Aminothiazole Derivatives. II. A Facile Synthesis of Condensed 4-Aminothiazole Derivatives using α-Bromolactams and Thioamides

Osamu Uchikawa* and Tetsuya Aono

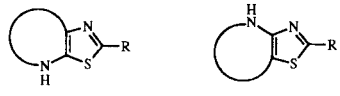
Pharmaceutical Research Laboratories, Pharmaceutical Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan

Received May 23, 1994

The reaction of an α-bromolactam with a thioamide was found to give a cyclic 4-aminothiazole derivative. Novel heterocyclic compounds such as 4,5,6,7-tetrahydrothiazolo[4,5-*b*]pyridines **10**, 5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*b*]azepines **11**, 4,5,6,7,8,9-hexahydrothiazolo[4,5-*b*]azocine **12** and 9,10-dihydro-4*H*-thiazolo[4,5-*b*][1]benzazepines **18** were thus prepared and the utility of this method in the construction of 4-aminothiazole-containing compounds was suggested.

J. Heterocyclic Chem., **31**, 1545 (1994).

In a previous paper [1], we reported a convenient procedure for the preparation of 5-aminothiazoles and their cyclic derivatives of the type A (Figure 1), from α-acylaminoamides and phosphorus pentasulfide or Lawesson's reagent. Among the compounds prepared therein, 4,5,6,7-tetrahydrothiazolo[5,4-*b*]pyridines, 5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*b*]azepines, 4,5,6,7,8,9-hexahydrothiazolo[5,4-*b*]azocine and 9,10-dihydro-4*H*-thiazolo[5,4-*b*]-[1]benzazepines have exhibited interesting biological activities, supposed to arise from their antioxidative activities [2]. These results led us to synthesize derivatives (type B) (Figure 1) of 4-aminothiazole and to test their biological activities.



Type A Type B

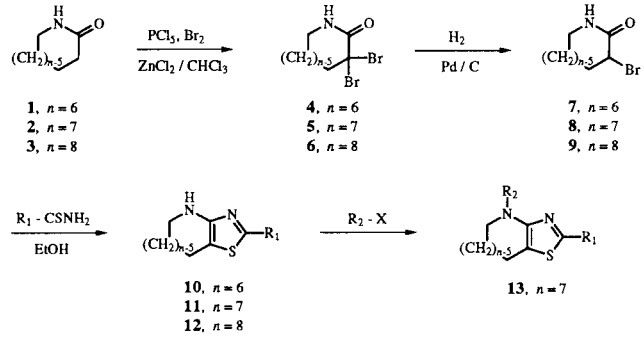
Figure 1

For the preparation of 4-aminothiazole derivatives, the Curtius rearrangement of thiazole-4-carbonyl azides [3], the reaction of 1,3-oxathiolium salts with cyanamides [4-6], the ring cyclization reaction of halogeno compounds with cyanamides [7-11] and the reaction of α-halonitriles and thioamides [12] have been reported. However, these methods are not adequate for the synthesis of cyclic derivatives (type B) of 4-aminothiazole. Judging from the structural arrangement, the reaction of α-halogenated lactams with thioamides seemed to provide a short way for our purpose, although the reaction between α-chloroacetamide and thiourea has been reported to give 2-aminothiazolidin-4-one after cleavage of the C-N bond [13]. We thus retested the reaction between α-halogenated amides and thioamides. In this paper, we will describe a simple method to prepare cyclic derivatives (type B) of 4-aminothiazoles such as 4,5,6,7-tetrahydrothiazolo[4,5-*b*]pyridines **10**, 5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*b*]azepines **11**, 4,5,6,7,8,9-hexahydrothiazolo[4,5-*b*]azocine **12** and 9,10-dihydro-4*H*-thiazolo-[4,5-*b*][1]benzazepines **18**.

Chemistry.

The starting compound, α-bromo-ε-caprolactam (**8**), was prepared according to the route shown in Scheme 1 [14]. ε-Caprolactam (**2**) was at first brominated to α,α-dibromo-ε-caprolactam (**5**) using phosphorus pentachloride and two equivalents of bromine with a small amount of zinc chloride as catalyst, and then **5** was reduced to α-bromo-ε-caprolactam (**8**) by catalytic hydrogenation over palladium on carbon in acetic acid at room temperature.

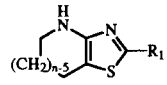
Scheme 1



α-Bromo-ε-caprolactam (**8**) thus obtained was then reacted with thiobenzamide in ethanol under reflux and after column chromatography on silica gel, 2-phenyl-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*b*]azepine (**11c**) was obtained as pale yellow crystals in 29% yield. The structural elucidations of **11c** were accomplished on the basis of the elemental analysis, infrared (ir), mass and proton nuclear magnetic resonance (^{1}H nmr) spectra. The ir spectrum showed no absorption due to an amide carbonyl

Table I

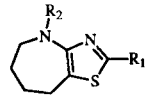
Bicyclic 4-Amino-2-substituted Thiazole Derivatives **10-12**



Compound No.	n	R_1	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Mass (M^+)	Analysis, % Calcd./Found C	H	N	S
10a	6	$(CH_3)_2CH$	18	oil	$C_9H_{14}N_2S \cdot 0.5H_2O$	182	56.51 56.89	7.90 7.87	14.64 14.73	16.76 16.36
10b	6	4-MeO-C_6H_4	23	105-107 (AcOEt-hexane)	$C_{13}H_{14}N_2OS$	246	63.39 63.21	5.73 5.79	11.37 11.38	13.02 12.75
11a	7	$(CH_3)_2CH$	26	44-46	$C_{10}H_{16}N_2S$	196	61.18 60.85	8.21 8.14	14.27 14.07	
11b	7	$C_6H_5CH=CH$	8	oil	$C_{15}H_{16}N_2S$	–	70.28 70.18	6.29 6.10	10.93 10.95	12.51 12.63
11c	7	C_6H_5	29	88-90 (hexane)	$C_{13}H_{14}N_2S$	230	67.79 67.56	6.13 6.09	12.16 12.09	13.92 13.92
11d	7	4-MeO-C_6H_4	35	103-104 (AcOEt-hexane)	$C_{14}H_{16}N_2OS$	260	64.59 64.66	6.19 6.13	10.76 10.53	12.32 12.29
11e	7	4-Cl-C_6H_4	30	113-115 (AcOEt-hexane)	$C_{13}H_{13}ClN_2S$	264	58.97 59.01	4.95 4.93	10.58 10.64	12.11 12.19
12	8	4-MeO-C_6H_4	3	80-83	$C_{15}H_{18}N_2OS$	274	65.66 65.48	6.61 6.31	10.21 10.28	11.68 11.57

Table II

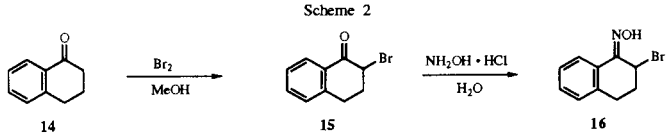
2,4-Disubstituted 5,6,7,8-Tetrahydro-4*H*-thiazolo[4,5-*b*]azepines **13**



Compound No.	R_1	R_2	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	MS (M^+)	Analysis, % Calcd./Found C	H	N	S
13a	Ph	C_2H_5	72	oil	$C_{15}H_{18}N_2S$	–	69.73 70.13	7.02 6.98	10.84 11.13	12.41 12.39
13b	Ph	CH_3CO	73	87-88 (AcOEt-hexane)	$C_{15}H_{16}N_2OS$	272	66.15 66.10	5.92 5.92	10.29 10.28	11.77 11.81
13c	Ph	CH_3SO_2	72	167-169 (AcOEt)	$C_{14}H_{16}N_2O_2S_2$	308	54.52 54.56	5.23 5.23	9.08 9.08	20.79 20.98

group. The electron-impact mass spectrum exhibited the molecular ion peak at m/z 230 corresponding to the molecular weight of **11c**. In order to get more information on the structure of **11c**, it was ethylated with triethyl phosphate, acetylated and sulfonated to afford **13a-c** in 72-73% yields. All the spectral data (Tables II and IV) of these three products were well consistent with the proposed structure **13** illustrated in Scheme 1. The structure of **11c** was finally substantiated by the X-ray structural analysis of compound **18c** obtained using the same methodology as shown later. Then other thioamides were

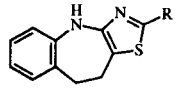
Scheme 2



Scheme 3

Table III

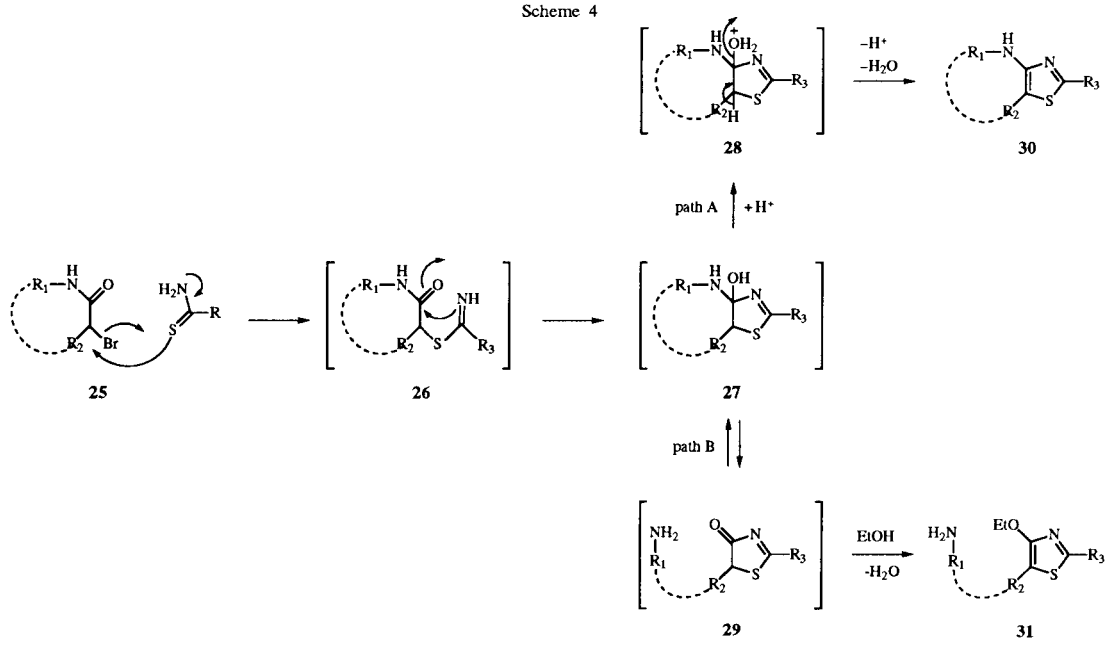
2-Substituted 9,10-Dihydro-4*H*-thiazolo[4,5-*b*][1]benzazepines **18**



Compound No.	R	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Mass (M+)	Analysis, % Calcd./Found C	H	N	S
18a	CH_3	40	115-117 (AcOEt-hexane)	$C_{12}H_{12}N_2S$	216	66.63 66.30	5.59 5.44	12.95 12.70	14.82 14.91
18b [a]	$(CH_3)_2CH$	57	119-122 (Et_2O-EtOH)	$C_{14}H_{17}ClN_2S$	244	59.88 59.80	6.10 6.08	9.98 9.97	11.42 11.37
18c	$C_6H_5CH_2$	46	130-132 (AcOEt-hexane)	$C_{18}H_{16}N_2S$	292	73.94 74.02	5.52 5.62	9.58 9.57	10.97 10.95
18d	$C_6H_5CH{=}CH$	37	202-204 (AcOEt-MeOH)	$C_{19}H_{16}N_2S{\cdot}0.5H_2O$	304	72.81 73.21	5.47 5.32	8.94 8.78	10.23 10.19
18e	C_6H_5	58	129-130 (AcOEt-hexane)	$C_{17}H_{14}N_2S$	278	73.35 73.23	5.07 4.88	10.06 9.92	11.52 11.74
18f	4-MeO-C_6H_4	69	173-176 (AcOEt)	$C_{18}H_{16}N_2OS$	308	70.10 70.13	5.23 5.18	9.08 8.88	10.40 10.37
18g	4-Cl-C_6H_4	48	165-167 (AcOEt-hexane)	$C_{17}H_{13}ClN_2S$	312	65.27 65.15	4.19 4.26	8.96 8.89	10.25 10.44
18h	4-Py	45	182-184 (AcOEt-hexane)	$C_{16}H_{13}N_3S$	279	68.79 68.65	4.69 4.47	15.04 15.00	11.48 11.59

[a] Hydrochloride.

Scheme 4



reacted with α-bromo-ε-caprolactam (**8**) to afford 5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*b*]azepines **11a,b,d,e** in 8-35% yields (Scheme 1, Table I). Thus, the novel 5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*b*]azepine skeleton was constructed by a simple method, although optimization of the reaction conditions was not examined. We then extended the reaction to other lactams having different ring sizes. Following the procedure for **11c**, 2-piperidone (**1**) and hexahydro-2(1*H*)-azocinone (**3**) were converted to monobromo derivatives **7** [15] and **9** [16], respectively, which were then reacted with thioamides in ethanol to give the

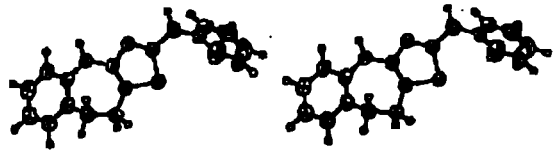


Figure 2. Stereoscopic Molecular View of **18c**.

Table IV

^{1}H NMR Spectral Data for the Compounds **10, 11, 12, 13** and **18**

Compound		Chemical Shifts (δ, ppm)
10a	[a]	1.33 (6H, d, J = 6.9 Hz), 1.96 (2H, m), 2.70 (2H, t, J = 6.4 Hz), 3.15 (1H, m), 3.31 (2H, t, J = 5.4 Hz)
10b	[a]	2.01 (2H, m), 2.76 (2H, t, J = 6.3 Hz), 3.35 (2H, t, J = 5.4 Hz), 3.84 (3H, s), 6.91 (2H, d, J = 8.5 Hz), 7.77 (2H, d, J = 8.5 Hz)
11a	[a]	1.31 (6H, d, J = 6.8 Hz), 1.60-1.85 (4H, m), 2.64 (2H, t, J = 5.7 Hz), 3.0-3.20 (3H, m), 4.52 (1H, broad s)
11b	[a]	1.60-1.90 (4H, m), 2.71 (2H, t, J = 5.7 Hz), 3.10 (2H, t, J = 5.1 Hz), 4.60 (1H, broad s), 7.02 (1H, d, J = 16.2 Hz), 7.15-7.52 (6H, m)
11c	[a]	1.60-1.90 (4H, m), 2.73 (2H, t, J = 5.7 Hz), 3.12 (2H, t, J = 4.5 Hz), 4.67 (1H, broad s), 7.30-7.43, (3H, m), 7.73-7.83 (2H, m)
11d	[a]	1.65-1.90 (4H, m), 2.71 (2H, t, J = 5.6 Hz), 3.12 (2H, t, J = 5.1 Hz), 3.84 (3H, s), 4.63 (1H, broad s), 6.90 (2H, d, J = 9.0 Hz), 7.74 (2H, d, J = 9.0 Hz)
11e	[a]	1.66-1.90 (4H, m), 2.73 (2H, t, J = 5.7 Hz), 3.12 (2H, t, J = 5.1 Hz), 7.34 (2H, d, J = 8.6 Hz), 7.72 (2H, d, J = 8.6 Hz.)
12	[a]	1.62-1.90 (6H, m), 2.97 (2H, t, J = 6.5 Hz), 3.44 (2H, t, J = 5.8 Hz), 3.83 (3H, s), 6.89 (2H, d, J = 9.0 Hz), 7.74 (2H, d, J = 9.0 Hz)
13a	[a]	1.24 (3H, t, J = 7.0 Hz), 1.62-1.77 (2H, m), 1.78-1.91 (2H, m), 2.75 (2H, t, J = 5.8 Hz), 3.10 (2H, t, J = 5.4 Hz), 3.56 (2H, q, J = 7.0 Hz), 7.30-7.43 (3H, m), 7.80-7.90 (2H, m)
13b	[a]	1.69-1.83 (2H, m), 1.85-2.00 (2H, m), 2.13 (3H, s), 2.84 (2H, t, J = 5.7 Hz), 3.73 (2H, broad s), 7.38-7.47 (3H, m), 7.80-7.91 (2H, m)
13c	[a]	1.70-1.82 (2H, m), 1.99-2.10 (2H, m), 2.92 (2H, t, J = 5.7 Hz), 3.41 (3H, s), 3.62 (2H, t, J = 5.3 Hz), 7.36-7.45 (3H, m), 7.99-7.90 (2H, m)
18a	[a]	2.55 (3H, s), 2.95-3.10 (4H, m), 6.61 (1H, broad s), 6.76-6.93 (2H, m), 7.05-7.17 (2H, m)
18b	[b]	1.27 (3H, s), 1.31 (3H, s), 2.94 (4H, s), 3.12 (1H, m), 5.76 (1H, broad s), 6.77 (1H, m), 7.00-7.14 (3H, m)
18c	[al	3.01 (4H, m), 4.14 (2H, s), 6.62 (1H, broad s), 6.76-6.92 (2H, m), 7.05-7.16 (2H, m), 7.25-7.37 (5H, m)
18d	[a]	3.09 (4H, m), 6.73 (1H, broad s), 6.82-6.97 (2H, m), 7.07 (1H, d, J = 16.2 Hz), 7.10-7.20 (2H, m), 7.37-7.43 (4H, m), 7.48-7.55 (2H, m)
18e	[a]	3.11 (4H, s), 6.76 (1H, broad s), 6.82-6.96 (2H, m), 7.10-7.20 (2H, m), 7.35-7.47 (3H, m), 7.78-7.88 (2H, m)
18f	[a]	3.09 (4H, s), 3.84 (3H, s), 6.72 (1H, broad s), 6.80-6.98 (4H, m), 7.12 (2H, d, J = 8.9 Hz), 7.76 (2H, d, J = 8.9 Hz)
18g	[a]	3.10 (4H, s), 6.74 (1H, broad s), 6.83-6.95 (2H, m), 7.10-7.20 (2H, m), 7.37 (2H, d, J = 8.7 Hz), 7.76 (2H, d, J = 8.7 Hz)
18h	[a]	3.13 (4H, s), 6.82 (1H, broad s), 6.90 (2H, m), 7.16 (2H, m), 7.68 (2H, dd, J = 1.6 and 4.6 Hz), 8.66 (2H, dd, J = 1.6 and 4.6 Hz)

[a] In deuteriochloroform. [b] In dimethyl sulfoxide-d_6.

desired 4,5,6,7-tetrahydrothiazolo[4,5-*b*]pyridines **10a,b** and 4,5,6,7,8,9-hexahydrothiazolo[4,5-*b*]azocine **12**. The yield varied with the size of the ring with which the thioamides condensed and decreased in the order of 7-, 6- and 8-membered rings. The yield seemed to reflect the stability of the bicyclic ring systems.

We next applied the procedure described above to the synthesis of 9,10-dihydro-4*H*-thiazolo[4,5-*b*]-[1]benzazepines (type B), because the isomeric 9,10-dihydro-4*H*-thiazolo[5,4-*b*][1]benzazepines (type A) exhibited prominent antioxidative activity and it was of particular interest to compare the activity of the two isomers.

According to the method of Wetter and coworkers [17], the key intermediate, 3-bromo-2,3,4,5-tetrahydro-1*H*-[1]-benzazepin-2-one (**17**), was prepared in 57% yield from α-tetralone (**14**) *via* three steps: 1) bromination of **14**, 2) oxime formation of **15** and 3) the Beckmann rearrangement of oxime **16** in polyphosphoric acid. 3-Bromo-2,3,4,5-tetrahydro-1*H*-[1]-benzazepin-2-one (**17**) was then treated with thioamides in ethanol to give the desired tricyclic 4-aminothiazole derivatives **18a-h** in 37-69% yields. All the spectral data of **18** supported the structure shown in Scheme 2 and the structure of **18c** was established by single-crystal X-ray structural analysis as shown in Figure 2.

Thus cyclic derivatives (type B) of 4-aminothiazole were obtained from α-brominated lactams and thioamides, whereas the corresponding reaction of acyclic α-halogenated amides and thioureas have been reported to give thiazolin-4-one [13], as a result of C-N bond fission under the reaction conditions. Therefore, in order to ascertain the difference between acyclic and cyclic amides, acyclic α-bromoamides **20a,b** were reacted independently with thiobenzamide under the conditions which converted α-brominated lactams into cyclic derivatives of 4-aminothiazoles. After the usual workup followed by purification by column chromatography on silica gel, the same oily product was obtained from **20a** and **20b** in 53% and 70% yield, respectively. The structure of the product was assigned to 4-ethoxy-5-methyl-2-phenylthiazole (**22**) on the basis mass spectra, ^{1}H nmr spectra and elemental analysis. In order to confirm the structure of **22**, an alternate synthesis of **22** was carried out. According to the method by Kerdesky and coworkers [18], ethyl 2-bromopropionate (**23**) and thiobenzamide were reacted on heating in a mixture of pyridine and toluene to give 4-hydroxy-5-methyl-2-phenylthiazole (**24**). Compound **24** was then *O*-ethylated by using triethyl phosphate in the presence of sodium hydride to provide a product **22** in 81% yield. All the spectral data of the product were completely consistent with those of **22** obtained from **20a,b**.

Compound **22** was not obtained by refluxing **24** in ethanol in the presence and absence of diethylamine hydrobromide, thus **24** could not be the precursor of **22**, suggesting that 5-methyl-2-phenylthiazolin-4-one might be the precursor. These results indicate that the C-N bond of the acyclic amide is easily cleaved under the reaction conditions.

The reaction of an α-halogenated amide and thioamide may be explained by the reaction pathway shown in Scheme 4. The α-bromoamide **25** reacts at first with the thiolate anion to give the intermediate **26** and then the nitrogen attacks the carbonyl carbon to give **27**, from which the reaction course might branch into path A and B. Whether path A or B takes precedence might depend on the structure of the intermediate **27**. From our results, the reaction of the acyclic α-bromoamide proceeds through the course corresponding to path B to give 4-ethoxythiazole **31** as the major product. On the other hand, bicyclic lactam **17** and thioamide reacts through path A resulting in the formation of 4-aminothiazole derivatives **18**. Monocyclic lactams afford bicyclic derivatives of 4-aminothiazole **30** though the yields were unsatisfactory, suggesting the possibility that some amount of 4-ethoxythiazole derivatives **31** were formed (path B). It seems also reasonable that the equilibrium between **27** and **29** exists. Of course, the occurrence of reannelation (**29**→**27**) depends on the nucleophilicity of the amino group of **29**. The possibility that 9,10-dihydro-4*H*-thiazolo[4,5-*b*][1]benzazepines **18** were formed *via* reannelation might be low because of the poor nucleophilicity of aniline.

In conclusion, we have developed a facile synthetic method for cyclic derivatives of 4-aminothiazole. This study was not designed to isolate thiazolin-4-one derivatives (products from path B) with the exception of 4-ethoxy-3-methyl-2-phenylthiazole (**22**), so further quantitative studies would be necessary to discuss in more detail. The biological activity of the compounds obtained in this study will be reported separately.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Varian Gemini-200 spectrometer in the solvent indicated. Chemical shifts are given in ppm with tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Chromatographic purifications were carried out on silica gel column (Kieselgel 60, 0.063-0.200 mm, Merck). Evaporation was carried out *in vacuo* on a rotary evaporator. Elemental microanalyses gave results for the elements stated within ± 0.4% of the theoretical values.

3,3-Dibromo-2-piperidone (**4**).

Phosphorus pentachloride (216.4 g, 1.04 moles) was added in small portions to a solution of **1** (51.5 g, 0.52 mole) in chloroform (700 ml) over a period of 40 minutes while the temperature was maintained between 0-10° by external cooling. To this mixture was added zinc chloride (2.6 g, 19.2 mmoles) and bromine (166 g, 1.04 moles). The mixture was allowed to reach room temperature and stirred for 5 hours. After evaporating the solvent, the residue was dissolved in chloroform and treated with saturated aqueous sodium bisulfite solution. The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with ethyl acetate as eluent. The fractions containing **4** were combined and concentrated to yield 109.8 g (82%) of **4**. An analytical sample was obtained by recrystallization from ethyl acetate, mp 177-179° (lit [15b] mp 172-173°); ^{1}H nmr (deuteriochloroform); δ 2.03 (2H, m), 2.99 (2H, m), 3.48 (2H, m), 6.86 (1H, broad s).

Anal. Calcd. for $C_5H_7Br_2NO$: C, 23.37; H, 2.75; N, 5.45; Br, 62.20. Found: C, 23.47; H, 2.83; N, 5.49; Br, 62.49.

3,3-Dibromo-2-oxohexamethyleneimine (**5**).

The same procedure as described for the preparation of **4** provided 106 g (78%) of **5** from **2** (56.6 g, 0.5 mole), phosphorus pentachloride (208 g, 1.0 mole), zinc chloride (2.5 g, 18.3 mmoles) and bromine (160 g, 1.0 mole). An analytical sample was obtained by recrystallization from ethyl acetate-hexane, mp 158-161° (lit [14] mp 162-163.5°); ^{1}H nmr (deuteriochloroform): δ 1.70 (2H, m), 1.99 (2H, m), 2.75 (2H, m), 3.38 (2H, m), 6.55 (1H, broad s).

Anal. Calcd. for $C_6H_9Br_2NO$: C, 26.60; H, 3.35; N, 5.17; Br, 58.98. Found: C, 26.72; H, 3.36; N, 5.22; Br, 58.68.

3,3-Dibromohexahydro-2(1*H*)-azocinone (**6**).

The same procedure as described for the preparation of **4** provided 17.1 g (19%) of **6** from **3** (40 g, 0.31 mole), phosphorus pentachloride (131 g, 0.63 mole), zinc chloride (1.6 g, 11.6 mmoles) and bromine (100.5 g, 0.63 mole). An analytical sample was obtained by recrystallization from ethyl acetate-hexane, mp 146-148° (lit [16] mp 147-148°); ^{1}H nmr (deuteriochloroform): δ 1.50-1.90 (6H, m), 3.03 (2H, t, J = 5.7 Hz), 3.50-3.70 (2H, m), 6.20 (1H, broad s).

Anal. Calcd. for $C_7H_{11}Br_2NO$: C, 29.50; H, 3.89; N, 4.92; Br, 56.08. Found: C, 29.49; H, 4.00; N, 4.90; Br, 55.80.

3-Bromo-2-piperidone (**7**).

A solution of **4** (106.5 g, 0.42 mole) in acetic acid (900 ml) was subjected to hydrogenation in the presence of 10% Pd-C (10 g) and sodium acetate (37.4 g, 0.46 mole). After hydrogen absorption ceased, the catalyst and sodium bromide were removed by filtration. The filtrate was then neutralized with saturated aqueous sodium hydrogen carbonate solution and extracted with chloroform. The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with chloroform:methanol (95:5, v/v) as eluent. The fractions containing **7** were combined and concentrated to yield 66.8 g (91%) of **7**. An analytical sample was obtained by recrystallization from chloroform, mp 135-137° (lit [15a] mp 147°); ^{1}H nmr (deuteriochloroform): δ 1.80 (1H, m), 2.10-2.36 (3H, m), 3.30-3.55 (2H,

m), 4.52 (1H, t, J = 4.3 Hz), 6.55 (1H, broad s).

Anal. Calcd. for C_5H_8BrNO: C, 33.73; H, 4.53; N, 7.87; Br, 44.88. Found: C, 33.56; H, 4.44; N, 7.89; Br, 44.78.

3-Bromo-2-oxohexamethyleneimine (**8**).

The same procedure as described for the preparation of **7** provided 10.7 g (88%) of **8** from **5** (106 g, 0.39 mole), Pd-C (11 g) and sodium acetate (35.3 g, 0.43 mole). An analytical sample was obtained by recrystallization from ethyl acetate-hexane, mp 114-116° (lit [14] mp 113-115°); ^{1}H nmr (deuteriochloroform); δ 1.43-2.20 (6H, m), 3.18-3.26 (1H, m), 3.50-3.70 (1H, m), 4.67 (1H, m), 6.40 (1H, broad s).

Anal. Calcd. for $C_6H_{10}BrNO$: C, 37.52; H, 5.25; N, 7.29; Br, 41.60. Found: C, 37.72; H, 5.23; N, 7.34; Br, 41.23.

3-Bromohexahydro-2(1*H*)-azocinone (**9**).

The same procedure as described for the preparation of **7** provided 10.7 g (88%) of **9** from **6** (16.9 g, 59.3 mmoles), Pd-C (1.5 g) and sodium acetate (5.35 g, 65.2 mmoles). An analytical sample was obtained by recrystallization from ethyl acetate-hexane, mp 169-170° (lit [16] mp 172-173°); ^{1}H nmr (deuteriochloroform): δ 1.35-1.85 (6H, m), 2.20-2.33 (2H, m), 3.33-3.48 (2H, m), 4.87 (1H, m), 6.18 (1H, broad s).

Anal. Calcd. for $C_7H_{12}BrNO$: C, 40.80; H, 5.87; N, 6.80; Br, 38.77. Found: C, 40.76; H, 5.67; N, 6.93; Br, 39.01.

Bicyclic 4-Amino-2-substituted Thiazole Derivatives **10-12** (Tables I and IV).

Typical Procedure.

5,6,7,8-Tetrahydro-2-phenyl-4*H*-thiazolo[4,5-*b*]azepine (**11c**).

A mixture of **8** (3.0 g, 15.6 mmoles) [16] and thiobenzamide (2.36 g, 17.2 mmoles) in ethanol (30 ml) was refluxed for 4 hours. After evaporating the solvent, the residue was dissolved in a mixture of chloroform (50 ml) and saturated aqueous sodium hydrogen carbonate solution (50 ml). The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with hexane:ethyl acetate (9:1, v/v) as eluent. The fractions containing **11c** were combined and concentrated. The residue was recrystallized from ethyl acetate-hexane to yield 1.1 g (29%) of **11c**. Compounds **10a,b, 11a,b, 11d,e** and **12** were prepared by similar procedures to those employed for the preparation of **11c** starting from **8**. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables I and IV.

4-Ethyl-5,6,7,8-tetrahydro-2-phenyl-4*H*-thiazolo[4,5-*b*]azepine (**13a**).

To a solution of **11c** (1.5 g, 6.5 mmoles) in triethyl phosphate (11.9 g, 65.1 mmoles) was added sodium hydride (60% in oil, 0.39 g, 9.77 mmoles) at 0° and the mixture was heated at 100° for 4 hours. After being cooled to room temperature, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with hexane:ethyl acetate (9:1, v/v) as eluent. The fractions containing **13a** were combined and concentrated to yield 1.21 g (72%) of **13a** as an oil. Resulting elemental analysis and spectral data of this compound are listed in Tables II and IV.

4-Acetyl-5,6,7,8-tetrahydro-2-phenyl-4*H*-thiazolo[4,5-*b*]azepine (**13b**).

A mixture of **11c** (1.0 g, 4.34 mmoles) and acetic anhydride (0.53 g, 5.21 mmoles) in pyridine (15 ml) was heated at 100° for 1 hour. After evaporating the solvent, the residue was dissolved in a mixture of chloroform (50 ml) and brine (50 ml). The organic layer was washed with water and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with hexane:ethyl acetate (7:3, v/v) as eluent. The fractions containing **13b** were combined and concentrated. The residue was recrystallized from ethyl acetate-hexane to yield 861 mg (73%) of **13b**. Melting point, resulting elemental analysis and spectral data of this compound are listed in Tables II and IV.

5,6,7,8-Tetrahydro-4-methanesulfonyl-2-phenyl-4*H*-thiazolo[4,5-*b*]azepine (**13c**).

To a solution of **11c** (1.0 g, 4.34 mmoles) in pyridine (10 ml) was added dropwise methanesulfonyl chloride (1.0 g, 5.21 mmoles) at 0° and the mixture was heated at 100° for 1 hour. After being cooled to room temperature, chloroform (50 ml) and brine (50 ml) were added to the mixture. The organic layer was washed with water and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with hexane:ethyl acetate (9:1, V/V) as eluent. The fractions containing **13c** were combined and concentrated. The residue was recrystallized from ethyl acetate to yield 970 mg (72%) of **13c**. Melting point, resulting elemental analysis and spectral data of this compound are listed in Tables II and IV.

2-Substituted 9,10-Dihydro-4*H*-thiazolo[4,5-*b*][1]benzazepine Derivatives **18a-h** (Tables III and IV).

Typical Procedure.

9,10-Dihydro-2-methyl-4*H*-thiazolo[4,5-*b*][1]benzazepine (**18a**).

A mixture of **17** (1.0 g, 4.16 mmoles) [19] and thioacetamide (0.47 g, 6.25 mmoles) in ethanol (10 ml) was refluxed for 5 hours. After evaporating the solvent, the residue was dissolved in a mixture of chloroform (50 ml) and saturated aqueous sodium hydrogen carbonate solution (50 ml). The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with hexane:ethyl acetate (9:1, v/v) as eluent. The fractions containing **18a** were combined and concentrated. The residue was recrystallized from ethyl acetate-hexane to yield 360 mg (40%) of **18a**. Compounds **18b-h** were prepared by similar procedures to those employed for the preparation of **18a**. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables III and IV.

2-Bromo-*N*,*N*-diethylpropionamide (**20a**).

To a solution of diethylamine (1.69 g, 23.2 mmoles) and triethylamine (3.5 g, 34.7 mmoles) in chloroform (30 ml) was added dropwise 2-bromopropionyl bromide (**19**) (5.0 g, 23.2 mmoles) at 0°. After stirring for 1 hour, the mixture was treated with water and extracted with chloroform. The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue

was purified by column chromatography with hexane:ethyl acetate (85:15, v/v) as eluent. The fractions containing **20a** were combined and concentrated to yield 4.03 g (84%) of **20a** as an oil; ^{1}H nmr (deuteriochloroform); δ 1.14 (3H, t, J = 7.0 Hz), 1.25 (3H, t, J = 7.3 Hz), 1.83 (3H, d, J = 6.6 Hz), 3.15-3.37 (2H, m), 3.43-3.65 (2H, m), 4.53 (1H, q, J = 6.6 Hz).

Anal. Calcd. for $C_7H_{14}BrNO$: C, 40.40; H, 6.78; N, 6.73; Br, 38.40. Found: C, 40.67; H, 6.58; N, 6.77; Br, 38.59.

2-Bromo-*N*-phenylpropionamide (**20b**).

To a solution of aniline (2.16 g, 23.2 mmoles) and triethylamine (3.5 g, 34.7 mmoles) in chloroform (30 ml) was added dropwise 2-bromopropionyl bromide (**19**) (5.0 g, 23.2 mmoles) at 0°. After stirring for 1 hour, the mixture was treated with water and extracted with chloroform. The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with chloroform as eluent. The fractions containing **20b** were combined and concentrated. The residue was recrystallized from ethyl acetate-hexane to yield 4.49 g (85%) of **20b**; ^{1}H nmr (deuteriochloroform): δ 1.97 (3H, d, J = 7.0 Hz), 4.55 (1H, q, J = 7.0 Hz), 7.10-7.60 (5H, m), 8.09 (1H, broad s).

Anal. Calcd. for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14; Br, 35.03. Found: C, 47.58; H, 4.19; N, 6.13; Br, 35.26.

4-Ethoxy-3-methyl-2-phenylthiazole (**22**).

Procedure **1** (From **20a,b**).

A mixture of **20a** (3.0 g, 14.4 mmoles) and thiobenzamide (1.98 g, 14.4 mmoles) in ethanol (10 ml) was refluxed for 10 hours. After evaporating the solvent, the residue was dissolved in a mixture of chloroform (50 ml) and saturated aqueous sodium hydrogen carbonate solution (50 ml). The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with hexane:ethyl acetate (95:5, v/v) as eluent. The fractions containing **22** were combined and concentrated to yield 1.67 g (53%) of **22** as an oil. Compound **22** was also prepared by similar procedures starting from **20b** and thiobenzamide in 70% yield; ^{1}H nmr (deuteriochloroform): δ 1.39 (3H, t, J = 7.1 Hz), 2.30 (3H, s), 4.41 (2H, q, J = 7.1 Hz), 7.38 (3H, m), 7.85 (2H, m); ^{13}C nmr (deuteriochloroform): δ 9.15 (methyl C-atom), 15.2 and 66.2 (ethyl C-atoms), 106.9 (thiazole C-atom), 125.2, 128.6, 129.1 and 133.9 (Ph C-atoms), 159.3 and 159.6 ppm (thiazole C-atoms); ms: m/z 219 (M^+).

Anal. Calcd. for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39; S, 14.62. Found: C, 65.79; H, 6.06; N, 6.14; S, 14.79.

Procedure 2 (From **24**).

To a solution of **24** [18] (2.1 g, 11.0 mmoles) in triethyl phosphate (25 g, 137 mmoles) was added sodium hydride (60% in oil, 0.66 g, 16.5 mmoles) at 0° and the mixture was heated at 100° for 2 hours. After being cooled to room temperature, water was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was successively washed with water and brine, and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by column chromatography with hexane:ethyl acetate (98:2, v/v) as eluent. The fractions containing **22** were combined and concentrated to yield 1.96 g (81%) of **22** as an oil. All the spectral data were identical with those obtained in Procedure 1.

Acknowledgement.

The authors are grateful to Dr. S. Terao for his encouragement throughout this work and also to Dr. S. Ohkawa for his helpful discussion. Thanks are also due to Dr. David G. Cork for reviewing the manuscript.

REFERENCES AND NOTES

[1] O. Uchikawa, K. Fukatsu and T. Aono, *J. Heterocyclic Chem.*, **31**, 877 (1994).

[2a] T. Aono, M. Suno and G. Kito: European Patent, 351,856 (1990); *Chem. Abstr.*, **113**, 40664c (1990); [b] T. Aono, M. Suno and G. Kito: European Patent, 443,588 (1991); *Chem. Abstr.*, **115**, 280006z (1991); [c] T. Aono and O. Uchikawa: Japanese Patent (Kokai), 5-239065 (1993).

[3] H. Erlenmeyer and D. Markees, *Helv. Chim. Acta*, **29**, 1229 (1946).

[4] H. Hartmann, *Z. Chem.*, **11**, 421 (1971).

[5] H. Von Hartmann, H. Schaefer and K. Gewald, *J. Prakt. Chem.*, **315**, 497 (1973).

[6] H. Schaefer, H. Hartmann and K. Gewald, *J. Prakt. Chem.*, **316**, 19 (1974).

[7] K. Hartke and B. Seib, *Arch. Pharm. Weinheim*, **303**, 625 (1970).

[8] D. Wobig, *Liebigs Ann. Chem.*, **764**, 125 (1972).

[9] K. Hartke and G. Golz, *Liebigs Ann. Chem.*, **10**, 1644 (1973).

[10] W. Walek, M. Pallas and M. Augustin, *Tetrahedron*, **32**, 623 (1976).

[11] D. Wobig, *Liebigs Ann. Chem.*, **6**, 1166 (1976).

[12] H. Schaefer and K. Gewald, *J. Prakt. Chem.*, **317**, 771 (1975).

[13] J. V. Metzger, Comprehensive Heterocyclic Chemistry, Vol **6**, K. T. Potts, ed, Pergamon Press, Oxford, 1984, p 316.

[14] R. J. Wineman, E. -P. T. Hsu and C. E. Anagno-stopoulos, *J. Am. Chem. Soc.*, **80**, 6233 (1958).

[15a] T. Takahashi and K. Kariyone, *Yakugaku Zasshi*, **78**, 1306 (1958); [b] A. Heymons, *Ber*, **66**, 846 (1933); [c] F. Korte and H. Wamhoff, *Ber.*, **97**, 1970 (1964).

[16] H. T. Nagasawa, J. A. Elberling, P. S. Fraser and N. S. Mizuno, *J. Med. Chem.*, **14**, 501 (1971).

[17a] S. K. Boyer, R. A. Pfund, R. E. Portmann, G. H. Sedelmeier and H. F. Wetter, *Helv. Chim. Acta*, **71**, 337 (1988); [b] W. H. Parsons and A. A. Patchett, US Patent 4,692,522 (1987); *Chem. Abstr.*, **109**, 54677p (1988).

[18] F. A. J. Kerdesky, J. H. Holms, J. L. Moore, R. L. Bell, R. D. Dyer, G. W. Carter and D. W. Brooks, *J. Med. Chem.*, **34**, 2158 (1991).