The Reaction of 2-(ω-Chloroalkyl)benzimidazoles with Thiourea. Studies on Heterocyclic Compounds. I

*H. Ogura, T. Itoh, and Y. Tajika**

College of Pharmaceutical Sciences, Kitasato University and Research Laboratories, Chugai Pharmaceutical Co., Ltd.*

By reaction of the appropriate 2-(ω-chloroalkyl)benzimidazoles with thiourea, 2-(α-mercaptoalkyl)benzimidazoles (IV) have been prepared. The attempted preparation of 2-(β- and γ-mercaptoalkyl)benzimidazoles failed. β-Elimination was observed by alkaline treatment of *S*-[2-(2-benzimidazolyl)-propyl]isothiuronium chloride (VII), whereas 2-(γ-chlorobutyl)benzimidazoles did not give an isothiuronium chloride.

The antiviral activity of some benzimidazoles containing hydroxyl groups have been reported by O'Sullivan and Sadler (1) and they have shown that the presence of an intramolecular hydrogen bond is a feature common to all the highly active antiviral agents. Kakimoto and Sekikawa (2) have prepared 2-(mercaptomethyl)benzimidazole which showed potential antitubercular activity.

The present paper describes the attempted preparation of 2-(α-, β-, and γ-mercaptoalkyl)benzimidazole derivatives as potential antifungal, antiviral, antibacterial, and antitumor agents and as potential radio-protectors. It seemed desirable to extend this synthetic work in several directions in order to obtain compounds having potential physiological activity as well as to study the relative activities of compounds forming intramolecular hydrogen bonds.

The synthesis of 2-(α-mercaptoethyl)benzimidazoles (IVa) has been reported by Milner *et al.* (3). The objective of this work was to synthesize 2-(α-mercaptoethyl)benzimidazoles (IVa, IVb, IVc) and 2-(β-, and γ-mercaptoalkyl)-benzimidazoles. 2-(α-Hydroxyethyl) benzimidazoles (Ia, Ib, Ic) (4) were converted into the corresponding chloro compounds (IIa, IIb, IIc) by treatment with thionyl chloride. *S*-[1-(2-Benzimidazolyl)ethyl]isothiuronium chloride hydrochlorides (IIIa, IIIb, IIIc) were prepared from the corresponding chloro compounds (IIa, IIb, IIc) by adding thiourea, and hydrolysis of the resulting thiuronium compounds with 1 *N* sodium hydroxide solution to the corresponding 2-(α-mercaptoethyl)benzimidazoles (IVa, IVb, IVc). On the other hand, authentic 2-(α-mercaptoethyl)benzimidazoles (IVa, IVb, IVc) were prepared from thiolacetic acid and *o*-phenylenediamines by the method of Phillips (5). All of them (IVa, IVb, IVc) were identified by comparisons of mixed melting points, infrared, ultraviolet and nuclear magnetic resonance spectra. Further support for the structure (IVa) was obtained by a comparison of the mass spectrum (M^+, 178).

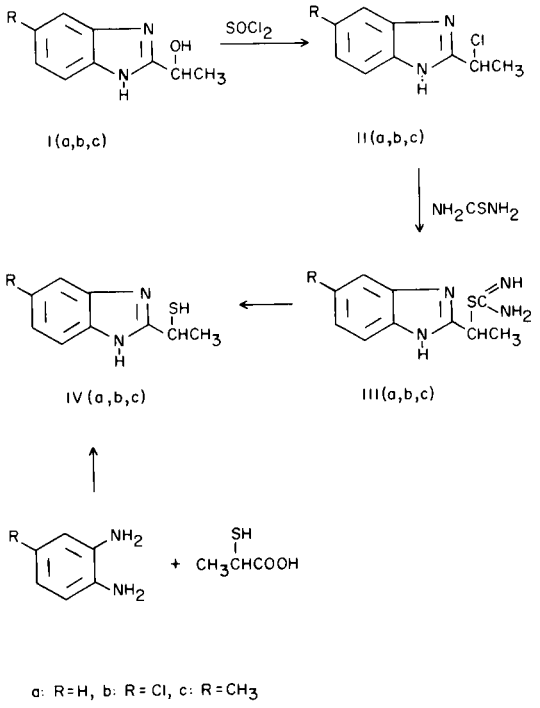
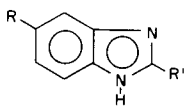


Figure 1

An attempted preparation of β-mercapto compounds was carried out by the reaction of *S*-[2-(2-benzimidazolyl)-propyl]isothiuronium chloride hydrochlorides (VIIa, VIIb, VIIc) and 1 *N* sodium hydroxide. 2-(β-Hydroxypropyl)-benzimidazoles (Va, Vb, Vc) were prepared from β-hydroxybutyric acid and *o*-phenylenediamine by the method of Phillips (5). The hydroxyl compounds (Va, Vb, Vc) were then converted into the corresponding chloro compounds (VIa, VIb, VIc) by treatment with thionyl chloride. The reaction of the chloro compounds (VIa, VIb, VIc) and

TABLE 2-Substituted Benzimidazoles



Compound	R	R′	M.p. (°C)	Yield (%)	Formula	Calcd.			Found			UV λ max (EtOH) mμ (log ε)
						C	H	N	C	H	N	
IIa	H	$CHCH_3$ | Cl	151 (a)	85	$C_9H_9ClN_2$ (c)	59.83	4.98	15.51	59.87	4.87	15.97	245 (4.05) 276 (4.06) 282 (4.06)
IIb	Cl	"	198	87	$C_9H_8Cl_2N_2 \cdot HCl$	42.94	3.18	11.13	43.12	3.24	11.38	249 (3.92) 284 (4.03) 290 (4.00)
IIc	CH_3	"	(b)	77								
IIIa	H	$CHCH_3$ | $SC(NH_2)^+Cl^-$	179 (d)	95	$C_{10}H_{12}N_4S \cdot HCl$	46.78	5.06	21.83	46.67	4.86	22.03	
IIIa	H	"	224 (d)		$C_{10}H_{12}N_4S \cdot 2HCl$	40.96	4.77	19.11	41.04	4.64	19.35	287 (3.96) 294 (3.95)
IIIb	Cl	"	212 (d)	90	$C_{10}H_{11}ClN_4S \cdot 2HCl$	36.64	3.96	17.09	36.87	3.90	17.16	286 (3.83) 293 (3.81)
IIIc	CH_3	"	223 (d)	85	$C_{11}H_{14}N_4S \cdot 2HCl$	42.97	5.21	18.23	43.14	5.01	18.04	286 (3.96) 294 (3.94)
IVa	H	$CHCH_3$ | SH	214	85	$C_9H_{10}N_2S$	60.67	5.66	15.73	60.67	5.45	15.67	254 (3.74) 281.5 (3.90)
IVb	Cl	"	165.5	82	$C_{15}H_{12}ClN_5O_7S$ (e)	40.77	2.74	15.85	40.78	2.83	15.53	
IVc	CH_3	"	231 (d)	75	$C_{16}H_{15}N_5O_7S$ (e)	45.60	3.57	16.67	45.74	3.60	16.41	
Va	H	CH_2CHCH_3 | OH	194	65	$C_{10}H_{12}N_2O$	68.16	6.86	15.90	68.25	6.62	15.88	241 (3.49) 270 (3.77) 277 (3.82)
Vb	Cl	"	196	67	$C_{10}H_{11}ClN_2O$	57.00	5.26	13.30	57.24	5.29	13.62	247 (3.55) 283 (3.62) 290 (3.62)
Vc	CH_3	"	208	63	$C_{11}H_{14}N_2O$	69.44	7.42	14.73	69.22	7.71	14.82	238 (4.19) 281 (4.36) 287 (3.61)
VIa	H	CH_2CHCH_3 | Cl	(b)	65								245 (3.76) 274 (3.82) 288 (3.86)
VIb	Cl	"	190	62	$C_{10}H_{10}Cl_2N_2$	52.40	4.36	12.27	52.60	4.40	12.38	245 (3.77) 278 (3.84) 292 (3.88)
VIc	CH_3	"	(b)	56								
VIIa	H	CH_2CHCH_3 | $SC(NH_2)^+Cl^-$	190 (d)	87	$C_{11}H_{14}N_4S \cdot HCl$	48.79	5.54	20.70	48.54	5.71	20.62	240 (4.70) 297 (4.61)
VIIb	Cl	"	180 (d)	85	$C_{11}H_{13}ClN_4S \cdot HCl$	43.27	4.59	18.36	43.35	4.69	18.56	242 (3.17) 304 (3.00)
VIIc	CH_3	"	192 (d)	83	$C_{12}H_{16}N_4S \cdot 2HCl$	44.85	5.60	17.44	45.06	5.68	17.36	
VIIIa	H	$CH{=}CHCH_3$	194	87	$C_{10}H_{10}N_2$	75.97	6.37	17.72	76.05	6.49	17.37	297 (4.54)
VIIIb	Cl	"	188	92	$C_{10}H_9ClN_2$	62.33	4.67	14.54	62.08	4.63	14.52	
VIIIc	CH_3	"	186.5	90	$C_{11}H_{12}N_2$	76.74	6.97	16.27	76.48	7.05	16.02	
XII	H	$CH_2CH_2CHCH_3$ | Cl	140	53	$C_{11}H_{13}ClN_2$ (c)	63.30	6.23	13.42	63.49	6.40	13.25	245 (3.76) 274 (3.82) 287 (3.86)

(a) Melting point was not reported by Siegart and Day (4). (b) Gummy solid. (c) NMR (p.p.m.): IIa, 9.45 (N*H*, singlet), 5.85 ($C\overset{Cl}{\overset{|}{H}}CH_3$, quartet), 2.45 ($CH_3$). XII, 9.50 (N*H*, singlet), 4.25 ($C\overset{Cl}{\overset{|}{H}}CH_3$, broad), 3.40 ($CH_2$, triplet), 2.50 ($CH_2$, multiplet), 1.50 ($CH_3$). (d) Decomposition. (e) Picrate, recrystallization from ethanol.

thiourea gave S-[2-(2-benzimidazolyl)propyl]isothiuronium chloride hydrochlorides (VIIa, VIIb, VIIc). The treatment of the thiuronium compounds with 1 *N* sodium hydroxide solution did not give compounds containing sulfur as shown by their elemental analysis. The products were shown by infrared and NMR spectra to possess C=C absorptions at 1610 ~ 1660 cm^{-1}, and 6 ~ 7 p.p.m. (multiplet) indicating an ethylenic system, and the band at 1.85 p.p.m. (doublet, J = 6 cps) was attributed to the terminal methyl group. From these results, it is obvious that a β-elimination reaction had occurred and 2-propenylbenzimidazoles (VIIIa, VIIIb, VIIIc) were obtained under alkaline conditions. Authentic 2-propylbenzimidazoles were synthesized by the method of Ried and Stahlhofen (6), and our products were shown to be identical by mixed melting point comparisons.

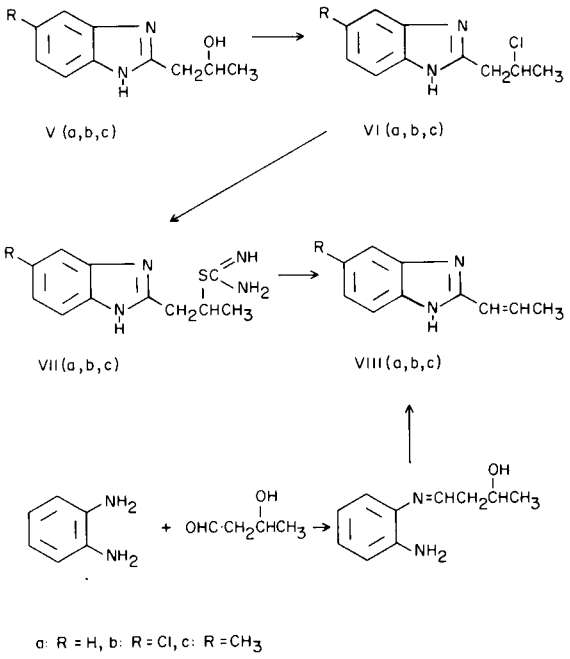


Figure II

The attempted preparation of the γ-mercapto compounds was carried out in a similar manner. The preparation of 2-(γ-hydroxypropyl)benzimidazole (XI) from methyl 3-hydroxyvalerate and *o*-phenylenediamine in 4 *N* hydrochloric acid by the method of Cescon and Day (7) failed. The reason for this failure may be due to the fact that methyl 3-hydroxyvalerate itself forms γ-valerolactone before the formation of the imidazole ring in hydrochloric acid solution can take place. 2-(γ-Ethyleneketalbutyl)benzimidazole (IX) was prepared from *o*-phenylenediamine and the ethyleneglycol ketal of methyl levulinate in the presence of sodium alkoxide. The ketal (IX) was readily hydrolyzed with 2 *N* hydrochloric acid into 2-(γ-oxobutyl)benzimidazole (X). Moreover, X was readily reduced with sodium borohydride in ethanol to form 2-(γ-hydroxybutyl)benzimidazole (XI). Although the chlorination was successful giving 2-(γ-chlorobutyl)-benzimidazole (XII), no reaction occurred with XII and thiourea under the same conditon as described above. It is assumed that the γ-halogeno compound is considerably more inactive than α- and β-halogeno compounds. Further treatment of the γ-halogeno compound with thiourea in methanol or ethanol gave only the starting material.

All of the products are being tested for phyisological activity and the results will be published elsewhere.

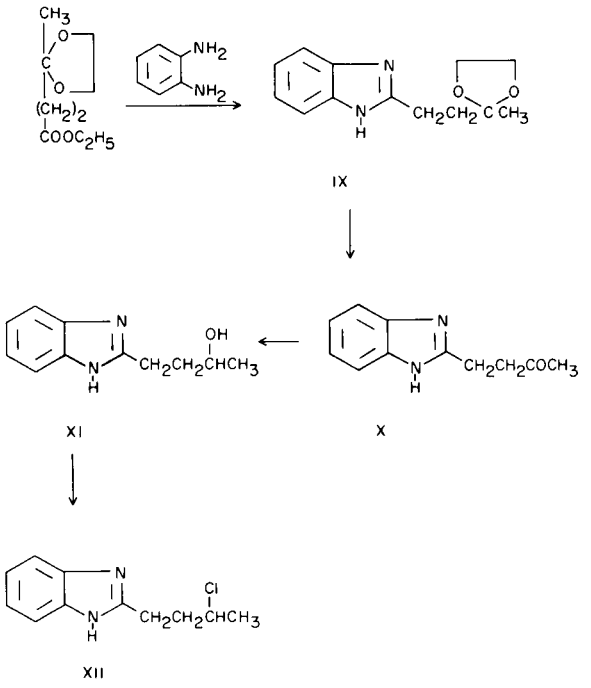


Figure III

EXPERIMENTAL

All melting points were determined on a Yanagimoto Micro-Melting Point Apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded at 60 Mc. with a Hitachi-Perkin H-60 spectrometer in deuteriochloroform, and tetramethylsilane as an internal reference. Mass spectra were taken with a Japan Electron Optics JMS-01S spectromater.

Preparation of 2-(α-, β-, and γ-Hydroxyalkyl)benzimidazoles.

These compounds, except XI, were prepared from the corresponding *o*-phenylenediamines (0.1 mole) and hydroxy acid (0.1 mole) by Phillips' method (5).

2-(γ-Ethyleneketalbutyl)benzimidazole (IX).

To a stirred solution containing sodium ethoxide (0.1 mole) in 150 ml. of ethanol was added *o*-phenylenediamine (0.1 mole)

and the ethyleneglycol ketal of methyl levulinate prepared by the usual method (8) (b.p. 82-83°/5 mm.) (0.1 mole). After evaporation of the ethanol, the reaction mixture was heated at 175° (oil bath) as a slurry with stirring for 3.5 hours. The slurry was cooled to room temperature, 60 ml. of ice water and 60 ml. of ethyl acetate were added and the mixture was stirred for 15 minutes. The ethyl acetate solution was separated, and the aqueous solution was extracted several times with 30 ml. of ethyl acetate. The combined organic layer was dried and the solvent removed *in vacuo*, leaving a syrup. Recrystallization of the product from methanol-water (charcoal) gave IX (35-40%) which melted at 174.5°, λ max (EtOH), mμ (log ε); 245 (3.81), 275 (3.86), 282 (3.91).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.24; H, 6.89; N, 12.06. Found: C, 67.17; H, 6.87; N, 12.15.

2-(γ-Oxobutyl)benzimidazole (X).

A solution of 20 g. of 2-(γ-ethyleneketalbutyl)benzimidazole in 100 ml. of 2 *N* hydrochloric acid was refluxed for 2 hours. When cooled the reaction mixture was made alkaline with dilute sodium hydroxide solution and extracted three times with ethyl acetate. The extract was dried and the solvent evaporated *in vacuo*. There was obtained 14 g. of 2-(γ-oxobutyl)benzimidazole (XI), m.p. 164.5°. ν max (potassium bromide), 1720 (C=O) cm^{-1}; λ max (EtOH) mμ (log ε); 245 (3.83), 275 (3.90), 282 (3.94).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.38; N, 14.88. Found: C, 69.83; H, 6.17; N, 14.80.

2-(γ-Hydroxybutyl)benzimidazole (XI).

To a solution of 1.88 g. of 2-(γ-oxobutyl)benzimidazole in 100 ml. of ethanol was added 0.38 g. of sodium borohydride under cooling with water. The reaction mixture was allowed to stand over-night at room temperature, then hydrolyzed with 10% hydrochloric acid. The reaction mixture was made alkaline with sodium bicarbonate and extracted several times with ethyl acetate. The extract was dried and filtered. The filtrate was evaporated *in vacuo* and 1.7 g. (89%) of 2-(γ-hydroxybutyl)benzimidazole (XI) was obtained as white leaflets after two recrystallizations from methanol, m.p. 123°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.37; N, 14.73. Found: C, 69.43; H, 7.23; N, 14.72.

Preparation of 2-(α-, β-, and γ-Chloroalkyl)benzimidazoles.

2-(α-, β-, and γ-Chloroalkyl)benzimidazoles were prepared from 0.1 mole of the corresponding hydroxyalkyl compound in 150 ml. of chloroform solution, to which was added 30 ml. of thionyl chloride with stirring under ice cooling. The reaction mixture was heated on a water bath for 2 ~ 3 hours. When cooled, dry ether was added until the hydrochloride was precipitated. After separation the hydrochloride was dissolved in cold water and the solution was slowly neutralized with sodium bicarbonate solution. The product was collected by filtration and then recrystallized from ethanol-water.

Preparation of 2-(α-, and β-Thiuroniumalkyl)benzimidazole Hydrochlorides.

The corresponding 2-(chloroalkyl)benzimidazole (0.1 mole) was mixed with 0.1 mole of thiourea and 50-60 ml. of acetone. After heating for 30 minutes, the mixture was allowed to stand over-night at room temperature. The crystals were then recrystallized from 50% aqueous ethanol, except IIIa was recrystallized from benzene.

Hydrolysis of Thiuronium Compounds.

The thiuronium compound (0.01 mole) was added to 10 ml. of sodium hydroxide solution and 10 ml. of methanol and the mixture was refluxed for 1 hour. Methanol was removed *in vacuo*, and the remaining aqueous solution was extracted with ethyl acetate which was dried over sodium sulfate. After removal of ethyl acetate *in vacuo*, the products (IVa, IVb, IVc) were purified by recrystallization. On the other hand, when precipitation occurred after methanol was removed, the resulting solid was collected by filtration and recrystallized from ethanol.

Acknowledgment.

The authors wish to thank Dr. T. Akiba, Director of Chugai Laboratory, and Dr. H. Kawabata, Director of Shoko Chemical Co. Ltd., for their helpful interest and encouragement in this work.

REFERENCES

(1) D. G. O. Sullivan and P. W. Sadler, Nature, 192, 341 (1961).
(2) S. Kakimoto and I. Sekikawa, *J. Chem. Soc. (Japan)*, 77, 78 (1955).
(3) E. S. Milner Jr., S. Snyder and M. M. Joullié, *J. Chem. Soc.*, 4151 (1964).
(4) W. R. Siegart and A. R. Day, *J. Am. Chem. Soc.*, 79, 4391 (1957).
(5) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).
(6) W. Ried and P. Stahlhofen, *Chem. Ber.*, **90**, 815 (1957).
(7) L. A. Cescon and A. R. Day, *J. Org. Chem.*, 27, 581 (1962).
(8) H. Ogura, *ibid.*, 25, 679 (1960).

Received November 1, 1967 Tokyo, Japan