Aminothiazole Derivatives. I. A Convenient Synthesis of Monocyclic and Condensed 5-Aminothiazole Derivatives

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Treatment of diamides derived from α-amino acids with phosphorus pentasulfide or Lawesson's reagent was shown to provide a convenient method to prepare 5-aminothiazoles. By this method, in addition to monocyclic 5-aminothiazoles **19**, novel bicyclic 5-aminothiazole derivatives such as 4,5,6,7-tetrahydrothiazolo[5,4-*b*]pyridines **11**, 5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*b*]azepines **7**, 4,5,6,7,8,9-hexahydrothiazolo[5,4-*b*]azocine **16** and related compounds were prepared in moderate to good yields from simple diamides, suggesting the wide versatility of the method.

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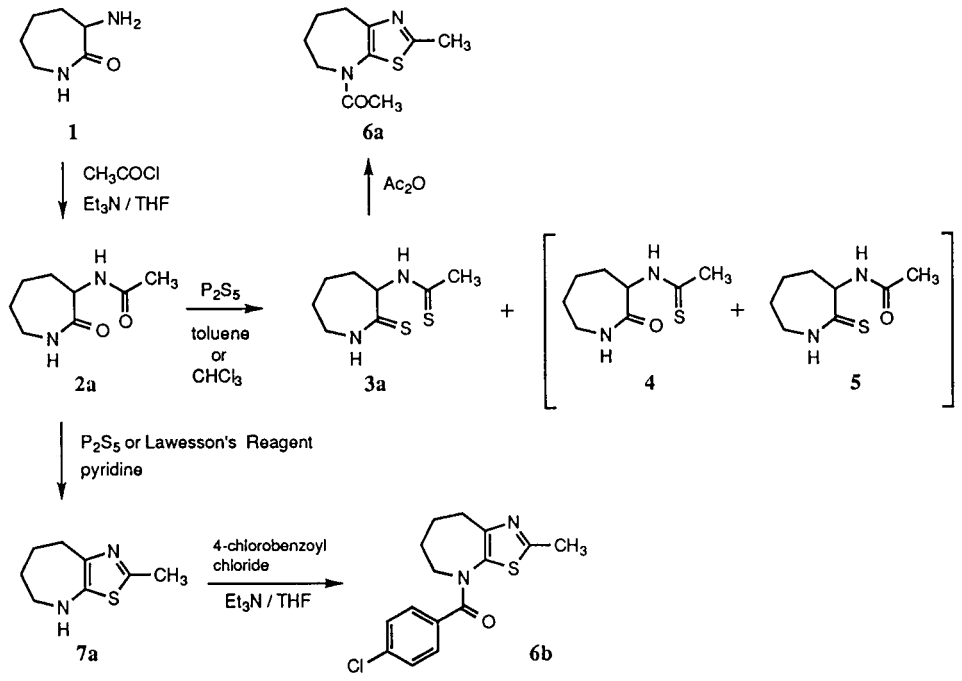
In the course of our research on heterocyclic compounds, we had the occasion to synthesize 5-aminothiazole derivatives. Usually 5-aminothiazoles have been prepared [1,2], *via* intramolecular attack of the thiolate anion upon a cyano or carbonyl group, from 2-(thioacylamino)acetonitriles [3], 2-(acylamino)thioacetamides [4] or their related compounds [5], most of which were derived from 2-aminoacetonitriles. However, these methods are not adequate to prepare a wide variety of 5-aminothiazoles efficiently because of the small number of commercially available 2-aminoacetonitriles and the tedious multi-step route for their preparation. Therefore, we were prompted to develop an efficient route to 5-aminothiazoles. After due consideration, it seemed reasonable to adopt 2-(acylamino)-acetamides (diamides) as starting materials because various types are easily obtainable from amino acids and they can be converted on treatment with thiating reagents to 2-(thioacylamino)acetamides and/or 2-(acylamino)thioacetamides (monothioamides) or 2-(thioacylamino)thioacetamides (dithioamides), which are expected to cyclize to give 5-aminothiazoles. In this paper, we will describe an efficient method for the preparation of 5-aminothiazole derivatives such as 5,6,7,8-tetrahydro-4*H*-thiazolo[5,4-*b*]azepines, 4,5,6,7-tetrahydrothiazolo[5,4-*b*]pyridines, 4,5,6,7,8,9-hexahydrothiazolo[5,4-*b*]azocine and 9,10-dihydro-4*H*-thiazolo[5,4-*b*][1]benzazepines.

Chemistry.

Because of the novelty and interesting ring systems of the products, 3-(acetylamino)-ε-caprolactam (**2a**) derived from commercially available 3-amino-ε-caprolactam (**1**) and acetyl chloride was chosen as the starting material

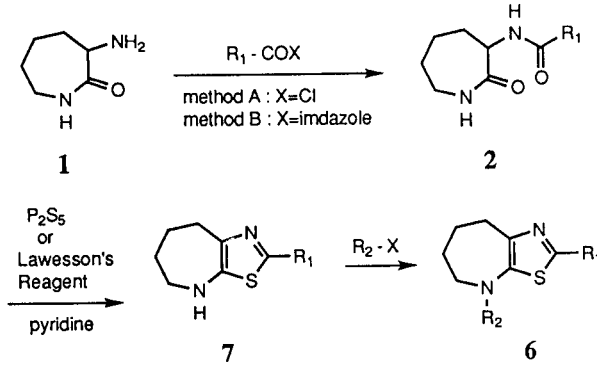
Scheme 1



(Scheme 1). 3-(Acetylamino)-ε-caprolactam (**2a**) was first treated with phosphorus pentasulfide [6] in toluene under reflux. After decomposing the excess phosphorus pentasulfide with aqueous sodium bicarbonate, three products were detected on thin layer chromatography (tlc). Of the three products, one was isolated as crystals by column chromatography on silica gel in 41% yield. The structure was determined as 3-(thioacetylamino)-ε-thiocaprolactam (**3a**) on the basis of elemental analysis, infrared (ir) and proton nuclear magnetic resonance (^{1}H nmr) spectra. The other two products could not be separated from each other by column chromatography on silica gel and were obtained as an oily mixture, the structures of which were deduced to be 3-(thioacetylamino)-ε-caprolactam (**4**) and 3-(acetylamino)-ε-thiocaprolactam (**5**) from ir and ^{1}H nmr spectra. Substantially the same results were obtained when the reaction was carried out using chloroform as the solvent. Then, in order to accomplish the cyclization to the thiazole ring, the dithioamide **3a** was treated with acetic anhydride [4a] under reflux to give 4-acetyl-5,6,7,8-tetrahydro-2-methyl-4*H*-thiazolo[5,4-*b*]azepine (**6a**) as an oil in 72% yield.

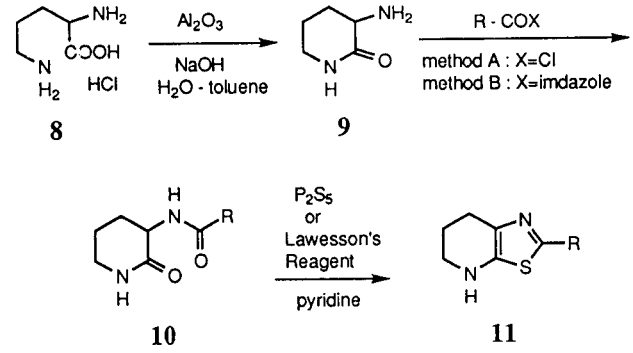
As it became apparent that a novel thiazolo[5,4-*b*]azepine, a bicyclic 5-aminothiazole derivative, was obtained from a simple diamide *via* only two steps, our efforts were focused on the direct formation of thiazolo[5,4-*b*]azepine from diamide **2a** and the reaction was examined under various conditions. As a result, an oily product which was different from those formed in toluene or chloroform was obtained by heating diamide **2a** with phosphorus pentasulfide in pyridine. The oily product **7a** was acylated with 4-chlorobenzoyl chloride to convert it into a crystalline compound **6b**. The structure of **6b** was characterized as 4-(4-chlorobenzoyl)-5,6,7,8-tetrahydro-2-methyl-4*H*-thiazolo[5,4-*b*]azepine (**6b**) on the basis of elemental analysis, ir and ^{1}H nmr spectra and then proved by single-crystal X-ray analysis, as shown in Figure 1. 2,4-Bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent) [7] in pyridine was also effective in thiazolo[5,4-*b*]azepine synthesis from diamide **2a**.

Scheme 2



Having confirmed that treatment of 3-(acetylamino)-ε-caprolactam (**2a**) with a thiating agent such as phosphorus pentasulfide or Lawesson's reagent gave a bicyclic thiazolo[5,4-*b*]azepine, we surveyed a series of related 3-(acylamino)-ε-caprolactams **2**. 3-(Acylamino)-ε-caprolactams **2** were prepared in good yields from 3-amino-ε-caprolactam (**1**) and activated acid derivatives, acyl chloride (Method A) or acylimidazolide (Method B). For the cyclization reaction, phosphorus pentasulfide (Method C) and Lawesson's reagent (Method D) were equally effective and a variety of

Scheme 3



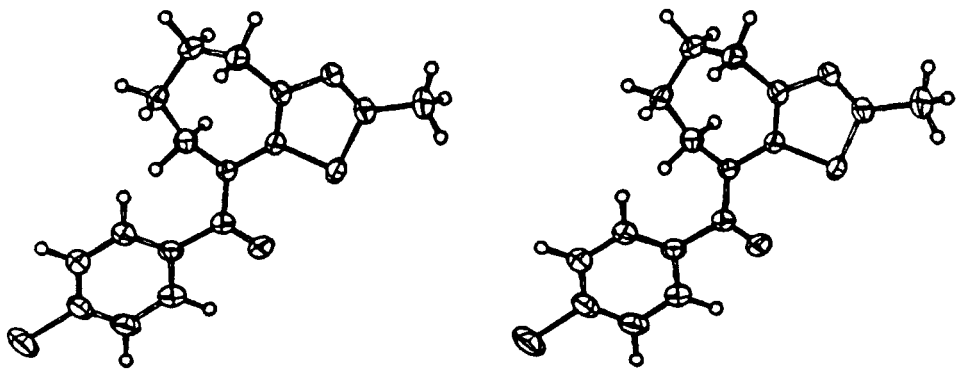
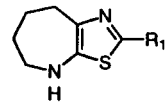


Figure 1. Stereoscopic Molecular View of **6b**.

Table I

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

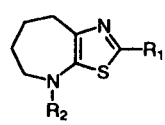


Compound No.	R_1	Method [a]	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	Cl	N	S
7a [b]	CH_3	D	23	167-170 (EtOH)	$C_8H_{13}ClN_2S$	46.94	6.40	17.32	13.68	15.66
						46.83	6.46	17.14	13.66	15.58
7b	MeOOC	C	54	166-168 (AcOEt)	$C_9H_{12}N_2O_2S$	50.92	5.70		13.20	15.11
						50.98	5.71		13.22	15.25
7c	$C_6H_5CH=CH$	C	80	169-170 (cyclohexane)	$C_{15}H_{16}N_2S$	70.27	6.29		10.93	
						70.53	6.30		10.94	
7d	C_6H_5	C	83	122-123 (cyclohexane)	$C_{13}H_{14}N_2S$	67.79	6.13		12.16	13.92
						67.91	6.27		12.20	13.78
7e	4-Cl-C_6H_4	C	90	163-165 (AcOEt)	$C_{13}H_{13}ClN_2S$	58.97	4.95	13.39	10.58	12.11
						58.93	4.97	13.42	10.51	12.32
7f [b]	4-MeO-C_6H_4	C	89	177-178 (Et_2O-MeOH)	$C_{14}H_{17}ClN_2OS$	56.65	5.77	11.94	9.44	10.80
						56.48	5.87	12.17	9.40	10.91
7g	4-CN-C_6H_4	C	57	163-164 (AcOEt)	$C_{14}H_{13}N_3S$	65.85	5.13		16.46	12.56
						66.15	4.93		16.52	12.48
7h	4-NO_2-C_6H_4	C	71	159-160 (cyclohexane)	$C_{13}H_{13}N_3O_2S$	56.71	4.76		15.26	11.64
						56.90	4.69		15.39	11.72
7i [c]	2-NH_2-3-Me-C_6H_3	C	70	208-211 (MeOH)	$C_{14}H_{19}Cl_2N_3S$	50.60	5.76	21.34	12.65	9.65
						50.69	5.73	21.41	12.58	9.64
7j	4-MeCSNH-C_6H_4	C	13	239-242 (AcOEt)	$C_{15}H_{17}N_3S_2$	59.37	5.65		13.85	21.13
						58.97	5.66		13.55	21.23
7k	2-Thienyl	C	67	123-124 (cyclohexane)	$C_{11}H_{12}N_2S_2$	55.90	5.12		11.85	27.13
						55.80	5.13		11.83	27.26
7l	2-Quinolyl	C	73	243-245 (AcOEt)	$C_{16}H_{15}N_3S$	68.30	5.37		14.93	11.40
						68.31	5.39		14.73	11.31
7m [b]	1-Me-triazol-4-yl	C	77	199-201 (MeOH)	$C_{10}H_{14}ClN_5S$	44.19	5.19	13.05	25.77	11.80
						44.20	5.12	13.12	25.61	11.56
7n [d]	5-Benzimidazolyl	C	80	208-210 (Et_2O-MeOH)	$C_{14}H_{18}Cl_2N_4OS$	46.54	5.02	19.63	15.51	8.88
						46.72	4.92	19.55	15.20	8.95

[a] See Experimental. [b] Hydrochloride. [c] Dihydrochloride. [d] Dihydrochloride Monohydrate.

Table II

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



Compound No.	R_1	R_2	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N	S
6a	CH_3	CH_3CO	72	oil	$C_{10}H_{14}N_2OS$	57.12	6.71	13.32	
						57.03	6.65	13.43	
6b	CH_3	4-Cl-C_6H_4CO	66	137-139 (cyclohexane)	$C_{15}H_{15}ClN_2OS$	58.72	4.93	9.13	
						58.82	4.92	8.93	
6c	C_6H_5	CH_3CO	81	89-90 (hexane)	$C_{15}H_{16}N_2OS$	66.15	5.92	10.29	11.77
						66.31	5.84	10.30	11.62
6d [a]	C_6H_5	CH_3	52	139-140 (Et_2O-EtOH)	$C_{14}H_{17}ClN_2S$	59.88	6.10	9.98	11.42
						59.70	6.00	9.86	11.51
6e	C_6H_5	CH_3SO_2	84	149-150 (AcOEt-hexane)	$C_{14}H_{16}N_2O_2S_2$	54.52	5.23	9.08	20.79
						54.30	5.24	8.81	20.47

[a] Hydrochloride.

3-(acylamino)-ε-caprolactams **2** provided the expected thiazolo[5,4-*b*]azepine derivatives **7** (Scheme 2, Tables I and II). Ester **7b**, double bond **7c**, chloro **7e**, methoxy **7f**, cyano **7g**, nitro **7h** and amino **7i** groups did not change the reaction pathway and yields, and were transferred intact to products. Needless to say, the acetylamino group was converted into thioacetylamino group **7j** and the existence of phenyl **7c-j**, thienyl **7k**, quinolyl **7l**, triazolyl **7m** and imidazolyl **7n** groups had no influence on the reaction. The amino groups at the 4-position of some cyclized products **7** were acylated, sulfonated or methylated to give **6** by usual way.

Next, we extended the reaction to 3-aminolactams of different ring size (valerolactam and heptalactam). 3-Amino-2-piperidone (**9**) was prepared [8-10] by lactamization of ornithine (**8**) (Scheme 3) and 3-aminohexahydro-2(1*H*)-azo-

Scheme 4

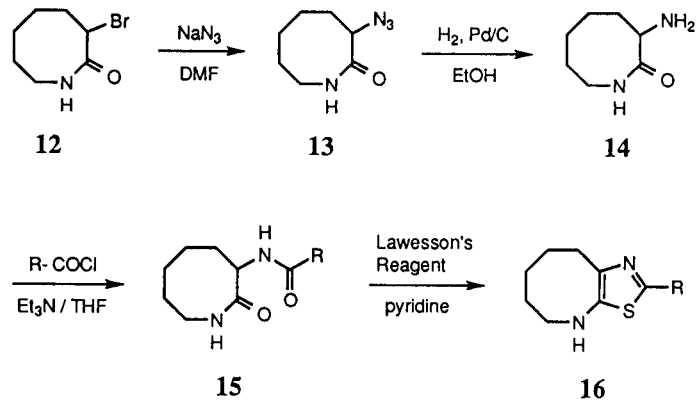
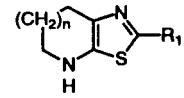


Table III

2-Substituted 4,5,6,7-Tetrahydrothiazolo[5,4-*b*]pyridines **11** and 2-Substituted 4,5,6,7,8,9-Hexahydrothiazolo[5,4-*b*]azocine **16**

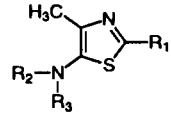


Compound No.	n	R_1	Method [a]	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N	S
11a	1	C_6H_5	C	35	120-121 (AcOEt-Et_2O)	$C_{12}H_{12}N_2S$	66.63 66.87	5.59 5.68	12.95 12.99	14.82 14.73
11b	1	3-NH_2-4-Me-C_6H_3	C	30	98-101 (AcOEt-hexane)	$C_{13}H_{15}N_3S$	63.64 63.36	6.16 6.40	17.13 16.88	13.07 13.08
11c	1	C_6H_5CH=CH	C	48	198-200 ($CHCl_3$-EtOH)	$C_{14}H_{14}N_2S$	69.39 68.72	5.82 5.82	11.56 11.13	13.23 13.52
11d	1	2,3-MeO-C_6H_3CH=CH	D	53	119-121 (AcOEt-hexane)	$C_{16}H_{18}N_2O_2S$	63.55 63.66	6.00 6.11	9.26 9.22	10.60 10.57
16a	3	4-MeO-C_6H_3	D	39	98-100 (AcOEt-Et_2O)	$C_{15}H_{18}N_2OS$	65.66 65.34	6.61 6.84	10.21 10.14	11.69 11.42

[a] See Experimental.

Table IV

2,5-Disubstituted 4-Aminothiazoles **19**

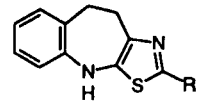


Compound No.	R_1	R_2	R_3	Method [a]	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N	S
19a	C_6H_5	C_6H_5	H	D	76	109-111 (AcOEt-hexane)	$C_{16}H_{14}N_2S$	72.15 72.12	5.30 5.15	10.52 10.45	12.04 12.15
19b [b]	C_6H_5	4-Picolyl	H	D	35	165-168 (EtOH)	$C_{16}H_{21}Cl_2N_3O_2S$	49.23 48.96	5.42 5.40	10.77 10.90	8.22 8.48
19c [c]	C_6H_5	Et	Et	D	58	91-94 (EtOH-hexane)	$C_{14}H_{19}ClN_2S$	59.45 59.25	6.77 6.65	9.90 9.88	11.34 11.24
19d	CH_3	C_6H_5	H	D	86	166-167 (AcOEt)	$C_{11}H_{12}N2S$	64.67 64.57	5.92 5.76	13.71 13.84	15.69 15.92

[a] See Experimental. [b] Dihydrochloride Dihydrate. [c] Hydrochloride.

Table V

2-Substituted 9,10-Dihydro-4*H*-thiazolo[5,4-*b*][1]benzazepines **22**

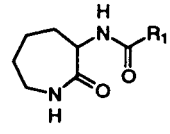


Compound No.	R	Method [a]	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N	S
22a	CH_3	C	50	189-191 (AcOEt-MeOH)	$C_{12}H_{12}N_2S$	66.63 66.49	5.59 5.55	12.95 12.83	14.82 14.79
22b	C_6H_5	C	74	182-184 (AcOEt-hexane)	$C_{17}H_{14}N_2S$	73.35 73.34	5.07 5.04	10.06 10.14	11.52 11.36
22c	4-MeO-C_6H_4	D	66	217-219 (AcOEt-EtOH)	$C_{18}H_{16}N_2OS$	70.10 69.84	5.23 5.20	9.08 9.04	10.40 10.36
22d	C_6H_5CH=CH	D	69	162-154 (AcOEt)	$C_{19}H_{16}N_2S$	74.97 74.78	5.30 5.35	9.20 9.43	10.53 10.43

[a] See Experimental.

Table VI

3-(Acylamino)-ε-caprolactams **2**



Compound No.	R_1	Method [a]	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N
2a	CH_3	A	45	160-162 (AcOEt)	$C_8H_{14}N_2O_2$	56.45 56.55	8.29 8.77	16.46 16.44
2b	MeOOC	A	37	146-148 (AcOEt-EtOH)	$C_9H_{14}N_2O_4$	50.46 50.30	6.59 6.65	13.08 12.91
2c	C_6H_5CH=CH	B	84	194-196 (EtOH)	$C_{15}H_{18}N_2O_2$	69.74 69.53	7.02 7.22	10.85 10.83
2d	C_6H_5	A	93	209-211 (EtOH)	$C_{13}H_{16}N_2O_2$	67.22 67.17	6.94 6.95	12.06 12.08
2e	4-Cl-C_6H_4	A	96	246-248 (EtOH)	$C_{13}H_{15}ClN_2O_2$	58.54 58.49	5.67 5.71	10.50 10.55
2f	4-MeO-C_6H_4	A	89	214-215 (EtOH)	$C_{14}H_{18}N_2O_3$	64.11 64.18	6.92 6.97	10.68 10.53
2g	4-CN-C_6H_4	B	70	189-190 (EtOH)	$C_{14}H_{15}N_3O_2$	65.36 65.32	5.88 5.75	16.33 16.42
2h	4-NO_2-C_6H_4	A	87	278-280 ($CHCl_3$-EtOH)	$C_{13}H_{15}N_3O_4$	56.32 56.18	5.45 5.47	15.15 15.01
2i	2-NH_2-3-Me-C_6H_3	B	54	188-190 (AcOEt-EtOH)	$C_{14}H_{19}N_3O_2$	64.35 64.23	7.33 7.18	16.08 16.07
2j	4-MeCONH-C_6H_4	B	79	254-256 (EtOH)	$C_{15}H_{19}N_3O_3$	62.27 62.10	6.62 6.82	14.52 14.54
2k	2-Thienyl	A	93	197-199 (AcOEt-EtOH)	$C_{11}H_{14}N_2O_2S$	55.44 55.20	5.92 5.67	11.76 11.64
2l	2-Quinolyl	B	95	248-250 (EtOH)	$C_{16}H_{17}N_3O_2$	67.83 67.77	6.05 6.12	14.83 14.74
2m	1-Me-triazol-4-yl	B	83	259-260 (EtOH)	$C_{10}H_{15}N_5O_2$	50.62 50.39	6.37 6.48	29.52 29.49
2n	5-Benzimidazolyl	B	65	297-299 (EtOH)	$C_{14}H_{16}N_4O_2$	61.75 61.81	5.92 5.86	20.57 20.35

[a] See Experimental.

Table VII

1H NMR Spectral Data for Compounds **2**, **6** and **7**

Compound	Chemical Shifts (δ, ppm)
2a [a]	1.10-1.95 (6H, m), 1.86 (3H, s), 3.09 (2H, m), 4.38 (1H, m), 7.79 (2H, m)
2b [a]	1.10-2.00 (6H, m), 3.15 (2H, m), 3.79 (3H, s), 4.42 (1H, m), 8.04 (1H, broad s), 8.50 (1H, d, J = 6.0 Hz)
2c [b]	1.20-2.35 (6H, m), 3.22 (2H, m), 4.60 (1H, m), 6.49 (1H, d, J = 15.5 Hz), 6.90-7.60 (5H, m), 7.61 (1H, d, J = 15.5 Hz)
2d [a]	1.15-2.00 (6H, m), 3.15 (2H, m), 4.62 (1H, m), 7.40-7.60 (3H, m), 7.80-7.90 (3H, m), 8.23 (1H, d, J = 7.0 Hz)
2e [a]	1.10-2.00 (6H, m), 3.15 (2H, m), 4.61 (1H, m), 7.53 (2H, d, J = 8.6 Hz), 7.80 (1H, m), 7.88 (2H, d, J = 8.6 Hz), 8.33 (1H, broad d, J = 7.2 Hz)
2f [a]	1.17-2.02 (6H, m), 3.21 (2H, m), 3.82 (3H, s), 4.60 (1H, m), 7.00 (2H, d, J = 9.0 Hz), 7.83 (2H, d, J = 9.0 Hz), 8.09 (1H, d, J = 6.0 Hz)
2g [a]	1.17-2.01 (6H, m), 3.18 (2H, m), 4.60 (1H, m), 7.96 (2H, d, J = 8.0 Hz), 8.03 (2H, d, J = 8.0 Hz)
2h [a]	1.15-2.05 (6H, m), 3.15 (2H, m), 4.64 (1H, m), 7.86 (1H, t, J = 5.9 Hz), 8.10 (2H, d, J = 8.9 Hz), 8.32 (2H, d, J = 8.9 Hz), 8.64 (1H, d, J = 7.2 Hz)
2i [a]	1.10-2.00 (6H, m), 2.09 (3H, s), 3.17 (2H, m), 4.55 (1H, m), 6.16 (2H, broad s), 6.50 (1H, t, J = 7.6 Hz), 7.08 (1H, d, J = 7.6 Hz), 7.34 (1H, d, J = 7.6 Hz), 7.90 (2H, m)
2j [a]	1.10-2.00 (6H, m), 3.07 (3H, s), 3.17 (2H, m), 4.59 (1H, m), 7.66 (2H, d, J = 8.8 Hz), 7.81 (2H, d, J = 8.8 Hz), 7.88 (1H, t, J = 6.2 Hz), 8.08 (1H, d, J = 6.7 Hz)
2k [a]	1.10-2.00 (6H, m), 3.15 (2H, m), 4.58 (1H, m), 7.15 (1H, m), 7.72-7.90 (3H, m), 8.28 (1H, d, J = 7.3 Hz)
21 [a]	1.15-2.20 (6H, m), 3.23 (2H, m), 4.67 (1H, m), 7.73 (1H, dt, J = 1.4 and 7.6 Hz), 7.89 (1H, dt, J = 1.4 and 7.6 Hz), 8.05-8.13 (4H, m), 8.60 (1H, d, J = 8.4 Hz), 9.18 (1H, d, J = 6.2 Hz)
2m [a]	1.13-2.07 (6H, m), 3.16 (2H, m), 4.09 (3H, s), 4.55 (1H, m), 8.05 (1H, t, J = 6.0 Hz), 8.26 (1H, d, J = 6.0 Hz), 8.54 (1H, s)
2n [a]	1.17-2.03 (6H, m), 3.18 (2H, m), 4.64 (1H, m), 7.57-8.05 (4H, m), 8.20 (1H, d, J = 6.0 Hz), 8.33 (1H, s)
7a [a]	1.62 (2H, m), 1.71 (2H, m), 2.72 (3H, s), 2.80 (2H, t, J = 5.8 Hz), 3.02 (2H, t, J = 5.0 Hz)
7b [b]	1.69 (2H, m), 1.84 (2H, m), 2.98 (2H, t, J = 5.8 Hz), 3.17 (2H, t, J = 4.4 Hz), 3.93 (3H, s), 4.46 (1H, s)
7c [b]	1.50-1.93 (4H, m), 2.86 (2H, m), 3.07 (2H, m), 7.05 (2H, s), 7.23-7.59 (5H, m)
7d [b]	1.66 (2H, m), 1.82 (2H, m), 2.95 (2H, t, J = 5.8 Hz), 3.12 (2H, t, J = 5.1 Hz), 3.91 (1H, broad s), 7.30-7.42 (3H, m), 7.73-7.82 (2H, m)
7e [b]	1.68 (2H, m), 1.83 (2H, m), 2.94 (2H, t, J = 5.8 Hz), 3.11 (2H, t, J = 5.2 Hz), 3.93 (1H, broad s), 7.32 (2H, d, J = 8.6 Hz), 7.68 (2H, d, J = 8.6 Hz)
7f [b]	1.50-1.90 (4H, m), 3.03-3.30 (4H, m), 3.80 (3H, s), 6.89 (2H, d, J = 9.0 Hz), 7.98 (2H, d, J = 9.0 Hz)
7g [b]	1.60-1.91 (4H, m), 2.96 (2H, t, J = 6.0 Hz), 3.15 (2H, t, J = 5.0 Hz), 4.10 (1H, broad s), 7.63 (2H, d, J = 8.0 Hz), 7.84 (2H, d, J = 8.0 Hz)
7h [b]	1.49-1.99 (4H, m), 2.95 (2H, m), 3.15 (2H, m), 4.14 (1H, broad s), 7.86 (2H, d, J = 8.6 Hz), 8.21 (2H, d, J = 8.6 Hz)
7i [a]	1.66 (2H, m), 1.81 (2H, m), 2.35 (3H, s), 2.90 (2H, m), 3.08 (2H, m), 6.29 (2H, broad s), 7.07 (1H, t, J = 7.6 Hz), 7.22 (1H, d, J = 7.0 Hz), 7.42 (1H, d, J = 6.6 Hz)
7j [a]	1.59 (2H, m), 1.72 (2H, m), 2.62 (3H, s), 2.80 (2H, broad s), 2.98 (2H, broad s), 6.25 (1H, s), 7.70 (2H, d, J = 8.7 Hz), 7.89 (2H, d, J = 8.7 Hz), 11.65 (1H, s)
7k [b]	1.47-1.95 (4H, m), 2.83-2.95 (2H, m), 3.00-3.11 (2H, m), 3.65 (1H, broad s), 6.90-7.00 (1H, m), 7.19-7.23 (2H, m)
7l [a]	1.69 (4H, m), 2.87 (2H, m), 3.05 (2H, m), 6.61 (1H, s), 7.55 (1H, dt, J = 1.3 and 6.8 Hz), 7.74 (1H, dt, J = 1.3 and 6.8 Hz), 7.94 (2H, broad d, J = 8.1 Hz), 8.09 (1H, d, J = 8.7 Hz), 8.34 (1H, d, J = 8.7 Hz)
7m [a]	1.55-1.85 (4H, m), 2.84 (2H, m), 3.08 (2H, m), 4.12 (3H, s), 9.61 (1H, s)
7n [a]	1.56-1.86 (4H, m), 2.90 (2H, m), 3.05 (2H, m), 7.89 (1H, d, J = 9.0 Hz), 7.97 (1H, dd, J = 2.0 and 9.0 Hz), 8.18 (1H, s), 9.66 (1H, s)
6a [b]	1.50-2.10 (4H, m), 2.10 (3H, s), 2.63 (3H, s), 2.92 (2H, m), 3.69 (2H, m)
6b [b]	1.60-2.30 (4H, m), 2.50 (3H, s), 3.02 (2H, m), 3.87 (2H, m), 7.30 (4H, s)
6c [b]	1.72 (2H, m), 1.93 (2H, m), 2.17, 2.32 (3H, s), 3.00 (2H, m), 3.75 (2H, m), 7.45 (3H, m), 7.90 (2H, m)
6d [a]	1.43-2.00 (4H, m), 2.76-3.16 (7H, m), 7.30-7.52 (3H, m), 7.70-7.93 (2H, m)
6e [b]	1.77 (2H, m), 1.99 (2H, m), 3.06 (2H, t, J = 5.8 Hz), 3.06 (3H, s), 3.78 (2H, t, J = 5.4 Hz), 7.42 (3H, m), 7.87 (2H, m)

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

Scheme 5

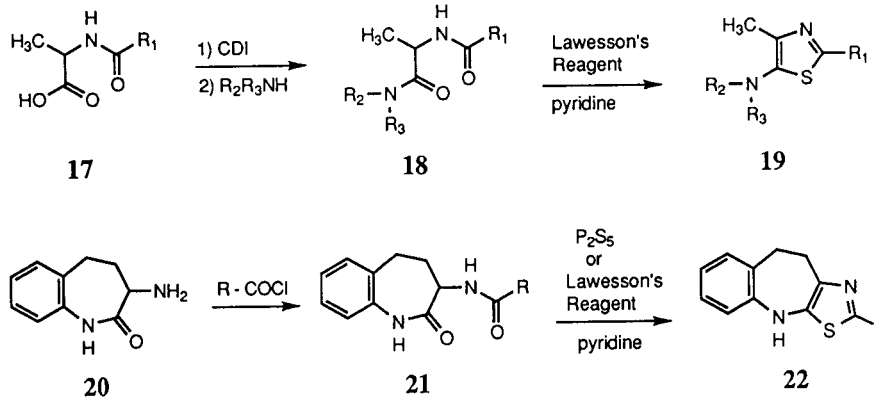
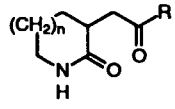
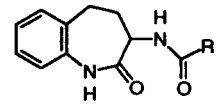


Table VIII

Diamides **10**, **15** and **21**



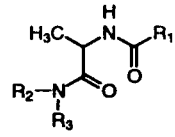


Compound No.	n	R	Method [a]	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N
10a	1	C_6H_5	A	52	184-186 (EtOH)	$C_{12}H_{14}N_2O_2$	66.04 65.62	6.47 6.81	12.84 12.78
10b	1	3-NH_2-4-Me-C_6H_3	B	81	161-164 (AcOEt-hexane)	$C_{13}H_{17}N_3O_2$	63.14 63.12	6.93 6.85	16.99 17.02
10c	1	C_6H_5CH=CH	A	92	229-230 (EtOH-hexane)	$C_{14}H_{16}N_2O_2$	68.83 68.73	6.60 6.42	11.47 11.47
10d	1	2,3-MeO-C_6H_3CH=CH	A	83	162-164 (AcOEt)	$C_{16}H_{20}N_2O_4$	63.14 63.45	6.62 6.72	9.20 9.07
15a	3	4-MeO-C_6H_4	A	92	257-260 ($CHCl_3$-EtOH)	$C_{15}H_{20}N_2O_3$	65.20 65.06	7.30 7.39	10.14 10.08
21a	-	CH_3	A	81	259-261 (AcOEt-EtOH)	$C_{12}H_{14}N_2O_2$	66.04 65.89	6.47 6.29	12.84 12.48
21b	-	C_6H_5	A	84	217-219 (AcOEt-EtOH)	$C_{17}H_{16}N_2O_2$	72.84 72.47	5.75 5.97	9.99 9.90
21c	-	4-MeO-C_6H_4	A	75	232-234 (AcOEt-EtOH)	$C_{18}H_{18}N_2O_3$	69.66 69.44	5.85 5.83	9.03 9.08
21d	-	C_6H_5CH=CH	A	72	209-211 (AcOEt)	$C_{19}H_{18}N_2O_2$	74.49 74.05	5.92 5.85	9.14 9.17

[a] See Experimental.

Table IX

Acyclic Diamides 18



Compound No.	R_1	R_2	R_3	Yield %	Mp, °C Recrystallization solvent	Molecular Formula	Analysis, % Calcd./Found C	H	N
18a	C_6H_5	C_6H_5	H	73	174-175 (AcOEt)	$C_{16}H_{16}N_2O_2$	71.62 71.65	6.01 6.00	10.44 10.46
18b	C_6H_5	4-Picolyl	H	88	153-155 (AcOEt)	$C_{16}H_{17}N_3O_2$	67.83 68.19	6.05 6.14	14.83 15.29
18c	C_6H_5	Et	Et	72	102-104 (AcOEt-hexane)	$C_{14}H_{20}N_2O_2$	67.72 67.75	8.12 8.00	11.28 11.35
18d	CH_3	C_6H_5	H	84	190-192 (EtOH)	$C_{11}H_{14}N_2O_2$	64.06 63.90	6.84 6.68	13.58 13.58

cinone (**14**) was obtained *via* a tedious multi-step pathway (Scheme 4), namely α,α-dibromination of 2-azacyclooctanone, reduction of dibromide to monobromide **12** [11,12], replacement of bromide by azide [13] and then catalytic hydrogenation of azide over Pd-C in ethanol to amino group. Acylation of amino groups of 3-aminolactams **9**, **14** thus obtained and the following reaction with phosphorus pentasulfide (or Lawesson's reagent) were carried out under similar conditions to those described for the thiazolo[5,4-*b*]azepine synthesis. Results obtained are shown in Table III. In these cases, too, 4,5,6,7-tetrahydrothiazolo[5,4-*b*]pyridines **11** and 4,5,6,7,8,9-hexahydrothiazolo[5,4-*b*]azocine **16** were obtained from the corresponding diamide **10**, **15** in moderate yields.

Then we applied this novel thiazole forming reaction to acyclic diamides **18** derived from *N*-acyl-α-amino acids

Table X

^{1}HNMR Spectral Data for the Compounds **10,11,15,16,18,19,21** and **22**

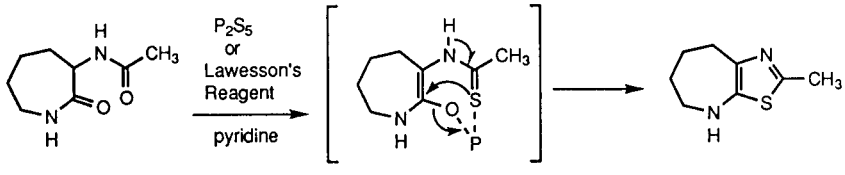
Compound	Chemical Shifts (δ, ppm)
10a [a]	1.70-2.10 (4H, m), 3.18 (2H, m), 4.37 (1H, m), 7.50 (3H, m), 7.64 (1H, broad s), 7.87 (2H, m), 8.60 (1H, d, J = 8.1 Hz)
10b [a]	1.68-2.10 (4H, m), 2.08 (3H, s), 3.16 (2H, broad s), 4.31 (1H, m), 4.97 (2H, broad s), 6.95-7.15 (3H, m), 7.61 (1H, broad s), 8.22 (1H, d, J = 8.1 Hz)
10c [a]	1.50-2.15 (4H, m), 3.17 (2H, broad s), 4.29 (1H, m), 6.71 (1H, d, J = 15.8 Hz), 7.35-7.63 (6H, m), 7.67 (1H, broad s), 8.31 (1H, d, J = 8.0 Hz)
10d [a]	1.50-2.10 (4H, m), 3.17 (2H, m), 3.76 (3H, s), 3.83 (3H, s), 4.28 (1H, m), 6.72 (1H, d, J = 16.0 Hz), 7.00-7.20 (3H, m), 7.63 (1H, broad s), 7.65 (1H, d, J = 16.0 Hz), 8.33 (1H, d, J = 8.3 Hz)
15a [a]	1.40-1.95 (8H, m), 3.33 (2H, m), 3.81 (3H, s), 4.87 (1H, m), 6.98 (2H, d, J = 8.9 Hz), 7.51 (1H, t, J = 6.7 Hz), 7.86 (2H, d, J = 8.9 Hz), 8.14 (1H, d, J = 6.7 Hz)
18a [a]	1.45 (3H, d, J = 7.0 Hz), 4.63 (1H, m), 7.04 (1H, t, J = 7.3 Hz), 7.30 (2H, t, J = 7.9 Hz), 7.40-7.70 (5H, m), 7.93 (2H, dd, J = 1.7 and 7.9 Hz), 8.61 (1H, d, J = 7.0 Hz), 10.03 (1H, broad s)
18b [a]	1.40 (3H, d, J = 7.0 Hz), 4.32 (2H, d, J = 5.9 Hz), 4.52 (1H, m), 7.26 (2H, d, J = 6.1 Hz), 7.40-7.60 (3H, m), 7.93 (2H, dd, J = 1.8 and 6.2 Hz), 8.48 (2H, d, J = 6.1 Hz), 8.56 (1H, t, J = 6.2 Hz)
18c [a]	1.03 (3H, t, J = 7.0 Hz), 1.23 (3H, t, J = 7.0 Hz), 1.30 (3H, d, J = 7.0 Hz), 3.06-3.50 (4H, m), 4.87 (1H, m), 7.39-7.60 (4H, m), 7.89 (2H, d, J = 7.3 Hz), 8.55 (1H, d, J = 7.3 Hz)
18d [a]	1.28 (3H, d, J = 7.2 Hz), 1.86 (3H, s), 4.42 (1H, m), 7.04 (1H, t, J = 7.3 Hz), 7.30 (2H, t, J = 7.9 Hz), 7.60 (2H, d, J = 8.1 Hz), 8.17 (1H, broad d, J = 7.3 Hz), 9.97 (1H, s)
21a [a]	1.81 (3H, s), 2.01 (1H, m), 2.24 (1H, m), 2.69 (2H, m), 4.19 (1H, m), 6.95-7.30 (4H, m), 8.08 (1H, d, J = 8.4 Hz), 9.78 (1H, s)
21b [a]	2.34 (2H, m), 2.76 (2H, m), 4.44 (1H, m), 7.00-7.60 (7H, m), 7.87 (2H, dd, J = 1.5 and 7.9 Hz), 8.53 (1H, d, J = 8.1 Hz), 9.85 (1H, s)
21c [a]	2.30 (2H, m), 2.76 (2H, m), 3.81 (3H, s), 4.43 (1H, m), 6.98 (2H, d, J = 8.9 Hz), 7.00-7.36 (4H, m), 7.85 (2H, d, J = 8.9 Hz), 8.37 (1H, d, J = 8.1 Hz)
21d [a]	2.04 (1H, m), 2.69 (1H, m), 2.97 (2H, m), 4.68 (1H, m), 6.47 (1H, d, J = 15.8 Hz), 6.81 (1H, d, J = 7.3 Hz), 7.00-7.54 (9H, m), 7.57 (1H, d, J = 15.8 Hz), 7.88 (1H, s)
11a [b]	2.00 (2H, m), 2.88 (2H, t, J = 6.4 Hz), 3.31 (2H, t, J = 5.4 Hz), 3.75 (1H, broad s), 7.29-7.42 (3H, m), 7.78 (2H, m)
11b [a]	1.93 (2H, broad s), 2.37 (3H, s), 2.77 (2H, broad s), 3.25 (2H, broad s), 7.39 (1H, d, J = 8.0 Hz), 7.64 (1H, broad d, J = 7.4 Hz), 7.83 (1H, broad s)
11c [b]	2.00 (2H, m), 2.83 (2H, t, J = 6.4 Hz), 3.31 (2H, t, J = 5.5 Hz), 3.82 (1H, broad s), 7.02 (1H, d, J = 16.4 Hz), 7.16 (1H, d, J = 16.4 Hz), 7.20-7.40 (3H, m), 7.42-7.50 (2H, m)
11d [b]	1.99 (2H, m), 2.83 (2H, t, J = 6.4 Hz), 3.31 (2H, t, J = 5.4 Hz), 3.85 (3H, s), 3.87 (3H, s), 6.84 (1H, dd, J = 1.6 and 8.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 7.16 (1H, dd, J = 1.6 and 7.9 Hz), 7.20 (1H, d, J = 16.4 Hz), 7.32 (1H, d, J = 16.4 Hz)
16a [b]	1.50-1.70 (4H, m), 1.78-1.91 (2H, m), 2.93 (2H, t, J = 6.2 Hz), 3.15 (2H, t, J = 5.2 Hz), 3.84 (3H, s), 6.90 (2H, d, J = 8.9 Hz), 7.76 (2H, d, J = 8.9 Hz)
19a [b]	2.35 (3H, s), 5.24 (1H, broad s), 6.50-6.92 (3H, m), 7.18-7.48 (5H, m), 7.85-7.93 (2H, m)
19b [b]	2.34 (3H, s), 4.65 (2H, s), 7.26-7.43 (3H, m), 7.64-7.72 (2H, m), 8.09 (2H, d, J = 6.8 Hz), 8.90 (2H, d, J = 6.8 Hz)
19c [b]	1.13 (6H, t, J = 7.1 Hz), 2.70 (3H, s), 3.11 (4H, q, J = 7.1 Hz), 7.50-7.61 (3H, m), 8.26-8.38 (2H, m)
19d [b]	2.24 (3H, s), 2.63 (3H, s), 5.12 (1H, broad s), 6.62-6.89 (3H, m), 7.15-7.28 (2H, m)
22a [b]	2.51 (3H, s), 3.00-3.20 (4H, m), 5.90 (1H, broad s), 6.77 (1H, dd, J = 1.2 and 7.9 Hz), 6.92 (1H, dt, J = 1.3 and 7.4 Hz), 7.06-7.20 (2H, m)
22b [b]	3.11 (2H, m), 3.27 (2H, m), 6.08 (1H, broad s), 6.81 (1H, dd, J = 1.0 and 7.8 Hz), 6.95 (1H, dt, J = 1.3 and 7.3 Hz), 7.09-7.20 (2H, m), 7.30-7.42 (3H, m), 7.60 (2H, m)
22c [b]	3.05-3.17 (2H, m), 3.18-3.30 (2H, m), 3.83 (3H, s), 6.03 (1H, broad s), 6.76-7.00 (2H, m), 6.90 (2H, d, J = 8.9 Hz), 7.08-7.20 (2H, m), 7.69 (2H, d, J = 8.9 Hz)
22d [b]	3.05-3.28 (4H, m), 6.14 (1H, broad s), 6.81 (1H, d, J = 8.0 Hz), 6.90-7.50 (10H, m)

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

(alanine) and bicyclic diamides, 3-(acylamino)-2,3,4,5-tetrahydro-1*H*-benzazepin-2-one **21** derived from **20** [14] (Scheme 5). In both cases, the corresponding 5-aminothiazole derivatives **19, 22** were obtained in reasonable yields and the widespread versatility of this simple method was suggested (Tables IV and V).

Although we have not carried out detailed mechanistic studies, we favor the sequence of events drawn for the conversion of **2a** → **7a** (Scheme 6). According to the report on sequence analysis of peptide chains by Barrett *et al.* [15], the intramolecular nucleophilic attack of thiolate anion upon carbonyl carbon is thought to give a thiazolone

Scheme 6



2a **23** **7a**

cleaving the C-N bond. A similar reaction (C-N bond cleavage) is well known as the Edman degradation [16]. Our results, however, show that in the presence of thiating agents the thiolate anion attacks the carbonyl carbon to give the 5-aminothiazole, cleaving the C-O bond instead of the C-N bond. Therefore, the thiating reagent seems to make the fission of the C-O bond easier.

The reaction of the diamide with phosphorus pentasulfide (or Lawesson's reagent) first may give the monothioamide, the carbonyl group of which seems to form a complex like **23** with phosphorus pentasulfide (or Lawesson's reagent), followed by intramolecular nucleophilic attack of thiolate anion upon the activated carbonyl carbon cleaving the C-O bond to form 5-aminothiazole, though the possibility of dithioamide formation as a precursor of 5-aminothiazole remains unresolved. The C-O bond cleavage seems to come from the high affinity of oxygen for phosphorus.

In conclusion, we have developed a new simple synthetic method for 5-aminothiazole derivatives. This method would be particularly useful for the preparation of new pharmacologically interesting aminothiazole derivatives. The biological properties of compounds obtained in this study are now under test and will be reported elsewhere.

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-(Acylamino)-ϵ-caprolactam Derivatives **2a-n** (Tables VI and VII).

Typical Procedure (Method A).

3-(Acetylamino)-ϵ-caprolactam (**2a**).

A solution of acetyl chloride (6.1 ml) in tetrahydrofuran (THF) (10 ml) was added to an ice-cold solution of 3-amino-ϵ-caprolactam (**1**) (10 g) and triethylamine (11.8 g) in THF (50 ml). After the mixture was stirred for 2 hours at 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 chloroform:methanol (95:5, v/v) as eluent. The fractions containing **2a** were combined and concentrated. The residue was recrystallized from ethyl acetate to yield 5.93 g (45%) of **2a**. Compounds (**2b**, **2d-f**, **2h** and **2k**) were prepared by the similar procedures employed in the preparation of **2a** using **1** and acyl chlorides. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables VI and VII.

Typical Procedure (Method B).

3-(Cinnamoylamino)-ϵ-caprolactam (**2c**).

To a solution of cinnamic acid (5.0 g) in THF (50 ml) was added 1,1'-carbonyldiimidazole (CDI) (6.0 g). After the mixture was stirred for 20 minutes at room temperature, 3-amino-ϵ-caprolactam (**1**) (4.76 g) was added to the mixture. After the mixture was stirred for 2 hours at 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 chloroform:methanol (95:5, v/v) as eluent. The fractions containing **2c** were combined and concentrated. The residue was recrystallized from ethanol to yield 7.3 g (84%) of **2c**. Compounds **2g**, **2i,j** and **2l-n** were prepared by similar procedures employed in the preparation of **2c** using **1** and carboxylic acids. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables VI and VII.

3-(Thioacetylamino)-ϵ-thiocaprolactam (**3a**).

A mixture of 3-(acetylamino)-ϵ-caprolactam (**2a**) (510 mg) and phosphorus pentasulfide (1.2 g) in toluene (10 ml) was refluxed for 20 hours. After being cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the product was extracted with chloroform. 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 chloroform:acetone (95:5, v/v) as eluent. The fractions containing **3a** were combined and concentrated. The residue was recrystallized from cyclohexane to yield 250 mg (41%) of **3a**, mp 156-158°; ^{1}H nmr (deuteriochloroform): δ 2.56 (3H, s), 1.20-2.60 (6H, m), 3.60 (2H, m), 5.16 (1H, d), 10.2-11.0 (2H, broad).

Anal. Calcd. for $C_8H_{14}N_2S_2$: C, 47.49; H, 6.97; N, 13.84. Found: C, 47.02; H, 6.97; N, 13.78.

2-Substituted 5,6,7,8-Tetrahydro-4*H*-thiazolo[5,4-*b*]azepine Derivatives **7a-n** (Tables I and VII).

Typical Procedure (Method C).

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

To a solution of diamide **2b** (5.2 g) in pyridine (50 ml) was added phosphorus pentasulfide (5.4 g) and the mixture was heated at 100° for 5 hours. After being cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the product was extracted with chloroform. 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 chloroform:methanol (98:2, v/v) as eluent. The fractions containing **7b** were combined and concentrated. The residue was recrystallized from ethyl acetate to yield 2.78 g (54%) of **7b**. Compounds **7c-n** were prepared by the similar procedures employed in the preparation of **7b** using phosphorus pentasulfide and 3-(acylamino)-ϵ-caprolactams. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables I and VII.

Typical Procedure (Method D).

5,6,7,8-Tetrahydro-2-methyl-4*H*-thiazolo[5,4-*b*]azepine Hydrochloride (**7a**).

To a solution of diamide **2a** (4.77 g) in pyridine (60 ml) was added Lawesson's reagent (11.3 g) [7] and the mixture was heated at 100° for 4 hours. After being cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the product was extracted with chloroform. 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 ethyl acetate:hexane (1:1, v/v) as eluent to give the free base of **7a**. It was converted into the hydrochloride by the treatment with an ethanol solution previously saturated with hydrogen chloride gas, followed by recrystallization from ether-ethanol to yield 1.32 g (23%) of **7a**. Melting point, resulting elemental analysis and spectral data of this compound are listed in Tables I and VII.

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

A mixture of **3a** (1.9 g) and acetic anhydride (20 ml) was refluxed for 30 minutes. 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 chloroform:acetone (95:5, v/v) as eluent. The fractions containing **6a** were combined and concentrated to yield 1.41 g (72%) of **6a**. Melting point, resulting elemental analysis and spectral data of this compound are listed in Tables II and VII.

4-(4-Chlorobenzoyl)-5,6,7,8-tetrahydro-2-methyl-4*H*-thiazolo[5,4-*b*]azepine (**6b**).

A solution of 4-chlorobenzoyl chloride (3.9 g) in dichloromethane (5 ml) was added to an ice-cold solution of **7a** (1.3 g) in pyridine (20 ml). After the mixture was stirred for 12 hours at 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 chloroform:acetone (98:2, v/v) as eluent. The fractions containing **6b** were combined and concentrated. The residue was recrystallized from cyclohexane to yield 1.56 g (66%) of **6b**. Melting point, resulting elemental analysis and spectral data of this compound are listed in Tables II and VII.

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

This compound was prepared from **7d** with acetic anhydride in the same manner as described for **6a**. Melting point, resulting elemental analysis and spectral data of this compound are listed in Tables II and VII.

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

A mixture of **7d** (0.83 g), iodomethane (0.6 g) and potassium carbonate (0.75 g) in *N,N*-dimethylformamide (DMF) (30 ml) was stirred at 90° for 4.5 hours. The reaction mixture was poured into water and extracted with chloroform. 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 chloroform as eluent to give the free base of **6d**. It was converted into the hydrochloride by the treatment with an ethanol solution previously saturated with hydrogen chloride gas, followed by recrystallization from ether-ethanol to yield 530 mg (52%) of **6d**. Melting point, resulting elemental analysis and spectral data are listed in Tables II and VII.

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

Methanesulfonyl chloride (0.6 g) was added to an ice-cooled solution of **7d** (1.0 g) in pyridine (10 ml). After the mixture was stirred for 3 hours at 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 ethyl acetate:hexane (4:6, v/v) as eluent. The fractions containing **6e** were combined and concentrated. The residue was recrystallized from ethyl acetate-hexane to yield 1.13 g (84%) of **6e**. Melting point, resulting elemental analysis and spectral data are listed in Tables II and VII.

Diamide Derivatives **10a-d, 15a** and **21a-d** (Tables VIII and X).

Compounds **10a-d, 15a** and **21a-d** were prepared from the corresponding amines **9, 14** and **20** with the appropriate carboxylic acid derivatives by the similar procedures employed in the preparation of **2**. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables VIII and X.

Preparation of Bi- and Tricyclic Aminothiazole Derivatives **11a-d, 16a** and **22a-d** (Tables III, V and X).

Compounds **11a-d, 16a** and **22a-d** were prepared from the corresponding diamides **10a-d, 15a** and **21a-d** with the appropriate thiating agent such as phosphorus pentasulfide or Lawesson's reagent by the similar procedures employed in the preparation of **7**. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables III, V and X.

3-Azidohexahydro-2(1*H*)-azocinone (**13**).

A mixture of 3-bromohexahydro-2(1*H*)-azocinone (**12**) (8.2 g) [11,12] and sodium azide (3.1 g) in DMF (50 ml) was stirred at 80° for 14 hours [13]. The reaction mixture was poured into water and extracted with chloroform. 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 ethyl acetate as eluent. The fractions containing **13** were combined and concentrated to yield 3.2 g (48%). An analytical sample was obtained by recrystallization from ethyl acetate-hexane, mp 103-106°; ^{1}H nmr (deuteriochloroform): δ 1.50-1.80 (6H, m), 1.93-2.12 (2H, m), 3.28-3.40 (2H, m), 4.04 (1H, m), 6.15 (1H, broad s).

Anal. Calcd. for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 50.01; H, 7.01; N, 32.95.

3-Aminohexahydro-2(1*H*)-azocinone (**14**).

A solution of **13** (3.0 g) in ethanol (30 ml) was subjected to hydrogenation in the presence of 10% Pd-C (300 mg). After hydrogen absorption ceased, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography with chloroform:methanol (9:1, v/v) as eluent. The fractions containing **14** were combined and concentrated to yield 2.4 g (96%). An analytical sample was obtained by recrystal-

lization from ethyl acetate, mp 147-149°; ^{1}H nmr (deuteriochloroform): δ 1.45-2.05 (8H, m), 3.15-3.60 (2H, m), 3.70-3.85 (1H, m), 6.02 (1H, broad s).

Anal. Calcd. for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 58.05; H, 9.95; N, 19.45.

Diamide Derivatives **18a-d** (Tables IX and X).

Typical Procedure.

N-Benzoyl-DL-alanine anilide (**18a**) [17,18].

To a solution of *N*-benzoyl-DL-alanine (5.0 g) in THF (30 ml) was added CDI (4.62 g). After the mixture was stirred for 20 minutes at room temperature, aniline (2.65 g) was added to the mixture. After the mixture was stirred for 4 hours at 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 chloroform:methanol (97:3, v/v) as eluent. The fractions containing **18a** were combined and concentrated. The residue was recrystallized from ethyl acetate to yield 5.1 g (73%) of **18a**. Compounds **18b-d** were prepared from alanine derivatives and a corresponding amine by the similar procedures employed in the preparation of **18a**. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables IX and X.

2,5-Disubstituted 4-methyl-5-aminothiazole Derivatives **19a-d** (Tables IV and X).

Typical Procedure.

5-Anilino-4-methyl-2-phenylthiazole (**19a**).

To a solution of diamide **18a** (4.83 g) in pyridine (50 ml) was added Lawesson's reagent (7.28 g) and the mixture was heated at 100° for 5 hours. After being cooled to room temperature, saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the product was extracted with chloroform:methanol (9:1, v/v). 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 ethyl acetate:hexane (9:1, v/v) as eluent. The fractions containing **19a** were combined and concentrated. The residue was recrystallized from ethyl acetate-hexane to give (3.62 g, 76%) of **19a**. Compounds **19b-d** were prepared by the similar procedures employed in the preparation of **19a** using Lawesson's reagent and diamide. Melting points, resulting elemental analyses and spectral data of these compounds are listed in Tables IV and X.

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