Heterocyclic Cation Systems. 14.[1] Synthesis of Thieno[3,2-e][1,4]diazepine, Thiazolo[4,5-e][1,4]diazepine, and s-Triazolo[3,4-c]thiazolo[4,5-e][1,4]diazepine Derivatives

Kentaro Hirai,* Hirohiko Sugimoto, and Teruyuki Ishiba

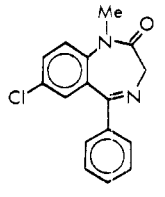
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Received July 16, 1979

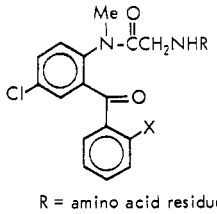
Synthesis of hetero[e][1,4]diazepines is described. The synthetic route involved reactions of the anion of malononitrile or cyanamide toward 2-substituted 1,3-oxathiolium cation **1** to give amino ketone derivatives **3** and **4** as the key intermediates. Introduction of a glycyl unit into **3** and **4** and subsequent cyclodehydration led to the title compounds.

1,3-Oxathiolium cation **1** is a positively charged 6π electronic species and reacts with nucleophiles to give a variety of heterocyclic compounds. Thus, it is a highly versatile reaction intermediate. We have investigated the reactivity of **1** toward a number of nucleophiles to afford thiophene, thiazole, thiazole *N*-oxide, thiadiazine, pyrazole, oxathiole, and thiazolidine derivatives.[2] Using **1**, we have also made thiazol-5-ylacetic acid derivatives which have shown strong antiinflammatory activity.[3] As an extension of this study, we have examined the reaction of malononitrile and cyanamide in the presence of base to yield amino ketone products **3** and **4**. This type of compound is a potential key intermediate for fusing of the [1,4]-diazepine ring to afford hetero[e][1,4]diazepines of the well-known 1,4-benzodiazepines.

1,4-Benzodiazepines (e.g., diazepam)[4] and their open-ring derivatives[5] are among the more interesting classes of



Diazepam



R = amino acid residue
X = H or halogen

compounds having strong activity on the central nervous system. A great deal of synthetic work describing the preparation of heteroring-fused diazepine has appeared.[6] However, few thiazolo[e][1,4]diazepines have been reported.

In this report, we describe the synthesis of hetero[e]-[1,4]diazepine derivatives from the 2-substituted 1,3-oxathiolium salts.

Results and Discussion

Reaction of 2-Substituted 5-Aryl-1,3-oxathiolium Cation with Malononitrile and Cyanamide in the Presence of Base. The key step in the synthetic route to the title compounds involves preparation of the amino ketones **3** and **4**. We have previously reported the nucleophilic reaction of active methylene compounds in the presence of base toward 2-(dialkylamino)-5-aryl-1,3-oxathiolium cation to give thiophene, 1,4-oxathiafulvene, and the ketene *S,N*-acetal, depending on the substituent of the active methylene compound. Thus, malononitrile was found to afford the desired amino ketone in one step in the reaction with 2-morpholino- (**1a**) or 2-piperidino-5-phenyl-1,3-oxathiolium hydrogen sulfate (**1b**) in the presence of triethylamine in CH_2Cl_2.[2g]

When cation **1a** was allowed to react with an excess of aqueous solution of cyanamide in the presence of 2 equiv of NaOH at room temperature, a yellow product precipitated. The structure proof of the product **4b** rests on its spectral data. NMR and IR spectra of this product, which showed strong UV absorption at 361 nm with log ϵ 4.36 in EtOH, indicated the presence of morpholino- (δ 3.33–3.92 in $CDCl_3$), amino- (δ 7.02; 3240 and 3370 cm^{-1} in KBr), and benzoyl-type phenyl groups (δ 7.20–7.80; 1600 cm^{-1}). The presence of the thiazole ring was evidenced by its ^{13}C NMR spectrum; i.e., the 2-, 4-, and 5-carbons of the thiazole ring are at 72.7, 165.7, and 94.8 ppm (from Me_4Si in $CDCl_3$), respectively, and the benzoyl ketone carbon is at 184.3 ppm. From these spectral and analytical data, the product was assigned as 4-amino-5-benzoyl-2-morpholinothiazole (**4b**). Hartmann[7] has reported the reaction of cyanamide with 2-aryl-1,3-oxathiolium cation. The reaction routes are summarized in Scheme I and the results in Table I.

As suggested in Scheme I, amino ketones **4a–e** were produced via intermediate **2** which was isolated by changing the reaction conditions. Reaction of cyanamide with cation **1b** in the absence of base resulted in the formation of intermediate **2** in 13% yield. The structure of **2** follows from its spectral and analytical data as well as from the fact that it is converted into **4a** upon treatment with aqueous base.

(1) Previous paper: K. Hirai and T. Ishiba, *Heterocycles*, **9**, 1223 (1978).

(2) (a) K. Hirai and T. Ishiba, *Chem. Pharm. Bull.*, **26**, 3017 (1978); (b) *ibid.*, **20**, 304 (1972); (c) *Chem. Commun.*, 1319 (1971); (d) K. Hirai, T. Ishiba, and H. Sugimoto, *Chem. Pharm. Bull.*, **20**, 1711 (1972); (e) *Tetrahedron*, **33**, 1595 (1977); (f) K. Hirai and T. Ishiba, *Heterocycles*, **3**, 217 (1975); (g) *Chem. Pharm. Bull.*, **20**, 2384 (1972).

(3) K. Hirai and H. Sugimoto, *Chem. Pharm. Bull.*, **25**, 2292 (1977).

(4) Recent review: L. H. Sternbach, *J. Med. Chem.*, **22**, 1 (1979).

(5) (a) K. Hirai, T. Ishiba, H. Sugimoto, K. Sasakura, T. Fujishita, Y. Tsukinoki, and K. Hirose, *Chem. Pharm. Bull.*, **26**, 1947 (1978); (b) C. H. Hassall, S. W. Holms, W. H. Johnson, A. Kröhn, C. E. Smitten, and W. A. Thomas, *Experientia*, **33**, 1492 (1977).

(6) (a) O. Hromatka, D. Binder, P. Stanetty, and G. Marischler, *Monatsh. Chem.*, **107**, 233 (1976), and references therein; (b) M. Nakanishi, T. Tahara, K. Araki, M. Shiroki, T. Tsumagiri, and Y. Takigawa, *J. Med. Chem.*, **16**, 214 (1973); (c) K. Maier and O. Hromatka, *Monatsh. Chem.*, **102**, 1010 (1971); (d) R. Littell and D. R. Allen, Jr., *J. Med. Chem.*, **8**, 722 (1965); (e) H. A. DeWald, I. C. Nordin, Y. J. L'Italien, and R. F. Parcell, *ibid.*, **16**, 1346 (1973); (f) E. E. Garcia, L. E. Benjamin, and R. I. Fryer, *J. Heterocycl. Chem.*, **10**, 51 (1971); (g) R. Jaunin, *Helv. Chim. Acta*, **57**, 1935 (1974); (h) L. Fontanella, L. Mariani, G. Tarzia, and N. Corsico, *Eur. J. Med. Chem.—Chim. Ther.*, **11**, 217 (1976); (i) A. S. Noravyan, A. P. Mkrtchyan, I. A. Dzhagatspanyan, and S. A. Vartanyan, *Khim.-Farm. Zh.*, **11**, 62 (1977); *Chem. Abstr.*, **88**, 22853 (1978); (j) W. H. Hong, C. Johnston, and D. Szulczewski, *J. Pharm. Sci.*, **66**, 1703 (1977).

(7) H. Hartmann, *Z. Chem.*, **11**, 421 (1971).

0022-3263/80/1945-0253$01.00/0

Scheme I

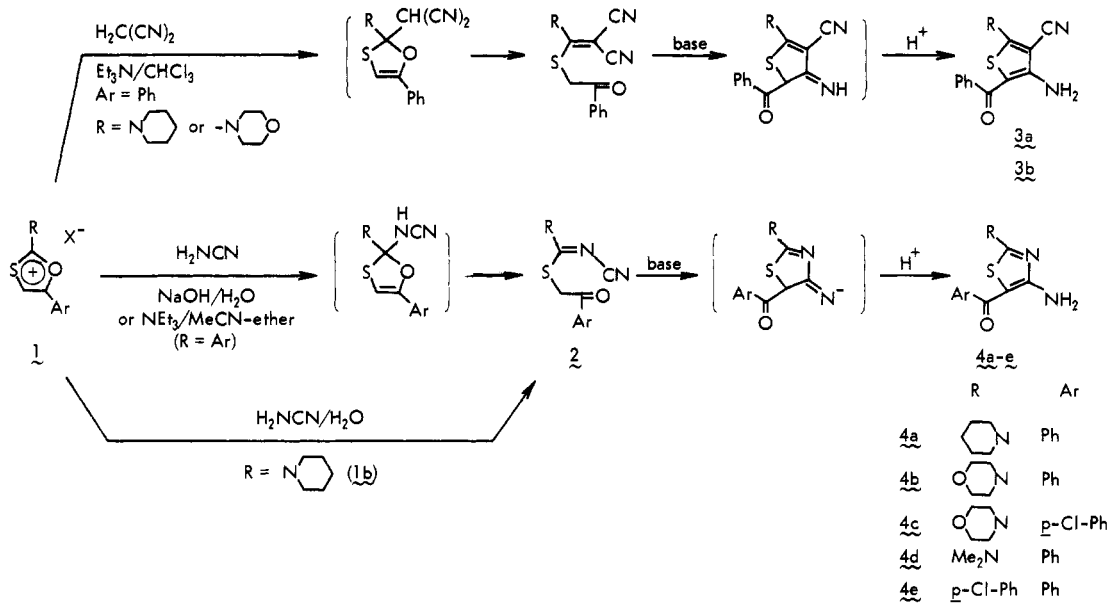
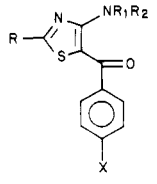


Table I. 2-Substituted 4-Amino-5-benzoylthiazoles 4a-e and 14a-d[a]



compd	R[e]	X	R_1	R_2	mp, °C[b]	yield, %	elemental analysis[d] C	H	N	S
4a	pip	H	H	H	159-160	76	c			
4b	morph	H	H	H	179-181	88	58.11	5.23	14.52	11.08
							58.28	5.13	14.33	11.99
4c	morph	Cl	H	H	151-152	87	51.93	4.36	12.98	9.90
							51.72	4.52	12.75	9.87
4d	Me_2N	H	H	H	154-155	85	58.28	5.30	16.99	12.97
							58.30	5.20	17.27	13.20
4e	*p*-ClPh	H	H	H	146-147	48	c			
14a	pip	H	Me	H	129-130	78	63.76	6.35	13.94	10.64
							64.01	6.38	13.92	10.78
14b	morph	Cl	Me	H	200-201	51	c			
14c	Me_2N	H	Me	H	144-145	98	59.74	5.78	16.08	12.27
							59.65	5.80	16.08	12.48
14d	morph	Cl	Me	Me	176-177	15	c			

[a] Satisfactory analytical data (±0.3%) were reported for all compounds in Tables I-IV. [b] Recrystallized from EtOH. [c] See Experimental Section. [d] The calculated value is given first, and the found value is given under it. [e] Abbreviations: morph = morpholino and pip = piperidino.

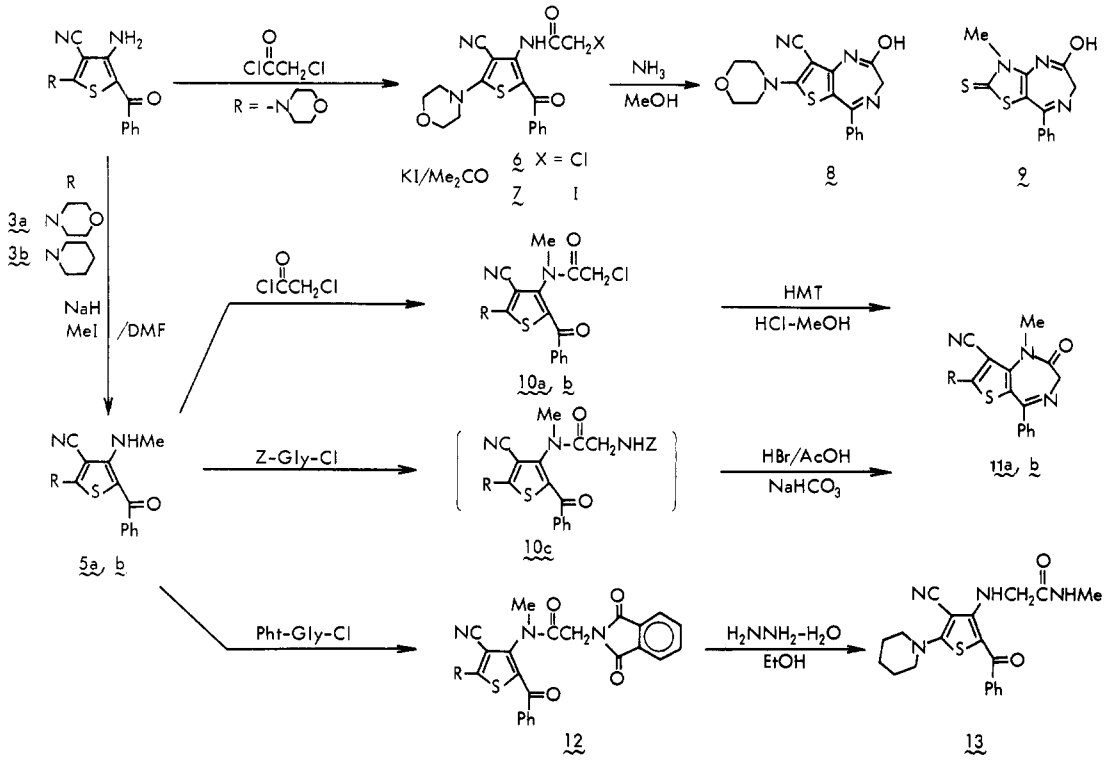
In contrast to **1a** or **1b**, 2,5-diaryl-1,3-oxathiolium cation **1e** was found to be readily attacked by hydroxide anion in water solvent, and hence a nonaqueous reaction medium was necessary to obtain **4e**.

Synthesis of Thieno[3,2-*e*][1,4]diazepine. The amino ketones **3** and **4** were transformed into thieno[*e*][1,4]-diazepines by the synthetic routes shown in Scheme II.

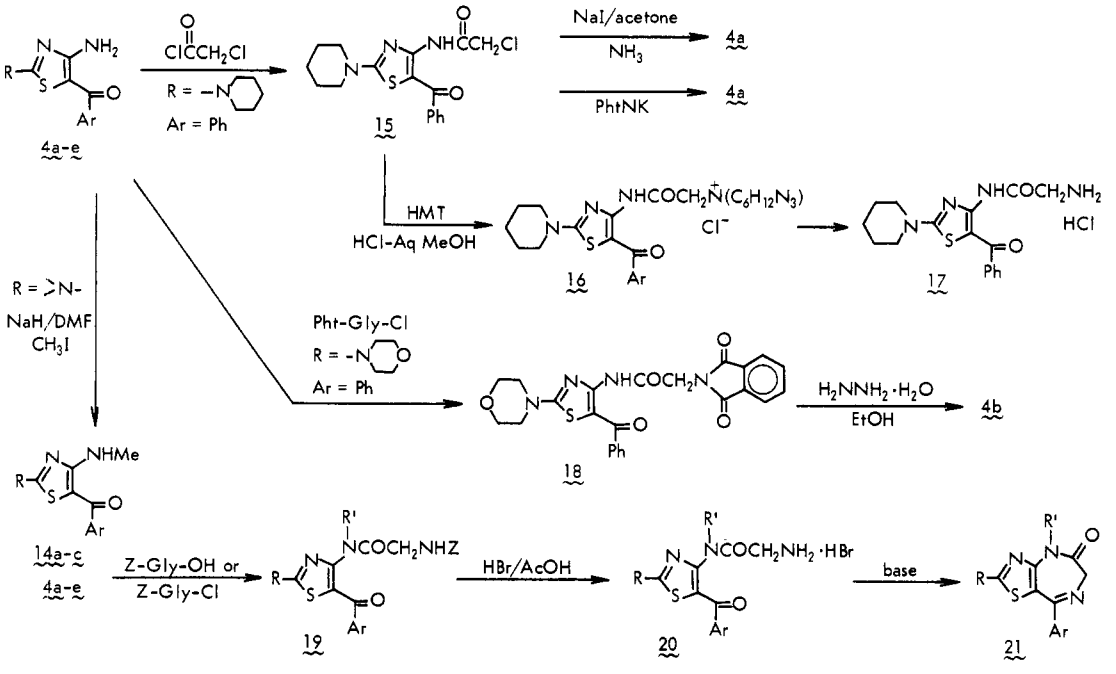
Chloroacetylation of **3a** with chloroacetyl chloride in refluxing benzene followed by halogen exchange with KI in acetone and ammonolysis afforded the thienodiazepine **8** in 55% yield. That diazepine **8** possesses the lactim form was demonstrated by its IR spectrum; i.e., no carbonyl stretching absorption in the amide region was observed, but OH stretching at 3450 cm^{-1} was found. Maier et al.[6c] have reported that the thiazolo[4,5-*e*][1,4]diazepine **9** had the lactim form as evidenced by ν_{OH} at 3580 cm^{-1}. Next, we tried to prepare the N-methylated analogue of **8**. The usual methylation of **3** with NaH in DMF gave N-methylated thiophene derivatives **5** in good yield. Chloroacetylation of **5a** gave **10a**, which showed two kinds of Me groups at δ 3.03 and 3.15 with an integral ratio of 1:2. This could be ascribed to the rotational isomers along the amide bond. As attempted halogen exchange of **10a** with KI in refluxing acetone was unsuccessful, ammonolysis was not performed. Delepiné reaction, that is, treatment of **10a** with hexamethylenetetramine (HMT) in acidic methanol, resulted in the formation of thienodiazepine **11a** in low yield.

Alternatively, **11** was synthesized by coupling **5** with carbobenzoxyglycyl chloride [(*Z*)-Gly-Cl] in THF-DMF at room temperature followed by deblocking with HBr in AcOH and finally cyclization with aqueous $NaHCO_3$. However, when phthalylglycyl chloride (Pht-Gly-Cl) was used, hydrazinolysis of the coupling product **12** with hydrazine hydrate in refluxing EtOH did not proceed to the desired product. The product obtained showed doublet

Scheme II



Scheme III



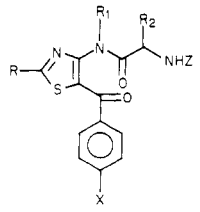
methylene (δ 4.37, J = 7 Hz) and doublet methyl (δ 2.88, J = 5 Hz) by NMR in $CDCl_3$[8a] and NH by IR (3320 cm^{-1}). The mass spectrum revealed the benzoyl group, the intensity of m/e 105 being 40% to the base peak (m/e M^+ − 58).[8b] From these data, the structure of the unexpected product was assigned to the Smiles rearranged compound **13**. This is in accord with the known example of *N*-methyl-4′-nitro-2-phthalimidoacetanilide, which is reported to rearrange on hydrazinolysis directly to *N*-methyl-2-[(4-nitrophenyl)amino]acetamide.[9] This rearrangement is facilitated by the electron-withdrawing group on the aromatic ring. The presence of cyano and benzoyl groups on the thiophene **12** made rearrangement easy. This appears to be the first example in which nitrogen to nitrogen Smiles rearrangement on a thiophene took place.

Thiazolo[4,5-*e*][1,4]diazepine. Methylation of **4** gave, in addition to mono-N-methylated thiazole **14**, dimethylated derivatives in some cases. A reaction sequence similar to that used for the introduction of a glycyl unit into amino ketones **3a,b** was employed for the synthesis of thiazolodiazepines. However, unforeseen difficulties were encountered at some stages. Scheme III depicts the

(8) (a) The elimination of the NH–CH_2 coupling by H–D exchange ($CDCl_3$–CD_3OD) was faster than that of the $NHCH_3$ coupling. (b) The relative intensities of m/e M^+ − 105 and M^+ − 164 are 19 and 4%, respectively.

(9) L. H. Sternbach, N. W. Gilman, and P. Levitan, *J. Org. Chem.*, **38**, 373 (1973).

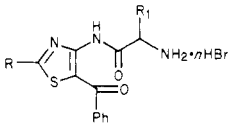
Table II. 2-Substituted 5-Benzoyl-4-[[((benzoxycarbonyl)amino)acetyl]amino]thiazoles 19a-i



compd	R[e]	X	R_1	R_2	mp, °C[a]	yield, %	elemental analysis[d] C	H	N	S
19a	pip	H	H	H	158-159	55	b			
19b	morph	H	H	H	132-134		59.99	5.03	11.66	6.67
							60.21	5.10	11.50	6.65
19c	Me_2N	H	H	H	120-121	77	60.26	5.06	12.78	7.31
							60.51	4.99	12.97	7.63
19d	Me_2N	H	H	Me[c]	154-156	50	61.05	5.35	12.38	7.08
							60.81	5.17	12.57	6.92
19e	Me_2N	H	H	CH_2Ph[c]	133-136	33	65.89	5.34	10.60	6.06
							65.78	5.16	10.75	6.27
19f	*p*-ClPh	H	H	H	107-108	76	61.72	3.98	8.30	6.34
							61.49	4.08	8.36	6.40
19g	pip	H	Me	H	123-125	35	63.39	5.73	11.37	6.51
							63.10	5.65	11.39	6.43
19h	morph	Cl	Me	H	75-76	91	56.76	4.76	10.59	6.06
							56.66	4.59	10.76	6.35
19i	Me_2N	H	H	H	134-136	88	61.05	5.35	12.38	7.08
							60.99	5.32	12.54	6.90

[a] Recrystallized from EtOH-AcOEt. [b] See Experimental Section. [c] A *dl*-amino acid was used. [d] The calculated value is given first, and the found value is given under it. [e] Abbreviations: morph = morpholino and pip = piperidino.

Table III. 2-Substituted 4-[(Aminoacetyl)amino]-5-benzoylthiazole Hydrobromides 20a-e



compd	R[e]	R_1	dec pt, °C[a]	yield, %	elemental analysis[e] C	H	N	S
20a	pip	H	210-211	81[b]	48.00	4.98	13.17	7.54
					47.75	4.92	13.33	7.72
20b	morph	H	214-215	90[b]	44.97	4.48	13.11	7.49
					44.70	4.36	12.81	7.25
20c	Me_2N	H	204-205	91[c]	34.73	4.16	11.57	6.62
					34.74	4.11	11.51	6.64
20d	Me_2N	Me[d]	172-174	85[c]	37.51	4.20	11.67	6.68
					37.41	4.51	11.81	6.36
20e	Me_2N	CH_2Ph[d]	160-163	90[c]	43.92	4.56	9.76	5.58
					44.12	4.34	10.05	5.42

[a] Reprecipitated from CH_3CN-ether. [b] $n = 1$. [c] $n = 2$. [d] A *dl*-amino acid was used. [e] See corresponding footnotes in Table I or II.

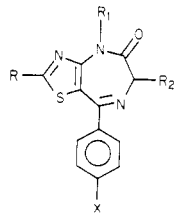
synthetic routes for thiazolodiazepines.

Chloroacetylation of **4a** in refluxing benzene with K_2CO_3 afforded amide **15**, and coupling of **4b** with Pht-Gly-Cl in THF-DMF-K_2CO_3 gave **18**. Ammonolysis and Gabriel synthesis of **15** and hydrazinolysis of **18** did not lead to the expected products. Both compounds underwent exclusive amide bond cleavage to the starting amino ketones **4a** and **4b**, respectively. It became clear that the amide bond of **15** and **18** was readily cleaved by base, and a nonbasic condition to obtain diazepine or its precursor was required. One such reaction is the Delepiné reaction. Treatment of **15** with HMT in HCl-H_2O-MeOH for 4 h at 50 °C gave only the initial adduct **16** which was identified by its spectral and analytical data. Under the same conditions, 4-chloro-2-[(chloroacetyl)amino]benzophenone or **10a** was converted into the corresponding [1,4]diazepine derivative in one step.[10] Further refluxing of the adduct **16**, after isolation, in the same solvent system gave a solid which was very difficult to purify. The spectral and analytical data indicate that it was a salt of (glycylamino)thiazole **17**. No further attempt to cyclize **17** was made because of the difficulty in purifying it.

Successful synthesis of the thiazolo[1,4]diazepine was achieved by the following method. Condensation of **4** with (*Z*)-Gly-OH was performed by using DCC in CH_2Cl_2-THF as the dehydrating reagent, but the yield was poor (<10%) with almost complete recovery of **4**. However, when the coupling was carried out in the HMPA-$SOCl_2$ system which was developed by Normant et al.,[11] the yield increased to 60–80%. The results for substituted acylamino derivatives **19** are shown in Table II.

(10) N. Blazevic and F. Kaifez, *J. Heterocycl. Chem.*, 7, 1173 (1970).
(11) J. F. Normant and H. Deshayes, *Bull. Soc. Chim. Fr.*, 2854 (1972).

Table IV. 4,6-Dihydro-8-aryl-2,4,6-trisubstituted-thiazolo[4,5-*e*][1,4]diazepin-5(5*H*)-ones 21a-i



compd	R[f]	X	R_1	R_2	mp, °C[a]	yield, %	elemental analysis[f] C	H	N	S
21a	pip	H	H	H	191-193	29[d]	*b*			
21b	morph	H	H	H	200-201	30[d]	58.52	4.91	17.06	9.76
							58.30	5.00	16.74	9.75
21c	Me_2N	H	H	H	226-227	17[d]	58.51	5.26	19.50	11.16
							58.55	5.25	19.53	11.07
21d	Me_2N	H	H	Me[c]	204-207	19[d]	59.98	5.37	18.65	10.65
							59.87	5.40	18.93	10.43
21e	Me_2N	H	H	CH_2Ph[c]	181-182	66[d]	67.00	5.35	14.88	8.52
							67.19	5.18	14.77	8.40
21f	*p*-ClPh	H	H	H	194-195	77[e]	61.10	3.40	11.88	9.06
							60.85	3.86	11.80	8.80
21g	pip	H	Me	H	145-147	16[e]	63.50	5.92	16.46	9.40
							63.50	5.76	16.35	9.28
21h	morph	Cl	Me	H	222-223	37[e]	54.18	4.56	14.87	8.51
							53.98	5.35	14.64	8.47
21i	Me_2N	H	Me	H	138-139	22[e]	59.98	5.37	18.65	10.65
							60.15	5.52	18.64	10.85

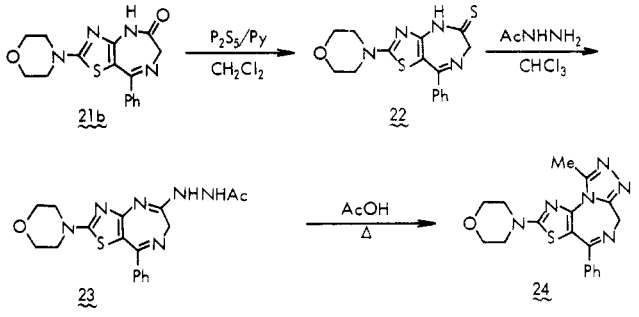
[a] Recrystallized from AcOEt. [b] See Experimental Section. [c] A *dl*-amino acid was used. [d] From 18. [e] From 17. [f] See corresponding footnotes in Table I or II.

Compounds **19** were subjected to deblocking with HBr–AcOH, which gave the amino derivatives **20**, summarized in Table III. The salts were usually hydrated. Direct base treatment (Dabco–MeCN) of this hydrate salt resulted in a complex mixture with only a poor yield of diazepine. But by simply refluxing the hydrobromide hydrate in MeCN, it was converted into anhydrous salt **20**. Stirring this dehydrated salt, **20a**, in MeCN with Dabco for 3 h at 50 °C yielded, after column separation, the expected thiazolo[1,4]diazepine **21a** in 29% yield. The results obtained with other diazepines are shown in Table IV.

***s*-Triazolo[3,4-*c*]thiazo[4,5-*e*][1,4]diazepine.** With the diazepines in hand, we further examined the synthesis of the tricyclic fused diazepine derivatives. Recently, interest has developed in synthesizing tricyclic derivatives in which another heteroring is fused to the amide moiety of benzo[1,4]diazepine or heteroring-fused [1,4]diazepine. They were reported to have different spectra of activity on the central nervous system.[12] The synthetic sequence utilized to prepare the title compound is outlined in Scheme IV.

A frequently used method to activate the carbonyl bond of a diazepine is to convert it into the thione.[13] Treatment of thiazolodiazepine **21b** with P_2S_5 in CH_2Cl_2 produced the thermally unstable thione **22**. This was condensed, without purification, with acetohydrazide in $CHCl_3$ at room temperature. Fast reaction afforded an orange-red product **23** in 43% yield from **21b**. Cyclization of **23** in refluxing AcOH resulted in the formation of the colorless tricyclic

Scheme IV



derivative **24**. The structural assignment was based on its spectral and analytical data.

Experimental Section

Melting points are uncorrected. The UV spectra were measured with a Hitachi EPS-2 spectrophotometer, IR spectra in KBr with a JASCO DS-403G spectrometer, NMR spectra with a Varian A-60 instrument with Me_4Si as an internal standard, ^{13}C spectra with a Varian NV-14FT NMR spectrometer, and mass spectra with a Hitachi RMU-6E spectrometer.

5-Aryl-2-(dialkylamino)-1,3-oxathiolium Cation (1). Starting cations 1 were prepared by a method described previously.[2b]

Reaction of 1b with Cyanamide in the Absence of Base. A solution of 1.00 g (2.89 mmol) of 5-phenyl-2-piperidino-1,3-oxathiolium perchlorate (**1b**) in 30 mL of an aqueous solution of excess cyanamide[14] and 10 mL of $CHCl_3$ was stirred for 6 h at room temperature. The organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was recrystallized from EtOH to give 110 mg (13%) of the ω-[piperidino(cyanoimino)-mercapto]acetophenone **2**: mp 103–104 °C; NMR ($CDCl_3$) δ 1.70 (br s, 6 H, piperidino), 4.90 (s, 2 H, CH_2), 3.85 (br s, 4 H, piperidino), 7.25–8.08 (m, 5 H, Ph); IR (KBr) ν 2160, 2180, 1683 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}N_3OS$: C, 62.70; H, 5.97; N, 14.61; S, 11.14. Found: C, 62.37; H, 5.96; N, 14.50; S, 11.17.

(12) (a) J. B. Hester, A. D. Rudzik, and B. V. Kamdar, *J. Med Chem.*, 14, 1078 (1971); (b) K. Meguro, H. Tawada, H. Miyano, Y. Sato, and Y. Kuwada, *Chem. Pharm. Bull.*, 21, 2382 (1973).

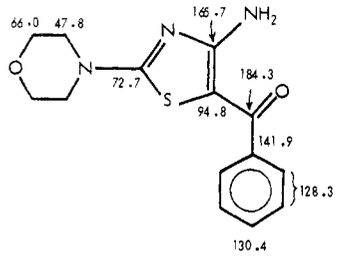
(13) (a) K.-H. Weber, A. Bauer, A. Langbeim, and H. Daniel, *Justus Liebigs Ann. Chem.*, 1257 (1978); (b) T. Tahara, K. Arai, M. Shiroki, H. Matsuno, and T. Munakata, *Arzneim.-Forsch.*, 28, 1153 (1978); (c) R. I. Fryer, J. V. Earley, and A. Walser, *J. Heterocycl. Chem.*, 15, 619 (1978); (d) H. Fujimori, Y. Kayama, T. Hara, K. Itoh, and T. Snami, *ibid.*, 14, 235 (1977).

(14) L. A. Pinck and J. M. Salisbury, *Inorg. Synth.*, 3, 39 (1950).

Reaction of 1b with Cyanamide in the Presence of Base. To an excess of cyanamide in aqueous solution containing 750 mg of NaOH was added 2.50 g (7.23 mmol) of **1b** portionwise. A yellow precipitate resulted. The mixture was stirred for 15 min at room temperature, and then the precipitate was separated by filtration and dissolved in $CHCl_3$. The organic layer was washed with water, separated, dried over Na_2SO_4, and concentrated. Recrystallization from EtOH afforded 1.48 g (76%) of **4a**: mp 159–160 °C; NMR ($CDCl_3$) δ 1.63 (br s, 6 H, piperidino), 3.50 (br s, 4 H, piperidino), 7.00–7.80 (m, 7 H, Ph and NH_2); IR (KBr) ν 3350, 3230, 3150, 1603 cm^{-1}.

Anal. Calcd for $C_{15}H_{17}N_3OS$: C, 62.70; H, 5.97; N, 14.61; S, 11.14. Found: C, 62.99; H, 5.77; N, 14.73; S, 10.90.

By the same procedure, **4b–e** were prepared. The results are summarized in Table I. ^{13}C NMR data of **4b** in $CDCl_3$ (ppm from Me_4Si) are shown in the following structure.



Reaction of 1e with Cyanamide in Nonaqueous Solvent. A mixture of 1.51 g (4.05 mmol) of 2-(*p*-chlorophenyl)-5-phenyl-1,3-oxathiolium perchlorate (**1e**), 0.60 mL of NEt_3, and 10 mL of CH_3CN in 200 mL of excess cyanamide in ether was refluxed for 2 h. The mixture was concentrated in vacuo, and the oily residue was triturated with AcOEt. The solid was separated by filtration, and subsequent recrystallization from AcOEt afforded **4e**. The filtrate and mother liquor were combined and concentrated in vacuo. The oily residue was separated by column chromatography on silica gel with $CHCl_3$ as eluant. After a forerun of *S*-(benzoylmethyl) *p*-chlorophenylthiobenzoate, which was recrystallized from EtOH to give 420 mg (34%) and had an IR spectrum identical with that of the authentic sample,[2f] **4e** was eluted. This was recrystallized from AcOEt. The total yield was 310 mg (48%): mp 146–147 °C; NMR ($CDCl_3$) δ 6.93 (br s, 2 H, NH_2), 7.23–7.97 (m, 9 H, Ar).

Anal. Calcd for $C_{16}H_{11}ClN_2OS$: C, 61.06; H, 3.50; N, 8.90; S, 10.19. Found: C, 61.22; H, 3.63; N, 8.86; S, 10.29.

Chloroacetylation of 3a. A mixture of 4.70 g (15.0 mmol) of 3-amino-2-benzoyl-4-cyano-5-morpholinothiophene (**3a**) and 2.20 g (19.5 mmol) of chloroacetyl chloride in 120 mL of benzene was refluxed for 1 h. The solvent was evaporated in vacuo, and the residue was washed with ether to give 5.80 g (99.0%) of **6**. An analytical sample was recrystallized from acetone: mp 165–166 °C; NMR ($CDCl_3$) δ 3.57–4.07 (m, 8 H, morpholino), 4.25 (s, 2 H, CH_2), 7.30–7.97 (m, 5 H, Ph).

Anal. Calcd for $C_{18}H_{16}ClN_3O_3S$: C, 55.45; H, 4.14; N, 10.78; S, 8.22; Cl, 9.09. Found: C, 55.59; H, 4.27; N, 11.00; S, 8.21; Cl, 9.24.

Iodization of 6. A mixture of 5.07 g (13.0 mmol) of 2-benzoyl-3-[(chloroacetyl)amino]-4-cyano-5-morpholinothiophene (**6**) and 2.37 g (14.3 mmol) of KI in 40 mL of acetone was refluxed for 1.5 h. The solvent was removed in vacuo. The residue was dissolved in $CHCl_3$, washed with water, dried over Na_2SO_4, and concentrated. The crude product was washed with ether and recrystallized from AcOEt to yield 6.00 g of **7**: mp 171–172 °C; NMR ($CDCl_3$) δ 3.48–3.98 (m, 8 H, morpholino), 3.88 (s, 2 H, CH_2), 7.25–7.78 (m, 5 H, Ph), 11.05 (br s, 1 H, NH).

Anal. Calcd for $C_{18}H_{16}IN_3O_3S$: C, 44.92; H, 3.35; N, 8.73; S, 6.67. Found: C, 45.41; H, 3.54; N, 8.76; S, 6.33.

Ammonolysis of 7. A suspension of 2.40 g (4.99 mmol) of 2-benzoyl-4-cyano-3-[(iodoacetyl)amino]-5-morpholinothiazole (**7**) in 100 mL of 20% NH_3–MeOH was stirred for 2.5 h at room temperature and then refluxed for 2 h. The mixture was cooled and then separated by filtration. The residue was dissolved in $CHCl_3$, washed with water, and dried over Na_2SO_4. Concentration of the extract followed by washing with ether yielded 1.00 g of 8-cyano-2-hydroxy-7-morpholino-5-phenyl-3*H*-thieno[3,2-*e*]-[1,4]diazepine (**8**): mp 235–236 °C (from $CHCl_3$); NMR ($CDCl_3$) δ 3.88 (s, 8 H, morpholino), 4.87 (s, 2 H, CH_2), 7.30–8.03 (m, 5 H, Ph); UV (EtOH) λ_{max} nm (log ϵ) 234 (4.32), 262 (4.30), 297 (4.12), 335 (4.27).

Anal. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90; S, 9.10. Found: C, 61.35; H, 4.73; N, 16.00; S, 9.23.

Methylation of 3a. To a stirred suspension of 2.09 g (0.67 mmol) of **3a** in 25 mL of DMF was added 0.33 g (6.88 mmol) of 50% NaH (oil dispersion). The red solution was stirred for 1.5 h at room temperature, and then 1.0 g (7.05 mmol) of CH_3I was added dropwise. After the mixture had been stirred for 1 h at room temperature, it was separated by filtration. The residue was dissolved in $CHCl_3$ and H_2O. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. The residue was washed with ether followed by recrystallization from AcOEt to yield 1.30 g of **5a**: mp 233–234 °C; NMR ($CDCl_3$) δ 3.37 (s, 3 H, Me), 3.43–3.97 (m, 8 H, morpholino), 7.27–7.77 (m, 5 H, Ph); UV (EtOH) λ_{max} nm (log ϵ) 252 (4.14), 298 (4.19), 324 (sh, 3.90), 374 (4.36).

Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83; S, 9.79. Found: C, 62.43; H, 5.28; N, 12.89; S, 9.88.

Compound **5b** was obtained by the same method: mp 149–151 °C; NMR ($CDCl_3$) δ 1.68 (br s, 6 H, piperidino), 3.30 (d, J = 5 Hz, 3 H, Me), 5.25 (br s, 4 H, piperidino), 7.27–7.93 (m, 5 H, Ph).

Anal. Calcd for $C_{18}H_{19}NOS$: C, 66.43; H, 5.88; N, 12.91; S, 9.85. Found: C, 66.60; H, 5.86; N, 12.94; S, 9.61.

Chloroacetylation of 5a. Chloroacetylation of **5a** was carried out by the same method as for **3a**. The yield of **10a** was 92%: mp 144–145 °C (from AcOEt); NMR ($CDCl_3$) δ 3.03, 3.15 (1:2 ratio, s, 3 H, Me), 3.50–4.07 (m, 8 H, morpholino), 4.00 (s, 2 H, CH_2), 7.33–7.83 (m, 5 H, Ph).

Anal. Calcd for $C_{19}H_{18}ClN_3O_3S$: C, 56.50; H, 4.49; N, 10.40; S, 7.94; Cl, 8.78. Found: C, 56.50; H, 4.63; N, 10.46; S, 8.01; Cl, 8.75.

Delepiné Reaction of 10a. A mixture of 1.05 g (2.60 mmol) of 2-benzoyl-3-[(chloroacetyl)methylamino]-4-cyano-5-morpholinothiophene (**10a**) and 0.364 g of hexamethylenetetramine in 20 mL of MeOH containing 3 drops of concentrated HCl was refluxed for 4.5 h. The solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$ and H_2O. The organic phase was separated, dried over Na_2SO_4, and concentrated. The crude product was separated by column chromatography on SiO_2 with AcOEt as eluant. After a forerun of starting material (0.48 g), 0.080 g of diazepine **11a** was obtained: mp 208–210 °C from AcOEt; NMR ($CDCl_3$) δ 3.47 (s, 3 H, Me), 3.13–4.03 (m, 10 H, morpholino and CH_2), 7.29–7.90 (m, 5 H, Ph).

Anal. Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.11; H, 4.91; N, 15.42; S, 8.54.

1,3-Dihydro-8-cyano-1-methyl-5-phenyl-7-piperidinothieno[3,2-*e*][1,4]diazepin-2(2*H*)-one(11b) from 5b. A mixture of 1.45 g (4.46 mmol) of **5b** and 0.650 g (5.76 mmol) of chloroacetyl chloride in 20 mL of benzene was refluxed for 1 h. The solvent was removed in vacuo. The residue was dissolved in AcOEt and aqueous $NaHCO_3$. The organic layer was washed with water, separated, and dried over Na_2SO_4. Removal of the solvent yielded 1.80 g of oil **10b**: NMR ($CDCl_3$) δ 1.73 (br s, 6 H, piperidino), 3.02, 3.12 (s, 3 H, Me), 3.72 (br s, 4 H, piperidino), 4.02 (s, 2 H, CH_2), 7.33–7.80 (m, 5 H, Ar). This oil was used without further purification. A mixture of 1.78 g (4.43 mmol) of the above oil and 1.83 g of HMT in 30 mL of MeOH containing 0.3 g of concentrated HCl was refluxed for 25 h. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and H_2O. The organic phase was separated, dried over Na_2SO_4, and concentrated. The crude product was washed with AcOEt to give 0.650 g of diazepine **11b**: mp 210–212 °C (from AcOEt); NMR ($CDCl_3$) δ 1.70 (br s, 6 H, piperidino), 3.43 (s, 3 H, Me), 3.57 (br s, 4 H, piperidino), 4.16, 4.83 (br s, 2 H, CH_2), 7.30–7.80 (m, 5 H, Ph).

Anal. Calcd for $C_{20}H_{20}N_4OS$: C, 65.91; H, 5.53; N, 15.37; S, 8.86. Found: C, 65.91; H, 5.50; N, 15.29; S, 8.71.

Alternate Route to 11b from 5b. To a solution of 1.65 g (5.07 mmol) of **5b** in 20 mL of THF and 2 mL of DMF was added 2.00 g (8.77 mmol) of (*Z*)-Gly-Cl.[15] The mixture was stirred overnight

(15) M. A. Grum-Grzhimailo, L. V. Volkova, G. A. Serebrennikova, and N. A. Preobrazhenskii, *Zh. Org. Khim.*, 3, 650 (1967); *Chem. Abstr.*, 67, 54418 (1967).

at room temperature. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 and aqueous saturated $NaHCO_3$ solution. The organic layer was separated, dried over Na_2SO_4, and evaporated. The crude product was separated by SiO_2 column chromatography with AcOEt as eluant to yield 0.70 g of oily **10c**: NMR ($CDCl_3$) δ 1.73 (br s, 6 H, piperidino), 2.83, 3.07 (s, 3 H, Me), 3.67 (br s, 4 H, piperidino), 3.90 (d, J = 4 Hz, 2 H, CH_2), 5.09 (s, 2 H, CH_2), 5.58 (br, 1 H, NH), 7.25–7.72 (m, 9 H, Ar). The oily product (0.70 g) was dissolved in 5 mL of 25% HBr–AcOH, and the solution was stirred for 2 h at room temperature. Excess ether was added, and the precipitate was collected by filtration. The residue was taken up in CH_2Cl_2 and aqueous $NaHCO_3$, and the mixture was stirred for 10 min at room temperature. The organic layer was separated, dried over Na_2SO_4, and concentrated to give 0.42 g (81%) of **11b**.

Coupling of 5b with Pht-Gly-Cl. A mixture of 2.60 g (7.99 mmol) of **5b** and 2.70 g (12.1 mmol) of Pht-Gly-Cl[16] in 27 mL of THF was stirred for 3 h at room temperature. The solvent was removed in vacuo, and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated to afford 3.90 g (95%) of **12**: mp 118–120 °C (from EtOH); NMR (Me_2SO-d_6) δ 1.65 (br s, 6 H, piperidino), 2.90–2.93 (s, 3 H, Me), 3.65 (br s, 4 H, piperidino), 4.27, 4.30 (s, 2 H, CH_2), 7.35–7.85 (m, 9 H, Ar).

Anal. Calcd for $C_{28}H_{24}N_4O_3S \cdot {}^3/_4H_2O$: C, 65.95; H, 5.04; N, 10.99; S, 6.29. Found: C, 65.88; H, 4.69; N, 11.03; S, 6.34.

Smiles Rearrangement of 12. A mixture of 3.48 g (6.78 mmol) of **12** and 0.92 mL of hydrazine hydrate in 40 mL of EtOH was refluxed for 1 h. Solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$. The organic layer was washed with aqueous $NaHCO_3$, separated, dried over Na_2SO_4, and concentrated to give 2.10 g of **13**: mp 171–173 °C (from AcOEt); NMR ($CDCl_3$) δ 1.70 (br s, 6 H, piperidino), 2.88 (d, J = 5 Hz, 3 H, Me), 3.65 (br s, 4 H, piperidino), 4.37 (d, J = 7 Hz, 2 H, CH_2), 6.45 (br, 1 H, $NHCH_3$), 7.32–7.82 (m, 5 H, Ph), 10.1 (br, 1 H, NH–CH_2).

Anal. Calcd for $C_{22}H_{22}N_4O_2S$: C, 62.81; H, 5.80; N, 14.65; S, 8.38. Found: C, 62.44; H, 5.72; N, 14.35; S, 8.09.

Methylation of 4c. A solution of 5.60 g (17.3 mmol) of 4-amino-5-(*p*-chlorobenzoyl)-2-morpholinothiazole (**4c**) in 30 mL of DMF was cooled to 0 °C, and 1.0 g (20.8 mmol) of NaH (50% oil dispersion) was added portionwise, giving a yellow suspension. After addition of NaH, the cooling bath was removed, and the mixture was stirred for 15 min at room temperature. A 3.0-g (21.1-mmol) portion of MeI was then added dropwise, and the mixture was stirred for 1 h at room temperature. The mixture was filtered, excess water was added to the filtrate, and then extraction with $CHCl_3$ followed. The organic phase was washed with water. The $CHCl_3$ extract and the above filtration residue were combined, washed with water, separated, and dried over Na_2SO_4. Removal of the solvent in vacuo followed by recrystallization from EtOH yielded 3.0 g (51%) of **14b**: mp 200–201 °C; NMR ($CDCl_3$) δ 3.16 (d, J = 5 Hz, 3 H, Me), 3.50–3.95 (m, 8 H, morpholino), 7.25–7.83 (q, 4 H, Ar).

Anal. Calcd for $C_{15}H_{16}ClN_3O_2S$: C, 53.33; H, 4.77; N, 12.44; S, 9.49; Cl, 10.50. Found: C, 53.30; H, 4.62; N, 12.53; S, 9.48; Cl, 10.48.

The mother liquor was concentrated in vacuo, and the residue was recrystallized from EtOH to give 0.90 g (15%) of **14d**: mp 176–177 °C; NMR ($CDCl_3$) δ 3.08 (s, 6 H, 2 Me), 3.35–3.87 (m, 8 H, morpholino), 7.18–7.70 (q, 4 H, Ar).

Anal. Calcd for $C_{16}H_{18}ClN_3O_2S$: C, 54.61; H, 5.16; N, 11.94; S, 9.11; Cl, 10.08. Found: C, 54.93; H, 4.71; N, 11.67; S, 9.16; Cl, 10.35.

The results of methylation are shown in Table I.

Chloroacetylation of 4a. A mixture of 2.60 g (9.05 mmol) of 4-amino-5-benzoyl-2-piperidinothiazole (**4a**), 1.50 g (13.3 mmol) of chloroacetyl chloride, and 4.0 g of K_2CO_3 in 50 mL of benzene was refluxed for 1 h. The mixture was then concentrated in vacuo. The residue was extracted with $CHCl_3$, washed with H_2O, separated, and dried over Na_2SO_4. Removal of the solvent followed by recrystallization from EtOH gave 2.82 g (77%) of **15**: mp 173–174 °C; NMR ($CDCl_3$) δ 1.68 (br s, 6 H, piperidino), 3.60 (br s, 4 H, piperidino), 4.37 (s, 2 H, CH_2), 7.25–7.85 (m, 5 H, Ph).

(16) S. Gabriel, *Ber. Dtsch. Chem. Ges.*, **40**, 2647 (1907).

Anal. Calcd for $C_{17}H_{18}ClN_2O_2S \cdot {}^1/_2H_2O$: C, 54.76; H, 5.14; N, 11.27; S, 8.60. Found: C, 54.84; H, 5.19; N, 11.39; S, 8.59.

Reaction of 4b with Pht-Gly-Cl. To a solution of 6.0 g (20.9 mmol) of 4-amino-5-benzoyl-2-morpholinothiazole (**4b**) in 20 mL of DMF was added 6.30 g of Pht-Gly-Cl. A solution of 3.0 g of NEt_3 in 10 mL of DMF was then added. The mixture was stirred for 1 h at room temperature. Excess water was added, and the mixture was neutralized with aqueous $NaHCO_3$. The precipitate was collected by filtration. Recrystallization from AcOEt gave 9.15 g (90%) of **18**: mp 226–227 °C; NMR ($CDCl_3$) 3.70 (br d, 8 H, morpholino), 5.03 (s, 2 H, CH_2), 7.37–8.00 (m, 9 H, Ar).

Anal. Calcd for $C_{24}H_{20}N_4O_5S \cdot {}^1/_2AcOEt$: C, 59.99; H, 4.65; N, 10.76; S, 6.16. Found: C, 59.87; H, 4.74; N, 10.73; S, 6.29.

Delepinê Reaction of 15. A mixture of 1.50 g (4.12 mmol) of **15**, 1.00 g (7.13 mmol) of hexamethylenetetramine in 3.2 mL of 2 N HCl, 13 mL of MeOH, and 1.3 mL of H_2O was stirred for 4 h at 50 °C, and then cooled to give a brown suspension. This was partitioned between $CHCl_3$ and H_2O. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. The oily residue was triturated with ether to afford 1.70 g (81.9%) of **16**: mp 80–83 °C dec; NMR ($CDCl_3$) δ 1.67 (br s, 6 H, piperidino), 2.8–4.8 (m, 18 H, piperidino and other CH_2's), 7.08–8.16 (m, 5 H, Ph). A mixture of 1.1 g (2.0 mmol) of **16** in 7.0 mL of MeOH and 2 mL of concentrated HCl was stirred for 4 h at 50 °C and then concentrated. The residue was dissolved in EtOH followed by addition of ether to give a pale yellow precipitate. This was collected by filtration and washed with ether to give 150 mg of **17**: mp 113–116 °C dec; NMR (Me_2SO-d_6) 1.63 (br s, 6 H, piperidino), 3.56 (br s, 4 H, piperidino), 4.23 (br s, 2 H, CH_2), 7.33–7.70 (m, 5 H, Ph), 8.20 (br s, 3 H, NH_3). As **17** was hygroscopic, cyclization was not carried out.

Reaction of 4a with (*Z*)-Gly-OH. To a solution of 1.45 g (6.90 mmol) of (*Z*)-Gly-OH in 4.0 mL of HMPA was added 0.60 g of $SOCl_2$ dropwise at −5 to −8 °C. The mixture was stirred for 5 min, 1.40 g (4.88 mmol) of **4a** was added in small portions, and the mixture was stirred for 3 h at −5 to 10 °C. Excess water was added, and the mixture was neutralized with aqueous $NaHCO_3$. Ether was added, and the mixture was stirred for about 30 min. The precipitates were collected by filtration. Recrystallization from EtOH–AcOEt gave 1.20 g of **19a**: mp 158–159 °C; NMR ($CDCl_3$) δ 1.70 (br s, 6 H, piperidino), 3.62 (br s, 4 H, piperidino), 4.52 (br d, 2 H, CH_2), 5.18 (s, 2 H, CH_2), 5.73 (br s, 1 H, NH), 7.28–7.98 (m, 10 H, Ar).

Anal. Calcd for $C_{25}H_{26}N_4O_4S$: C, 62.74; H, 5.48; N, 11.71; S, 6.71. Found: C, 63.02; H, 5.53; N, 11.93; S, 6.78.

By the same method, **19b–i** were prepared, and the results are summarized in Table II.

Removal of the Protecting Group of 19. A solution of 400 mg (0.836 mmol) of 5-benzoyl-4-[[((benzoxycarbonyl)amino)-acetyl]amino]-2-piperidinothiazole (**19a**) in 4.0 mL of 25% HBr–AcOH was stirred for 1 h at room temperature. Excess ether was added, and the supernatant ether was removed by decantation. The crude product was filtered out, washed with ether, and recrystallized from EtOH to afford 310 mg of the corresponding amine hydrobromide monohydrate, dec 160–162 °C.

A yellow suspension of 700 mg of the above monohydrate in 8.0 mL of CH_3CN was refluxed for 30 min. The reaction mixture became a colorless suspension. The crude product was separated by filtration followed by washing with ether to give 650 mg of **20a**, dec 210–211 °C.

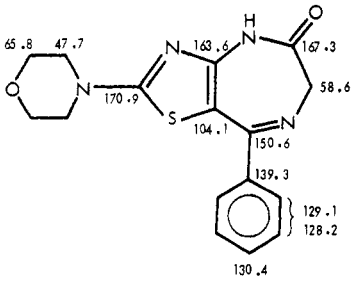
The results obtained with similarly prepared salts are summarized in Table III.

4,6-Dihydro-8-phenyl-2-piperidinothiazolo[4,5-*e*][1,4]-diazepin-5(5*H*)-one (21a). A suspension of 900 mg (2.11 mmol) of **20a** and 250 mg (2.23 mmol) of Dabco in 15 mL of CH_3CN was stirred for 30 min at 50 °C. The reaction mixture turned red. It was cooled to room temperature and filtered. The filtrate was concentrated in vacuo, and the residue was separated by column chromatography on silica gel with AcOEt as eluant. Recrystallization from AcOEt afforded 203 mg (29%) of **21a**: mp 191–193 °C; NMR ($CDCl_3$) δ 1.67 (br s, 6 H, piperidino), 3.47 (br s, piperidino), 4.43 (s, 2 H, CH_2), 7.28–7.75 (m, 5 H, Ph).

Anal. Calcd for $C_{17}H_{18}N_4OS$: C, 62.56; H, 5.56; N, 17.17; S, 9.83. Found: C, 62.55; H, 5.79; N, 17.43; S, 9.79.

By the same procedure, diazepines **21b–i** were synthesized, and the results are listed in Table IV. The ^{13}C NMR results ($CDCl_3$,

ppm from Me_4Si) of **21b** are shown in the following structure.[17]



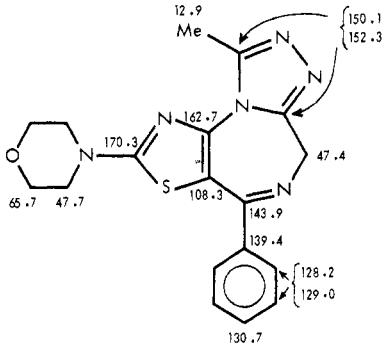
5-Acethydrazino-2-morpholino-8-phenyl-6*H*-thiazolo[4,5-*e*][1,4]diazepine (23). Thiazolodiazepine (**21b**; 6.95 g, 21.2 mmol) was dissolved in 50 mL of CH_2Cl_2. To this were added 6.50 g (29.2 mmol) of P_2S_5 and 40 mL of pyridine, and the mixture was stirred for 3.5 h at 40–50 °C. The mixture was poured onto ice–water and extracted with CH_2Cl_2. The organic layer was washed with water, separated, and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was separated by column chromatography on SiO_2 with AcOEt as eluant. The thione derivative (4.10 g, 13.1 mmol) obtained was taken up in 40 mL of $CHCl_3$ to which 1.20 g (16.2 mmol) of acethydrazide was added. The mixture was stirred for 1 h at 50 °C. The mixture was concentrated in vacuo, and the residue was triturated with acetone to give 3.60 g (44% from **21b**) of **23**: mp 226–228 °C (from acetone); NMR ($CDCl_3$) δ 1.90 (s, 3 H, Me), 3.66 (br d, 8 H, morpholino), 4.27 (s, 2 H, CH_2), 7.25–7.28 (m, 5 H, Ph), 9.67 (br s, 1 H, NH).

Anal. Calcd for $C_{18}H_{20}N_6O_2S$: C, 56.23; H, 5.20; N, 21.86; S, 8.34. Found: C, 56.21; H, 5.50; N, 21.68; S, 8.41.

1-Methyl-8-morpholino-6-phenyl-4*H*-*s*-triazolo[3,4-*c*]thiazolo[4,5-*e*][1,4]diazepine (24). A solution of 2.18 g (5.67 mmol) of **23** in 15 mL of AcOH was refluxed for 1 h. The solvent was removed in vacuo, and the residue was extracted with AcOEt and then washed with aqueous $NaHCO_3$. The organic layer was separated, washed with water, and then dried over Na_2SO_4. Evaporation of the solvent followed by recrystallization from AcOEt gave 0.996 g (48%) of **24**: mp 215–216 °C; NMR ($CDCl_3$) δ 2.72 (s, 3 H, Me), 3.40–3.97 (m, 8 H, morpholino), 4.92 (s, 2 H, CH_2), 7.25–7.28 (m, 5 H, Ph).

Anal. Calcd for $C_{18}H_{18}N_6OS$: C, 59.00; H, 4.95; N, 22.93; S, 8.75. Found: C, 59.26; H, 5.07; N, 22.64; S, 9.25.

The ^{13}C NMR results ($CDCl_3$, ppm from Me_4Si) of **24** are shown in the following structure.



Registry No. 1a, 72100-42-6; **1b**, 72100-44-8; **1c**, 72100-46-0; **1d**, 72100-48-2; **1e**, 72100-49-3; **2**, 72100-50-6; **3a**, 72100-51-7; **4a**, 72100-52-8; **4b**, 72100-53-9; **4c**, 72100-54-0; **4d**, 72100-55-1; **4e**, 72100-56-2; **5a**, 72100-57-3; **5b**, 72100-58-4; **6**, 72121-20-1; **7**, 72100-59-5; **8**, 72100-60-8; **10a**, 72100-61-9; **10c**, 72100-62-0; **11a**, 72100-63-1; **11b**, 72100-64-2; **12**, 72100-65-3; **13**, 72100-66-4; **14a**, 72100-67-5; **14b**, 72100-68-6; **14c**, 72100-69-7; **14d**, 72100-70-0; **15**, 72100-71-1; **16**, 72100-72-2; **17**, 72100-73-3; **18**, 72100-74-4; **19a**, 72100-75-5; **19b**, 72100-76-6; **19c**, 72100-77-7; (±)-**19d**, 72100-78-8; (±)-**19e**, 72100-79-9; **19f**, 72100-80-2; **19g**, 72100-81-3; **19h**, 72100-82-4; **19i**, 72100-83-5; **20a**, 72100-84-6; **20b**, 72100-85-7; **20c**, 72100-86-8; (±)-**20d**, 72100-87-9; (±)-**20e**, 72100-88-0; **21a**, 72100-89-1; **21b**, 72100-90-4; **21c**, 72100-91-5; (±)-**21d**, 72100-92-6; (±)-**21e**, 72100-93-7; **21f**, 72100-94-8; **21g**, 72100-95-9; **21h**, 72100-96-0; **21i**, 72100-97-1; **23**, 72100-99-3; **24**, 72101-00-9; cyanamide, 420-04-2; *S*-(benzoylmethyl) *p*-chlorophenylthiobenzoate, 56494-76-9; chloroacetyl chloride, 79-04-9; CH_3I, 74-88-4; (Z)-Gly-Cl, 15050-24-5; Pht-Gly-Cl, 6780-38-7; hydrazine hydrate, 7803-57-8; hexamethylenetetramine, 100-97-0; (Z)-Gly-OH, 72100-98-2; acethydrazide, 2440-60-0.

(17) The ^{13}C NMR results of benzo[1,4]diazepines were reported: S. P. Singh, S. S. Parmar, S. A. Farnum, and V. I. Stenberg, *J. Heterocycl. Chem.*, 15, 1083 (1978).