the filtrate was washed twice with H_2O. Evaporation of the solvent gave crude 3-(bornan-2-yloxy)-propen-1. Distillation of the crude product gave 138.2 g (0.71 mol, 71%) of colorless oil: bp 93—95° (11 mmHg), IR ν_{max}^{neat} cm^{-1}: 1650, 995, 930.

To a stirred solution of allylether (129 g, 0.66 mol), 30% H_2O_2 (94 g, 0.83 mol), CH_3CN (34 g, 0.83 mol) and $Na_2HPO_4 \cdot 12H_2O$ (0.1 N, 8.3 ml) in MeOH (600 ml) was added dropwise NaOH (0.5 N, 58 ml) over period of 4 hr with warming (50—53°). The mixture was further stirred for 1 hr at the same temperature. The reaction mixture was concentrated to 200 ml and the solution was diluted with H_2O and extracted with ether. The extract was dried and evaporated *in vacuo*, leaving 132.5 g of colorless oil. The oil was distilled and the fraction boiling at 103—104° (4 mmHg) was collected. 63.8 g (0.30 mol, 46%) of **13** was yielded. IR ν_{max}^{neat} cm^{-1}: 845, 860 (epoxide). NMR (CCl_4) δ: 0.75, 0.77 (9H, s, ring $C\underline{H}_3$), 0.78—2.2 (8H, m, ring proton), 2.4—2.75 (2H, m, $\overline{C\underline{H}\text{–}C\underline{H}_2O}$), 2.9—3.05 (1H, m, $\overline{C\underline{H}\text{–}CH_2O}$), 3.35—3.8 (2H, m, $OC\underline{H}_2\overline{C\underline{H}\text{–}CH_2O}$). *Anal.* Calcd. for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.36; H, 10.54.

13 (24.5 g, 0.12 mol) and iso-$PrNH_2$ (25 g, 0.42 mol) in EtOH (100 ml) was heated under reflux for 2 hr. The reaction mixture was concentrated to dryness *in vacuo*. HCl (1 N, 130 ml) was added to the oily residue and the mixture was extracted twice with ether. The aq. acidic solution was made alkaline with 3 N NaOH and extracted with EtOAc. The extract gave **2** as an oil which was converted to its hydrochloride: yield 27.5 g (0.09 mol, 75%). IR ν_{max}^{KBr} cm^{-1}: 3250, 1130. NMR (D_2O) δ: 1.35, 1.4 (9H, s, ring $C\underline{H}_3$), 1.75 (6H, d, $NCH(C\underline{H}_3)_2$), 1.4—2.3 (8H, m, ring proton), 3.5—3.75 (2H, m, $CHOHC\underline{H}_2N$), 3.75—4.1 (3H, m, $OC\underline{H}_2C\underline{H}OH$), 4.0 (1H, m, $NC\underline{H}(CH_3)_2$). *Anal.* Calcd. for $C_{16}H_{32}ClNO_2$: C, 60.52; H, 10.16; N, 5.04. Found: C, 60.74; H, 10.15; N, 5.31.

1-Isopropylamino-3-(1-phenylethoxy)-propan-2-ol (4)——Using the procedure for synthesizing **2**, α-phenylethanol (61 g, 0.5 mol), $NaNH_2$ (23.4 g, 0.6 mol) and allyl chloride (53.5 g, 0.7 mol) yielded 53 g (0.33 mol, 65.4%) of 3-(1-phenylethoxy)-propen-1: bp 93—94° (18 mmHg). IR ν_{max}^{neat} cm^{-1}: 1650, 1100, 995, 930.

A solution of 3-(1-phenylethoxy)-propen-1 (18 g, 0.11 mol) and N-bromosuccinimide (19.8 g, 0.11 mol) in H_2O (29 ml) and THF (100 ml) was stirred for 5 hr at room temperature. The THF was evaporated and the oily product was extracted with ether. Evaporation of the extract gave bromohydrin (27.2 g, 0.105 mol, 95.5%): bp 163—167° (2 mmHg). IR ν_{max}^{neat} cm^{-1}: 3400.

Crude bromohydrin (27.2 g, 0.105 mol) was added dropwise to NaOH solution (8 g NaOH/20 ml H_2O) at 10—15°. The mixture was stirred for 2 hr at 10°. Crude **15** was isolated by ether extraction. Distillation of the crude product gave 14 g (0.079 mol, 74.8%) of pure **15**: bp 131—132° (18 mmHg). IR ν_{max}^{neat} cm^{-1}: 1100, 850. NMR (CCl_4) δ: 2.2—2.7 (2H, m, $\overline{C\underline{H}\text{–}C\underline{H}_2O}$), 3.1 (1H, m, $\overline{C\underline{H}\text{–}CH_2O}$), 3.4 (3H, double doublet, $C\underline{H}_3$), 3.1—3.6 (2H, m, $OC\underline{H}_2\overline{C\underline{H}\text{–}CH_2O}$), 4.4 (1H, octet, $CH_3C\underline{H}O$), 7.23 (5H, s, arom.). *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.38; H, 7.88.

15 (5.4 g, 0.03 mol) and iso-$PrHN_2$ (17.7 g, 0.3 mol) in EtOH (40 ml) were heated under reflux for 2 hr. Crude **4** was obtained by the same procedure as described for synthesizing **2**. 5.61 g (0.024 mol, 78.9%) of **4** was yielded as an oil. NMR (CCl_4) δ: 1.0 (6H, d, $CH(C\underline{H}_3)_2$), 1.8 (3H, d, CH_3), 2.3—2.65 (2H, m, $CHOHC\underline{H}_2N$), 2.7—3.3 (3H, m, $C\underline{H}_2C\underline{H}OH$), 3.5—3.85 (1H, m, $C\underline{H}(CH_3)_2$), 4.35 (1H, q, $CH_3C\underline{H}O$), 7.2 (5H, s, arom.). The base was converted to its oxalate in acetone. *Anal.* Calcd. for $C_{15}H_{24}NO_4$: C, 63.81; H, 8.57; N, 4.96. Found: C, 63.72; H, 8.88; N, 4.97.

1-Isopropylamino-3-[4-(2,5-dioxopyrrolidin-1-yl)-phenoxy]-propan-2-ol (6)——A mixture of *p*-hydroxyphenylsuccinimide[18] (38.2 g, 0.2 mol), epichlorohydrin (56 g, 0.6 mol) and K_2CO_3 (46 g, 0.3 mol) in acetone

18) Piutti, *Ber.*, **29**, 84 (1896).

(300 ml) was refluxed for 12 hr. After cooling the solid was filtered off. The filtrate was evaporated to dryness under reduced pressure. To the residue was added toluene and the solution was washed twice with H_2O and dried and evaporated. The residual solid was recrystallized twice from EtOH to give 24 g (0.097 mol, 48.5%) of **16**. IR ν_{max}^{neat} cm^{-1}: 1770, 1705, 860. NMR ($CDCl_3$) δ: 2.6—3.0 (2H, m, $\underline{CH}$–$\underline{CH_2}O$), 2.83 (4H, s, $COCH_2CH_2CO$), 3.32 (1H, m, $\underline{CH}$–CH_2O), 3.6—4.4 (2H, m, $OCH_2\underline{CH}$–CH_2O), 7.07 (4H, q, arom.), *Anal.* Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.16; H, 5.35; N, 5.49.

A solution of **16** (10 g, 0.04 mol) and iso-$PrNHCH_2Ph$ (24.1 g, 0.162 mol) in EtOH (100 ml) was heated for 3 hr 80°. After cooling, EtOH and excess iso-$PrNHCH_2Ph$ were evaporated under reduced pressure. Work up the same as in the previous description gave a isopropylbenzylaminopropanol derivative (11.9 g, 0.03 mol, 75%) as an oil.

A solution of the above compound (16 g, 0.04 mol) and concentrated HCl (3.5 ml) in MeOH (300 ml) was hydrogenated over Pd/C (3%, 3 g) at room temperature and at atmospheric pressure. White powder (12 g) which was obtained by usual work up of the reaction mixture, was recrystallized twice to give 3.8 g (0.011 mol, 27.7%) of **6**. IR ν_{max}^{KBr} cm^{-1}: 3360, 1708, 1700. NMR (D_2O) δ: 1.83 (6H, d, $CH(C\underline{H_3})_2$), 3.35 (4H, s, $COC\underline{H_2}C\underline{H_2}CO$), 3.5 (2H, m, $CHOHC\underline{H_2}N$), 3.85—4.2 (1H, m, $C\underline{H}(CH_3)_2$), 4.5—4.9 (3H, m, $OC\underline{H_2}C\underline{H}OH$), 7.6 (4H, s, arom.). *Anal.* Calcd. for $C_{16}H_{24}ClN_2O_4$: C, 56.31; H, 6.82; N, 8.21. Found: C, 56.06; H, 6.76; N, 8.17.

1-Isopropylamino-3-(benzothiazol-6-yloxy)-propan-2-ol (7)——A mixture of **25** (4 g, 0.026 mol) epichlorohydrin (8.5 g, 0.092 mol) and K_2CO_3 (5.5 g, 0.04 mol) in acetone (80 ml) was heated to reflux with stirring for 10 hr. The precipitates were removed by filtration and the filtrate was evaporated under reduced pressure. To the residual oil was added EtOH (100 ml) and undissolved resinous solid was filtered off with charcoal. Removal of the solvent *in vacuo* gave 3.86 g (0.019 mol, 71.7%) of **17** as a pale reddish oil. IR ν_{max}^{neat} cm^{-1}: 850 (epoxide).

A solution of **17** (4.7 g, 0.023 mol) and iso-$PrNH_2$ (6 g, 0.1 mol) in EtOH (10 ml) was refluxed for 1 hr. The solution was evaporated to dryness and the residue was crystallized from PhH-ligroine. 4.75 g (0.018 mol, 77.5%) of **7** was yielded; mp 101—102°, *Rf* 0.17 (MeOH–$CHCl_3$, 1: 3, on silica gel F). The base was converted to its succinate in acetone. NMR (D_2O) δ: 1.75 (6H, d, $CH(C\underline{H_3})_2$), 3.5—4.17 (3H, m, $C\underline{H_2}NHC\underline{H}$-$(CH_3)_2$), 4.26—4.84 (3H, m, $OC\underline{H_2}C\underline{H}OH$), 6.83—7.67 (3H, m, arom.), 9.7 (1H, s, N=C$\underline{H}$–S). UV $\lambda_{max}^{H_2O}$ nm (ε): 255 (5.32×10^3). *Anal.* Calcd. for $C_{15}H_{21}N_2O_4S$: C, 55.37; H, 6.51; N, 8.61. Found: C, 55.66; H, 6.75; N, 8.52.

Isopropylamino-3-(benzothiazol-5-yloxy)-propan-2-ol (9)——Using the procedure for synthesizing **7**, **26** (2.5 g, 0.017 mol), epichlorohydrin (15.9 g, 0.116 mol) and K_2CO_3 (4.6 g, 0.033 mol) in acetone yielded **18** (3.3 g, 0.0124 mol, 72.9%). IR ν_{max}^{neat} cm^{-1}: 850 (epoxide).

Compound **9** was obtained by the reaction of **18** (3.3 g, 0.0159 mol) with iso-$PrNH_2$ 5.6 g (0.095 mol) as described for **7**: yield 3.1 g (73%); *Rf* 0.24 ($CHCl_3$–MeOH, 1: 1), mp 111.5—112.5° (from PhH-ligroine). The base was converted to its succinate in acetone: *Rf* 0.53 (*n*-BuOH–AcOH–H_2O, 4: 1: 1), NMR (D_2O) δ: 1.55 (6H, d, $CH(C\underline{H_3})_2$), 3.3—4.2 (3H, m, $C\underline{H_2}NHC\underline{H}(CH_3)_2$), 4.1—4.8 (3H, m, $OC\underline{H_2}C\underline{H}OH$), 7.0—8.05 (3H, m, arom.), 9.3 (1H, s, N=C$\underline{H}$–S). UV $\lambda_{max}^{H_2O}$ nm (ε): 255 (5.35×10^3). *Anal.* Calcd. for $C_{15}H_{21}N_2O_4S$: C, 55.37; H, 6.51; N, 8.61. Found: C, 55.21; H, 6.55; N, 8.59.

1-Isopropylamino-3-(benzothiazol-4-yloxy)-propan-2-ol (11)——Using the procedure described above, free **11** was obtained as an oil in 85% yield from 4-hydroxybenzothiazole[13]: *Rf* 0.35 ($CHCl_3$–MeOH, 1: 1). The base was converted to its succinate in acetone. NMR (D_2O) δ: 1.45 (6H, d, $CH(C\underline{H_3})_2$), 3.3—4.1 (3H, m, $C\underline{H_2}NHC\underline{H}(CH_3)_2$), 4.0—4.8 (3H, m, $OC\underline{H_2}C\underline{H}OH$), 6.8—7.7 (3H, m, arom.), 9.43 (1H, s, N=C$\underline{H}$–S). UV $\lambda_{max}^{H_2O}$ nm (ε): 255 (5.35×10^3). *Anal.* Calcd. for $C_{15}H_{21}N_2O_4S$: C, 55.37; H, 6.51; N, 8.61. Found: C, 55.42; H, 6.64; N, 8.48.

1-Isopropylamino-3-(1*H*-benzotriazol-5-yloxy)-propan-2-ol (12)——4-Acetoamino-3-nitrophenol[9] (47 g, 0.24 mol) was added to a stirred solution of CH_3ONa (Na 5.4 g in 60 ml of MeOH). The mixture was warmed for 1 hr and epichlorohydrin (111 g, 1.2 mol) was added to the solution. The mixture was heated to reflux for 3 hr and evaporated. The residue was dissolved in $CHCl_3$. The solution was washed with H_2O, dried and evaporated to give crude **20**: yield 17.9 g (0.071 mol, 29.6%). IR (KBr) ν_{max}^{KBr} cm^{-1}: 3350, 1703, 1560, 1035, 870. *Anal.* Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.37; H, 4.81; N, 11.48.

20 (16.9 g, 0.067 mol) and iso-$PrNH_2$ (40 g, 0.67 mol) in EtOH (400 ml) was heated at reflux for 3 hr. White powder which was obtained by usual work up of the reaction mixture, was crystallized from EtOH. 18 g (0.058 mol, 86.3%) of isopropylaminopropanol derivative was yielded. IR ν_{max}^{KBr} cm^{-1}: 3350, 3260, 1685, 1515, 1030. NMR ($CDCl_3$) δ: 1.13 (6H, d, $CH(C\underline{H_3})_2$), 2.3 (3H, s, $NHCOC\underline{H_3}$), 2.7—3.1 (5H, m, $CHOHC\underline{H_2}N$, $O\underline{H}$, $N\underline{H}$-iso-Pr), 3.95—4.1 (2H, m, $OC\underline{H_2}CHOH$), 3.9—4.15 (1H, m, $C\underline{H}(CH_3)_2$), 7.1—8.7 (3H, m, arom.), 10.5 (1H, s, $N\underline{H}COCH_3$). *Anal.* Calcd. for $C_{14}H_{21}N_3O_5$: C, 54.01; H, 6.80; N, 13.50. Found: C, 54.33; H, 6.81; N, 13.49.

A solution of the derivative (7.5 g, 0.024 mol) in MeOH (500 ml) was hydrogenated over Raney-Ni (5 g) at 40° at atmospheric pressure. The mixture was filtered. The filtrate was evaporated to dryness and crude **24** was recrystallized twice from EtOH: yield 3.9 g (0.0139 mol, 57.8%). IR ν_{max}^{KBr} cm^{-1}: 3280, 1650, 1620. *Anal.* Calcd. for $C_{14}H_{23}N_3O_3$: C, 59.76; H, 8.24; N, 14.94. Found: C, 59.43; H, 8.27; N, 14.84.

To a stirred solution of **24** (2.6 g, 9.2 mmol) in HCl–H_2O (12 N HCl 3 ml, H_2O 40 ml) was added dropwise $NaNO_2$ solution ($NaNO_2$ 0.64 g/H_2O 4.5 ml) at 0°. The mixture was further stirred for 1 hr. Then the pH of the reaction mixture was adjusted at 8.6. The reaction mixture was additionally stirred for 1 hr and evaporated to dryness *in vacuo*. Crude **12** was obtained by $CHCl_3$ extraction and purified by chromatography on florisil (100 g) in MeOH–$CHCl_3$ (1: 3). The base was converted to its HCl salt as usual manner: yield (1.03 g, 3.2 mmol, 34.6%, as 2HCl salt): *Rf* 0.47 (*n*-BuOH–AcOH–H_2O, 4: 1: 1). IR ν_{max}^{KBr} cm^{-1}: 1630, 1295, 1180. NMR (D_2O) δ: 1.83 (6H, d, $CH(C\underline{H}_3)_2$), 3.6—4.15 (3H, m, $C\underline{H}(CH_3)_2$, $CHOHC\underline{H}_2N$), 4.15—5.0 (3H, m, $OC\underline{H}_2C\underline{H}OH$), 6.8—7.9 (3H, m, arom.), CMR (D_2O) δ: 18.92, 19.31 (C-8), 47.60 (C-11), 52.09 (C-7), 66.38 (C-10), 70.42 (C-9), 93.74 (C-6), 117.39, 118.71 (C-2, C-3), 136—80 (C-4, C-5), 158.01 (C-1). *Anal.* Calcd. for $C_{12}H_{20}Cl_2N_4O_2$: C, 44.59; H, 6.24; N, 17.33. Found: C, 44.39; H, 6.18; N, 16.98.

Attempted Preparation of 12 from 1-Acetyl-5-hydroxybenzotriazole (21)——A mixture of **21** (3 g, 16.9 mmol), epichlorohydrin (1.9 g) and K_2CO_3 (1.17 g, 8.47 mmol) in acetone (20 ml) was heated under reflux for 1 hr. The precipitates were removed by filtration and the filtrate was evaporated under reduced pressure. To the residue H_2O and $CHCl_3$ were added. Two layers were separated. H_2O layer gave 5-hydroxybenzotriazole, mp 227—229° (lit[19] 228°), upon neutralization. The $CHCl_3$ layer was dried and evaporated to give crude **22** (2.5 g, 8.02 mmol) as an oil. The crude **22** was separated into compound A and B on preparative TLC (PLC plate silica gel 60, Merck) using benzene–methanol (6: 1) as developing solvent. Compound A (0.7 g, 2.2 mmol) and compound B (1.0 g, 3.2 mmol) were obtained. The physical properties of compound A and B were shown in Table III. *Anal.* (compound A) Calcd. for $C_{13}H_{14}N_3O_4Cl$: C, 50.09; H, 4.53; N, 13.48. Found: C, 50.11; H, 4.78; N, 13.22. *Anal.* (compound B) Calcd. for $C_{13}H_{14}N_3O_4Cl$: C, 50.09; H, 4.53; N, 13.48. Found: C, 50.12; H, 4.35; N, 13.43.

A solution of compound B (0.7 g, 2.2 mmol), iso-$PrNH_2$ (1.3 g, 22 mmol) in EtOH (3 ml) was refluxed for 3 hr. The reaction mixture was evaporated under reduced pressure. The residue was dissolved in MeOH (3 ml). To the solution 2 N NaOH (1 ml) was added. The solution was stirred for 3 hr at room temperature. The solution was diluted with H_2O and neutrized. The product was obtained by EtOAc extraction and converted to its HCl salt as usual manner. Recrystallization from iso-PrOH gave 0.4 g of **23**: mp 228—229° *Rf* 0.51 (*n*-BuOH–AcOH–H_2O, 4: 1: 1). NMR (D_2O) δ: 1.78 (6H, d, $CH(C\underline{H}_3)_2$), 3.5—3.85 (2H, m, $C\underline{H}_2NH$-iso-Pr), 3.9—4.1 (1H, m, $C\underline{H}(CH_3)_2$), 4.7—5.2 (3H, m, $NC\underline{H}_2C\underline{H}OH$), 7.1—8.0 (3H, m, arom.). CMR (D_2O) δ: 18.78, 19.26 (C-8), 47.79 (C-11), 52.09 (C-7, C-9), 66.91 (C-10), 93.93 (C-6), 111.98, 117.53 (C-2, C-3), 135.44 (C-5), 140.36 (C-4), 157.29 (C-1). *Anal.* Calcd. for $C_{12}H_{20}Cl_2N_4O_2$: C, 44.59; H, 6.24; N, 17.33. Found: C, 44.47; H, 6.37; N, 17.01.

6-Hydroxybenzothiazole (25)——To a stirred solution of 2-amino-6-methoxybenzothiazole (11.2 g, 0.062 mol) in H_2SO_4 (16.6%, 100 ml) was added dropwise $NaNO_2$ solution ($NaNO_2$ 4.5 g/H_2O 7 ml) at −10°. The mixture was stirred for 1 hr at the same temperature. HBF_4 solution (47%, 17.7 ml, 0.124 mol) was added to the mixture. The mixture was stirred for 2 hr at 0°. The precipitates were filtered and washed with cold H_2O. The cake was added to cold H_3PO_2 solution (50%, 60 ml). The mixture was stirred over night at room temperature and filtered with charcoal. The filtrate was neutralized and the product was obtained by EtOAc extraction and crystallized from ligroine. 3.6 g (0.022 mol, 35%) of 6-methoxybenzothiazole was yielded; mp 72—73° (lit[12] 72.5°).

A mixture of 6-methoxybenzothiazole (4.5 g, 27.2 mmol), AcOH (4.5 ml), HI (22.6 ml) and phosphorus red (0.5 g) was heated under reflux for 5 hr. The mixture was diluted with H_2O and filtered. The filtrate was neutralized and the crystals were filtered, washed with H_2O and recrystallized from EtOH–H_2O to give 3.5 g (23.2 mmol, 85.3%) of **25**: mp 190.5—191° (lit[11] 181—182°). *Anal.* Calcd. for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.26. Found: C, 55.64; H, 3.34; N, 9.12.

5-Hydroxybenzothiazole (26)——A mixture of 4-methoxy-2-aminothiophenol·HCl[15] (21.2 g, 0.11 mol), boric acid (30 g) and HCOOH (95%, 210 ml) was heated under reflux for 2.5 hr. The reaction mixture was cooled and diluted with H_2O. The solution was made alkaline and the product was obtained by PhH extraction. Oily 5-methoxybenzothiazole 15 g (0.091 mol, 82.7%) was yielded.

A mixture of 5-methoxybenzothiazole (15 g, 0.091 mol) and HI (48%, 120 g) was heated under reflux for 5 hr. Crude product was obtained by the sample procedure as described for synthesizing **25** and recrystallized twice from dilute EtOH: yield 11.7 g (0.077 mol, 85%): mp 156—157° (lit.[11] 155—156°). *Anal.* Calcd. for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.26. Found: C, 55.34; H, 3.67; N, 9.04.

1-Acetyl-5-hydroxybenzotriazole (21)——To a solution of 4-acetoamino-3-aminophenol (8.6 g, 51.7 mmol) in conc. HCl (9.15 ml) and H_2O (129 ml) was added a solution of $NaNO_2$ (3.58 g, 51.9 mmol) in H_2O (34.8 ml) at 0—5° with stirring. After the addition was completed, the mixture was further stirred for 1 hr. The precipitates were collected by filtration and washed with H_2O and dried. The crude product was recrystallized from benzene–ligroine. **21** (7.37 g, 41.6 mmol) was obtained in 80.5% yield: mp 147—149°. IR ν_{max}^{KBr} cm^{-1}: 1750. NMR (DMSO-d_6) δ: 2.97 (s, 3H, $COC\underline{H}_3$). *Anal.* Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.43; H, 4.17; N, 23.99.

19) K. Fries, H. Güterbock, and H. Kuhn, *Justus Liebigs Ann. Chem.*, **511**, 213 (1934).