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Derivatives of Thiazolo[3,2-*a*]benzimidazole[1,2] (Studies on Heterocyclic Compounds. II[3])

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Depending upon reaction conditions, 2-mercaptobenzimidazole (I) treated with α-chloroacetaldehyde dimethylacetal under acidic or with ethylene dichloride under alkaline conditions undergo cyclization (V and VIII). Thioethers (IX and XI) are treated with acetic anhydride in pyridine to yield 2-alkyl-3-oxothiazolidino[3,2-*a*]benzimidazoles (X) and *p*-substituted 3-phenylthiazolo[3,2-*a*]benzimidazoles (XII).

In the previous paper,[3] we reported the synthesis of 2-mercaptoalkylbenzimidazoles as potential physiological agents. This paper describes our efforts to extend this synthesis to thiazolo[3,2-*a*]benzimidazole (VI) and some of its aryl derivatives. 3-Oxothiazolidino [3,2-*a*]benzimidazole (III) was first prepared by Stephen and Wilson[5] from the ester (IIb: R=C_2H_5) by its treatment with sodium metal in benzene. This compound was also obtained by the dehydration of the acid (IIa: R=H) by treatment in acetic anhydride–pyridine mixture.[6] It has already been reported that the reaction of chloroacetone with 2-mercaptobenzimidazole afforded 3-methylthiazolidino[3,2-*a*]benzimidazole (IV).[7,8] Moreover, the reaction of 2-mercaptobenzimidazole with propynyl bromide has recently been reported to give the same compound (IV).[9] Derivatives of 3-methylthiazolo[3,2-*a*]benzimidazole were prepared by D' Amico, *et al.*[10]

The present paper describes the synthesis and physical properties of thiazolo[3,2-*a*] benzimidazoles. A mixture of 2-mercaptobenzimidazole (I) and ethyl monochloroacetate in the presence of sodium ethoxide gave ethyl 1-(2-benzimidazolylthio)acetate (IIb), melting at 96.5°, which was 23.5° higher than the reported value (73°).[5] The resulting ester (IIb) was cyclized with ethyl polyphosphate to 3-oxothiazolidino[3,2-*a*]-benzimidazole (III) in a good yield. On the other hand, the reaction of 2-mercaptobenzimidazole (I) with monochloroacetaldehyde dimethylacetal gave the product, 3-hydroxythiazolidino[3,2-*a*]benzimidazole (V), which showed the absence of a carbonyl group in its infrared (IR) spectrum. Oxidation of V with chromium trioxide afforded 3-oxothiazolidino[3,2-*a*]benzimidazole (III), which was identical in all respects with an authentic sample of III. Dehydration of V with polyphosphoric acid gave thiazolo[3,2-*a*]benzimidazole (VI), which was confirmed by nuclear magnetic resonance (NMR), ultraviolet absorption (UV), and IR spectra.

The reaction of 2-mercaptobenzimidazole (I) with ethylene dichloride in the presence of potassium hydroxide or sodium ethoxide furnished thiazolidino[3,2-*a*]benzimidazole (VII)

1) Presented before the 87th Annual Meeting of the Pharmaceutical Society of Japan, (April 1967), p. 425.
2) In preparation of this manuscript, A.E. Alper and A. Taurins [*Canadian J. Chem.*, **45**, 2903 (1967)] have published the similar report.
3) Part I: H. Ogura, T. Itoh and T. Tajika, *J. Heterocyclic Chem.*, **5**, 319 (1968).
4) Location: *Shiba Shirogane Sankocho, Minato-ku, Tokyo.*
5) H.W. Stephen and F.J. Wilson, *J. Chem. Soc.*, **1926**, 2531.
6) G.F. Buffin and J.D. Kendall, *J. Chem. Soc.*, **1956**, 361.
7) A.R. Todd, F. Bergol, and Karimullah, *Chem. Ber.*, **69B**, 217 (1936).
8) H. Andersag and K. Westphal, *Chem. Ber.*, **70**, 2035 (1937).
9) I. Iwai and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), **12**, 814 (1964).
10) J.J. D'Amico, R.H. Campbell and E.C. Guinn, *J. Org. Chem.*, **27**, 865 (1964).

and 1,2-bis(2-benzimidazolylthio)ethane (VIII), respectively. The melting point of VII (110°) was lower (32°) than the reported value (142°).[11] The authentic VII was prepared by the procedure of Mukherjee[11] in isopropanol, afforded the same compound (110°). NMR, UV, IR and mass (VII: M^+, *m/e* 176; VIII: M^+, *m/e* 326) spectral data are in agreement for the proposed structures VII and VIII.

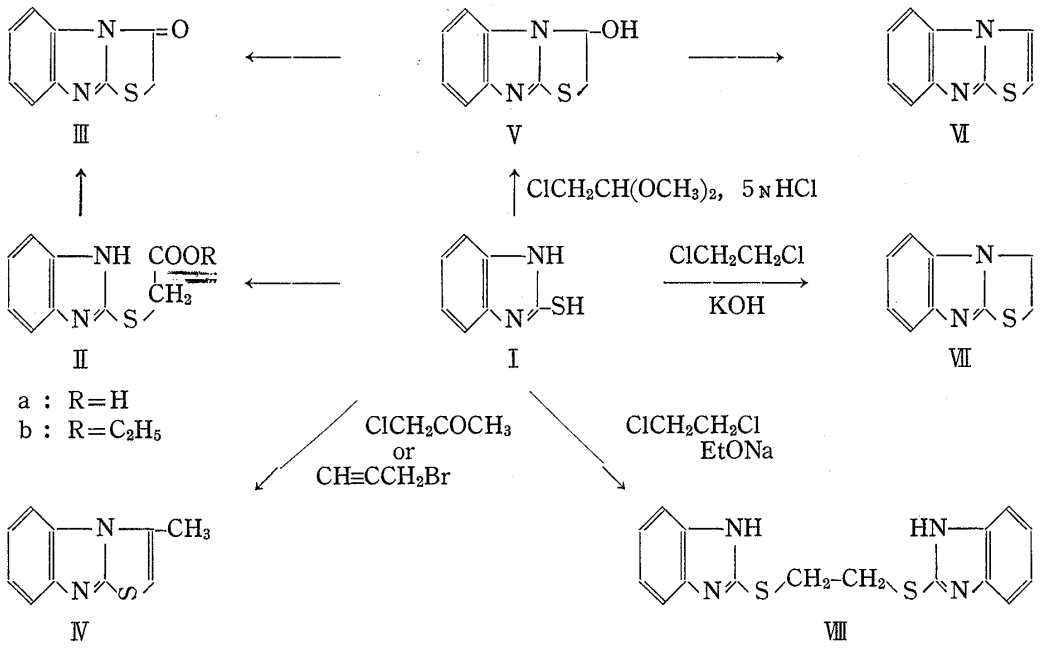

Fig. 1

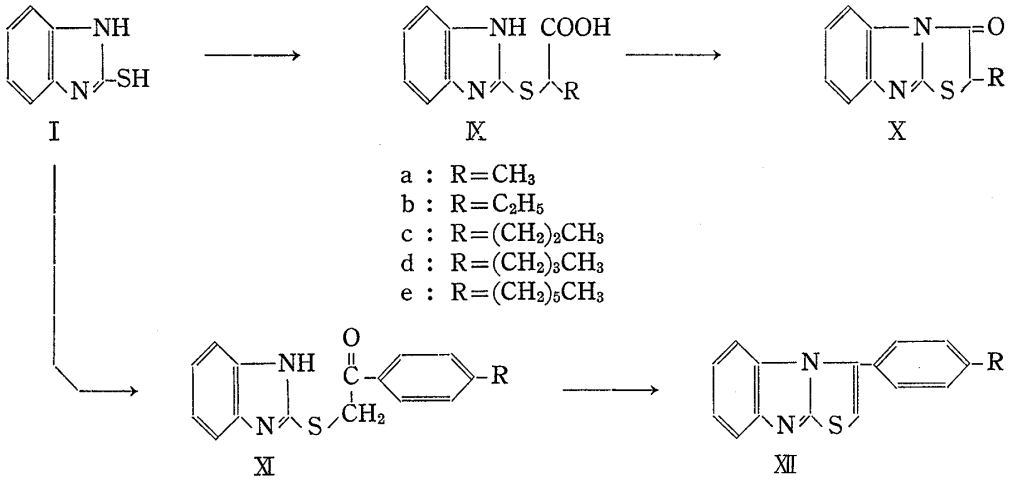

Fig. 2

The potassium salt of 2-mercaptobenzimidazole (I) was allowed to react with an α-halogenoalkylcarboxylic acid to form the sulfides ($IX_{a,b,c,d,e}$), and cyclization of the sulfides occurred readily with acetic anhydride-pyridine mixture to give 2-alkyl-3-oxothiazolidino-[3,2-*a*]benzimidazoles ($X_{a,b,c,d}$). The IR spectra of the products do not show the characteristic absorption bands of the imidazole group in the region of 2500—3200 cm^{-1}.[12] Physical properties of these intermediates and cyclized products are summarized in Table I.

11) S.L. Mukherjee, *Current Sci.* (India), **32**, 454 (1963) [*C.A.*, **59**, 15275 (1965)].
12) W. Otting, *Chem. Ber.*, **89**, 2887 (1956).

Table I. 2-Alkyl-3-oxothiazolidino[3,2-*a*]benzimidazoles

Compound	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)
Ⅸa	179	93	$C_{10}H_{10}O_2N_2S$							250 (3.83) 285 (4.16) 292 (4.16)
Ⅸb	172	90	$C_{11}H_{12}O_2N_2S$							250 (3.83) 285 (4.08) 292 (4.07)
Ⅸc	163	87	$C_{12}H_{14}O_2N_2S$	57.59	5.64	11.20	57.50	5.78	10.88	250 (4.33) 286 (4.65) 292 (4.63)
Ⅸd	162.5	85	$C_{13}H_{16}O_2N_2S$	59.08	6.10	10.60	59.05	5.97	10.65	250 (3.76) 285 (4.11) 292 (4.11)
Ⅸe	152	85	$C_{15}H_{20}O_2N_2S$	61.63	6.90	9.58	61.77	7.01	9.46	250 (3.82) 285 (4.05) 292 (4.05)
Ⅹa	101	79	$C_{10}H_8ON_2S$	58.82	3.92	13.72	58.92	4.06	13.56	239 (4.49) 283 (3.94) 292 (3.92)
Ⅹb	oil	82	$C_{11}H_{10}ON_2S$	60.57	4.57	12.85	60.81	4.74	12.94	240 (4.10) 283 (4.06) 292 (3.84)
Ⅹc	58	78	$C_{12}H_{12}ON_2S$	62.07	5.17	12.06	62.25	5.34	12.12	240 (4.62) 283 (4.08) 292 (4.01)
Ⅹd	90	75	$C_{13}H_{14}ON_2S$	63.38	5.69	11.37	63.35	5.85	11.37	240 (4.46) 283 (3.89) 292 (3.78)

NMR (ppm): Ⅹa, 1.85 (3H, doublet J=7 cps, $CHC\underline{H}_3$), 4.65 (1H, quartet J=7 cps, $C\underline{H}CH_3$)
Ⅹb, 1.12 (3H, triplet J=7 cps, $CHCH_2C\underline{H}_3$), 2.20 (2H, broad, $C\underline{H}CH_2CH_3$), 4.68 (1H, quartet J=9 cps, $C\underline{H}CH_2CH_3$)
Ⅹc, 1.01 (3H, triplet J=7 cps, $CH_2C\underline{H}_3$), 4.55 (1H, quartet J=8 cps, $C\underline{H}CH_2$–)
Ⅹd, 1.00 (3H, triplet), 4.60 (1H, quartet)

Table II. 3-Phenylthiazolo[3,2-*a*]benzimidazoles

Compound	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)
Ⅺa	174	100	$C_{15}H_{12}ON_2S$	67.20	4.42	10.44	67.04	4.57	10.56	247 (4.20) 284 (4.11) 291 (4.12)
Ⅺa	224.5		$C_{15}H_{12}ON_2S \cdot HCl$	59.11	4.28	9.18	59.24	4.39	9.03	
Ⅺb	220	100	$C_{15}H_{11}ON_2SCl \cdot HBr$	46.93	3.13	7.30	47.10	3.32	7.48	253 (4.17) 284 (4.07) 291 (4.07)
Ⅺc	202[a]	68	$C_{15}H_{11}ON_2SBr$	51.87	3.17	8.07	52.02	3.17	8.12	257 (4.26) 284 (4.16) 291 (4.14)
Ⅻa	140	85	$C_{15}H_{10}N_2S$	72.00	4.00	11.20	71.95	4.04	10.33	235 (4.30) 270 (4.15)
Ⅻb	203	77	$C_{15}H_9N_2SCl$	63.26	3.16	9.84	63.25	3.15	9.71	235 (4.29) 275 (4.12)
Ⅻc	197	72	$C_{15}H_9N_2SBr$	54.72	2.73	8.50	54.65	2.86	8.69	236 (4.37) 275 (4.18)

a) Recrystallized from dimethylformamide.

The treatment of 2–mercaptobenzimidazole (I) with phenacyl halide furnished phenacylmercaptans ($XI_{a,b,c}$) in a good yield, and their cyclization was carried out in polyphosphoric acid. Properties of the resulting 3–phenylthiazolo[3,2–*a*]benzimidazoles ($XII_{a,b,c}$) are summarized in Table II.

Experimental[13]

Preparation of Ethyl 1-(2-Benzimidazolylthio)acetate (IIb)——A mixture of 0.1 mole of 2–mercaptobenzimidazole and 0.1 mole of ethyl monochloroacetate in 150 ml of ethanol was heated under reflux for 3 hr, ethanol was removed by evaporation under reduced pressure, and the residue was treated with 60 ml of ice–water. The resulting solution was made alkaline with 10% sodium bicarbonate solution, the product was taken up in ethyl acetate, and the extract was dried over anhydrous sodium sulfate. After evaporation of ethyl acetate and the remaining solid was recrystallized from benzene. There was obtained 19.5 g of ethyl 1–(2–benzimidazolylthio)acetate, mp 96.5°. Reported mp 73°.[5] *Anal.* Calcd. for $C_{11}H_{12}O_2N_2S$: C, 55.93; H, 5.08; N, 11.86. Found: C, 56.08; H, 4.88; N, 12.06.

Preparation of 3-Oxothiazolidino[3,2-*a*]benzimidazole (III) (a) Cyclization of Ethyl 1-(2-Benzimidazolylthio)acetate (IIb)——Ethyl polyphosphate was prepared using essentially the same method described by Mukaiyama.[14] To 71 g of phosphorous pentoxide was added 31 g of ethanol, dropwise under cooling and with continuous stirring. The mixture was heated on a boiling water bath until phosphorous pentoxide completely dissolved. To the viscous homogeneous liquid so obtained, a solution of 5.4 g of ethyl 1–(2–benzimidazolylthio)acetate (IIb) in 25 ml of dimethylformamide was added, and the mixture was heated at 100° for 2 hr. After cooling to room temperature, the reaction mixture was poured into 250 ml of ice–water under vigorous stirring, the separated precipitate was collected by filtration, and recrystallized from methanol to give 3.8 g of 3–oxothiazolidino[3,2–*a*]benzimidazole (III) as needles, mp 181°. Reported mp 181°.[5]

(b) **By the Oxidation of 3-Hydroxythiazolidino[3,2-*a*]benzimidazole (V)**——A solution of 1.0 g of chromium trioxide in 10 ml of pyridine. The reaction flask was stoppered, the contents were mixed and allowed to stand at room temperature overnight. The reaction mixture was poured into water and extracted with chloroform. The chloroform solution was washed with water, dried over anhydrous magnesium sulfate, and concentrated. The remaining solid was recrystallized from methanol to 3–oxothiazolidino[3,2–*a*]-benzimidazole (III), mp 181°. The two compounds prepared by the methods (a) and (b) were identical by comparison of the mixed melting point, UV, and IR spectra.

3-Hydroxythiazolidino[3,2-*a*]benzimidazole (V)——A solution of 15.0 g of mercaptobenzimidazole and 6.3 g of chloroacetaldehyde dimethylacetal in 100 ml of 5 N hydrochloric acid was heated under reflux for 3 hr and then cooled. The precipitate was collected by filtration, dissolved in ethanol and the solution treated with 1 N sodium hydroxide. Removal of ethanol by distillation *in vacuo* gave the free base, which was recrystallized from methanol to 17.0 g of 3–hydroxythiazolidino[3,2–*a*]benzimidazole (V), mp 200—202° (decomp.). UV λ_{max}^{EtOH} mμ (log ε): 250 (3.96), 282 (4.02), 291 (4.06). *Anal.* Calcd. for $C_9H_8ON_2S$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.33; H, 4,08; N, 14.36.

V-HCl——mp 192° (deocmp.). *Anal.* Calcd. for $C_9H_8ON_2S$–HCl: C, 47.30; H, 3.94; N, 12.25. Found: C, 47.45; H, 3.92; N, 12.38.

Thiazolo[3,2-*a*]benzimidazole (VI)——A mixture of 4.2 g of 3–hydroxythiazolidino[3,2–*a*]benzimidazole (V) and polyphosphoric acid (prepared from 32 g each of 85% H_3PO_4 and P_2O_5) was heated at 150° for 4 hr. When cooled, the mixture was poured into ice–water, the pH was adjusted to 7 with ammonium hydroxide, and the separated precipitate was collected by filtration. Recrystallization from aqueous methanol gave 3.1 g (94%) of thiazolo[3,2–*a*]benzimidazole (VI) as needles, mp 140°. UV λ_{max}^{EtOH} mμ (log ε): 250 (3.76), 286 (3.84), 293 (3.94), 306 (3.75) (sh.). NMR, ppm: 6.62 (1H, s. C_2 or C_3 H), 6.71 (1H, s. C_2 or C_3 H). *Anal.* Calcd. for $C_9H_6N_2S$: C, 62.07; H, 3.44; N, 16.09. Found: C, 62.21; H, 3.43; N, 16.30.

Thiazolidino[3,2-*a*]benzimidazole (VII)——Thiazolidino[3,2–*a*]benzimidazole (VII) was prepared by essentially the same method as that of Mukerjee.[11] The product was recrystallized from methanol–water, mp 110°. Reported mp 142°.[11] UV λ_{max}^{EtOH} mμ (log ε): 251 (3.93), 286 (4.08), 293 (4.10). NMR, ppm: 3.97 (4H, m. $-CH_2CH_2-$). *Anal.* Calcd. for $C_9H_8N_2S$: C, 61.36; H, 4.54; N, 15.90. Found: C, 61.22; H, 4.61; N, 15.79.

1,2-Bis(2-benzimidazolylthio)ethane (VIII)——To a sodium ethoxide solution prepared from 2.3 g of sodium metal in 120 ml of absolute ethanol, 0.1 mole of 2–mercaptobenzimidazole was added. To the resulting solution, 0.1 mole of ethylene dichloride was added, the mixture was heated under reflux for 4 hr, and

13) All melting points are uncorrected. NMR spectra were recorded at 60 Mc with a Hitachi–Perkin H–60 spectrometer in deuteriochloroform, and tetramethylsilane was used as internal reference. Mass spectra were taken with a Japan Electron Optics JMS–OlS mass spectrometer operating with continuous ionization. Samples were introduced from a stainless steel inlet system at 150°.

14) T. Mukaiyama and T. Hata, *J. Am. Chem. Soc.*, **82**, 5339 (1960).

removal of the solvent by distillation *in vacuo* left 18 g of a solid. The product was recrystallized from methanol as needles, mp 244°. IR ν_{max}^{KBr}: 3100—2500 cm^{-1} (NH). UV λ_{max}^{EtOH} mμ (log ε): 250 (4.15), 285 (4.42), 292 (4.45). *Anal.* Calcd. for $C_{16}H_{14}N_4S_2$: C, 58.89; H, 4.29; N, 17.17. Found: C, 58.90; H, 4.37; N, 17.19.

Synthesis of 2-Alkyl-3-oxothiazolidino[3,2-*a*]benzimidazoles (X) (Table I). (a) **2-(2-Benzimidazolylthio)-alkylcarboxylic Acid (IX)**——To a mixture of 0.1 mole of 2-mercaptobenzimidazole, 150 ml of ethanol, and 28 ml (0.1 mole) of 20% potassium hydroxide, 2-bromoalkylcarboxylic acid (0.1 mole) was added, and the resulting mixture was heated under reflux for 4 hr. The reaction mixture was allowed to stand at room temperature over-night. The separated sodium bromide was removed by filtration, the filtrate was concentrated under a reduced pressure, and diluted with 30 ml of water. The precipitate so formed was recrystallized from methanol.

(b) **2-Alkyl-3-oxothiazolidino[3,2-*a*]benzimidazoles (X)**——A mixture of 0.05 mole of 2-(2-benzimidazolylthio)alkylcarboxylic acid (IX), 10 ml of acetic anhydride, and 20 ml of pyridine was heated at 95—100° for 3 hr. After removal of the solvent by distillation under reduced pressure, the product was distillated *in vacuo*. The product crystallized on standing in a refrigerator for several hours and was recrystallized from methanol.

Synthesis of 3-Phenylthiazolo[3,2-*a*]benzimidazoles (XII) (Table II). (a) **(2-Benzimidazolylthio)acetophenone (XI)**——A mixture of 0.1 mole of mercaptobenzimidazole and 0.1 ml of phenacyl bromide in 120 ml of ethanol was heated in a sealed tube for 3 hr on a water bath. After evaporation of ethanol, the residue was diluted with water and neutralized with diluted sodium hydroxide. The precipitated product was collected and recrystallized from methanol or ethanol.

(b) **3-Phenylthiazolo[3,2-*a*]benzimidazoles (XII)**——To a stirred polyphosphoric acid, prepared from 16 g of phosphorous pentoxide and 16 g of 85% phosphoric acid, 0.02 mole of XI was added and the mixture was heated at 150—170° for 3—4 hr with stirring. When cooled, the mixture was poured into ice-water, the pH was adjusted to 7 with ammonia, and the resulting precipitate was collected by filtration. The cyclized product (XII) was recrystallized from ethanol.