Condensed Thienopyrimidines. I. Synthesis and Gastric Antisecretory Activity of 2,3-Dihydro-5*H*-oxazolothienopyrimidin-5-one Derivatives

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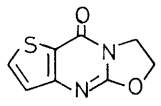
A practical preparation of various 2,3-dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]-, [3,4-*d*]-, and [2,3-*d*]pyrimidin-5-one derivatives was developed starting from the corresponding aminothiopheneesters in two steps, and their chloro-substituted derivatives were prepared. These compounds were evaluated for gastric antisecretory activity in pylorus-ligated rats, compared to the anti-ulcer standard, cimetidine, and their structure–activity relationships are discussed.

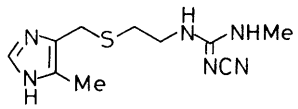
Keywords aminothiophenecarboxylate; 2-haloethyl isocyanate; tricyclic thienopyrimidine; oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one; oxazolo[3,2-*a*]thieno[3,4-*d*]pyrimidin-5-one; oxazolo[3,2-*a*]thieno[2,3-*d*]pyrimidin-5-one; gastric antisecretory activity; structure–activity relationship

In the treatment of peptic ulcers it is generally considered important to improve an imbalance between gastric acid secretion factors and defensive factors.[1] Since the discovery of cimetidine, clinically applied as a histamine H_2 receptor antagonist, inhibitors of acid secretion have received much attention.

In the previous paper[2] we reported the practical preparation of a new heterocyclic compound, 2,3-dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one (**1a**). In the biological screening of **1a**, a significant gastric antisecretory activity was found in the pylorus-ligated rat model of Shay *et al.*[3] Histamine H_2 receptor antagonists share common structural features, *i.e.*, an ethylthiomethyl chain connecting a basic substituted heterocyclic or aromatic ring to a neutral moiety incorporating a guanidine substituted with an electron-withdrawing moiety, as in the typical example of cimetidine. However, **1a** does not satisfy the above common structural requirement and it appears to be an anti-ulcer agent of a new structural type. We modified the



1a



Cimetidine

Fig. 1

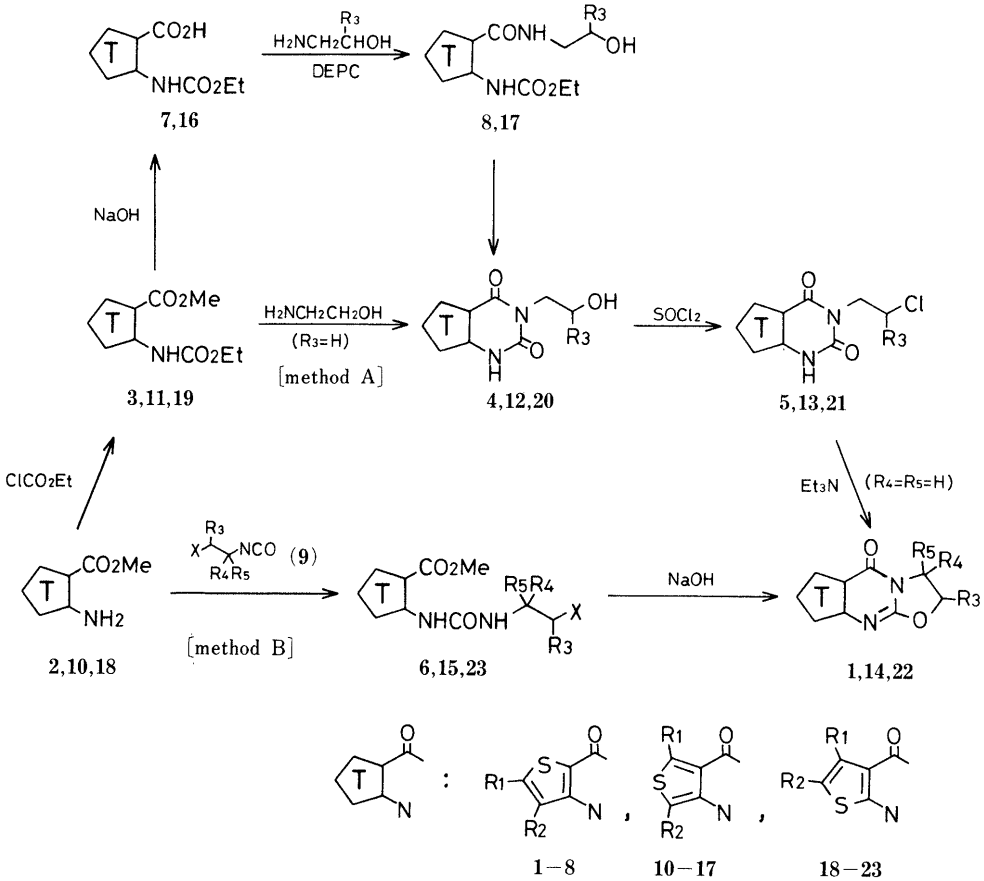
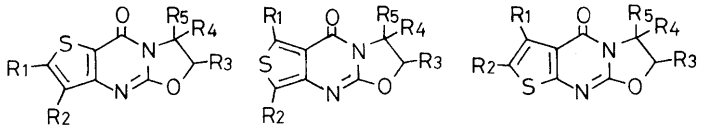


Chart 1

TABLE I. Alkyl-Substituted 2,3-Dihydro-5*H*-oxazolothienopyrimidin-5-ones (**1**, **14** and **22**)



1 **14** **22**

Compd. No.	R_1	R_2	R_3	R_4	R_5	Method[a]	Yield (%)	mp (°C) (Recryst. solv.)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	S
1a[c]	H	H	H	H	H	A, B		183—185 (dec.)	$C_8H_6N_2O_2S$				
1b	H	H	Me	H	H	A	78	162—164 (E)	$C_9H_8N_2O_2S$	51.91 (52.01	3.87 3.87	13.45 13.42	15.40 15.29)
1c	H	H	Et	H	H	A	76	132—134 (E)	$C_{10}H_{10}N_2O_2S$	54.02 (54.22	4.54 4.65	12.60 12.68	14.42 14.48)
1d	H	H	H	Me	Me	B	70	139—141 (EA–H)	$C_{10}H_{10}N_2O_2S$	54.04 (54.20	4.54 4.44	12.60 12.28	14.42 14.47)
1e	Me	H	H	H	H	A (B)	78 (71)	179—181 (E–EA)	$C_9H_8N_2O_2S$	51.91 (51.87	3.87 3.70	13.45 13.52	15.40 15.27)
1f	Et	H	H	H	H	A	74	119—121 (EA–H)	$C_{10}H_{10}N_2O_2S$	54.04 (54.10	4.54 4.42	12.60 12.71	14.43 14.37)
1g	Ph	H	H	H	H	B	58	240—242 (EA)	$C_{14}H_{10}N_2O_2S$	62.21 (62.29	3.73 3.57	10.36 10.33	11.86 11.67)
1h	Me	H	Me	H	H	A	86	114—116 (EA–H)	$C_{10}H_{10}N_2O_2S$	54.04 (54.24	4.54 4.63	12.60 12.51	14.42 14.58)
1i	Me	H	H	Et	H	B	27	115—117 (EA–H)	$C_{11}H_{12}N_2O_2S$	55.91 (56.07	5.12 5.18	11.86 11.64	13.57 13.89)
1j	Me	H	H	Me	Me	B	76	188—189 (EA)	$C_{11}H_{12}N_2O_2S$	55.92 (56.03	5.12 5.23	11.86 11.74	13.57 13.88)
1k	H	Me	H	H	H	A	74	260—262 (C–E)	$C_9H_8N_2O_2S$	51.91 (51.87	3.87 3.72	13.45 13.56	15.40 15.47)
1l	H	Ph	H	H	H	B	63	150—152 (EA)	$C_{14}H_{10}N_2O_2S$	62.21 (62.27	3.73 3.64	10.36 10.46	11.86 11.62)
1m	Me	Me	H	H	H	B	72	182—184 (EA–H)	$C_{10}H_{10}N_2O_2S$	54.04 (54.23	4.54 4.40	12.60 12.69	14.43 14.61)
14a	H	H	H	H	H	A	79	151—154 (EA)	$C_8H_6N_2O_2S$	49.48 (49.45	3.11 3.20	14.42 14.39	16.51 16.37)
14b	H	H	Me	H	H	A	45	117—119 (EA)	$C_9H_8N_2O_2S$	51.91 (51.83	3.87 3.62	13.45 13.30	15.40 15.55)
14c	H	H	H	Me	Me	B	39	112—113 (EA–H)	$C_{10}H_{10}N_2O_2S$	54.04 (54.32	4.54 4.53	12.60 12.72	14.43 14.78)
14d	H	H	Me	Me	Me	B	27	126—128 (EA–H)	$C_{11}H_{12}N_2O_2S$	55.91 (55.65	5.12 5.03	11.86 11.78	13.57 13.51)
14e	Me	H	H	H	H	B	93	145—147 (EA–H)	$C_9H_8N_2O_2S$	51.91 (51.57	3.87 3.95	13.45 13.36	15.40 15.35)
14f	H	Me	H	H	H	B	87	129—130 (EA–H)	$C_9H_8N_2O_2S$	51.91 (51.77	3.87 3.80	13.45 13.26	15.40 15.56)
14g	H	Et	H	H	H	B	94	117—121 (EA–H)	$C_{10}H_{10}N_2O_2S$	54.04 (53.90	4.54 4.46	12.60 12.46	14.42 14.41)
14h	Me	Me	H	H	H	B	65	193—194 (EA–H)	$C_{10}H_{10}N_2O_2S$	54.04 (53.97	4.54 4.52	12.60 12.68	14.42 14.76)
22a	H	H	H	H	H	A (B)	72 (9)	203—205 (E)	$C_8H_6N_2O_2S \cdot 1/5\,H_2O$	48.58 (48.55	3.26 3.06	14.16 13.96	16.21 16.45)
22b	Me	H	H	H	H	B	77	>270 (E)	$C_9H_8N_2O_2S \cdot 1/5\,H_2O$	51.03 (51.28	3.99 4.12	13.22 13.17	15.13 15.18)
22c	Ph	H	H	H	H	B	20	232—234 (M)	$C_{14}H_{10}N_2O_2S$	62.21 (62.14	3.73 3.62	10.36 10.43	11.86 11.82)
22d	H	Me	H	H	H	A (B)	69 (19)	187—188 (E)	$C_9H_8N_2O_2S$	51.91 (51.62	3.87 3.81	13.45 13.43	15.40 15.35)
22e	H	Ph	H	H	H	A[d]	74	252—254 (C–EA)	$C_{14}H_{10}N_2O_2S \cdot 1/5\,H_2O$	61.39 (61.57	3.83 3.69	10.23 10.44	11.70 11.63)
22f	Et	Me	H	H	H	B	35	123—125 (EA–H)	$C_{11}H_{12}N_2O_2S$	55.91 (55.94	5.12 5.03	11.86 11.92	13.57 13.82)
22g	$(CH_2)_4$		H	H	H	B	20	196—198 (EA)	$C_{12}H_{12}N_2O_2S$	58.05 (57.99	4.87 4.73	11.28 11.12	12.91 12.84)

a) Experimental section. *b*) C, $CHCl_3$; E, EtOH; EA, AcOEt; H, hexane; M, MeOH. *c*) Ref. 2. *d*) This compound could not be obtained by method B.

structure of **1a** in an attempt to improve its pharmacological activity. In the present paper, we describe the preparation of positional isomers of the thiophene ring moiety in **1a**, alkyl(chloro)-substituted derivatives, and the determination of their structure–activity relationships for gastric antisecretory activity.

Chemistry The two methods used for the preparation of 2,3-dihydro-5*H*-oxazolothienopyrimidin-5-one derivatives (**1a—m**, **14a—h**, and **22a—g**) are shown in Chart 1. The first one involves carbamates (**3**, **11**, and **19**) as intermediates (method A). Reaction of methyl 3-aminothiophene-2-carboxylates (**2a**, **e**, **f**, **k**) with ethyl chloroformate in toluene followed by heating with ethanolamine gave cyclized products, 3-(2-hydroxyethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*, 3*H*)-diones (**4a**, **e**, **f**, **k**). Treatment of **4** with thionyl chloride ($SOCl_2$) afforded the 3-(2-chloroethyl) derivatives **5a**, **e**, **f**, **k**, which yielded the corresponding tricyclic compounds **1a**, **e**, **f**, **k** by heating with triethylamine (Et_3N) in ethanol (EtOH).

The other method involves ureas (**6**, **15**, and **23**) as intermediates (method B). Treatment of **2a**, **e**, **g**, **l**, **m** with 2-chloroethyl isocyanate or alkyl-substituted 2-bromoethyl isocyanates **9**, which were obtained by Kampe's method,[4] gave the *N'*-(2-haloethyl) ureas **6a**, **d**, **e**, **g**, **i**, **j**, **l**, **m** in excellent yields. The desired tricyclic compounds **1a**, **d**, **e**, **g**, **i**, **j**, **l**, **m** were formed by the intramolecular cyclization of **6** with a base. By proceeding with method A or method B, the corresponding **14a**, **c—h** and **22a—g** were synthesized

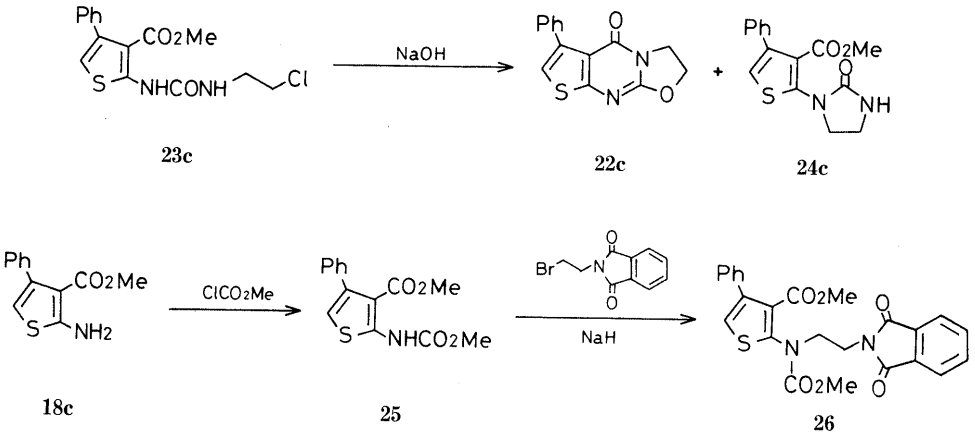


Chart 2

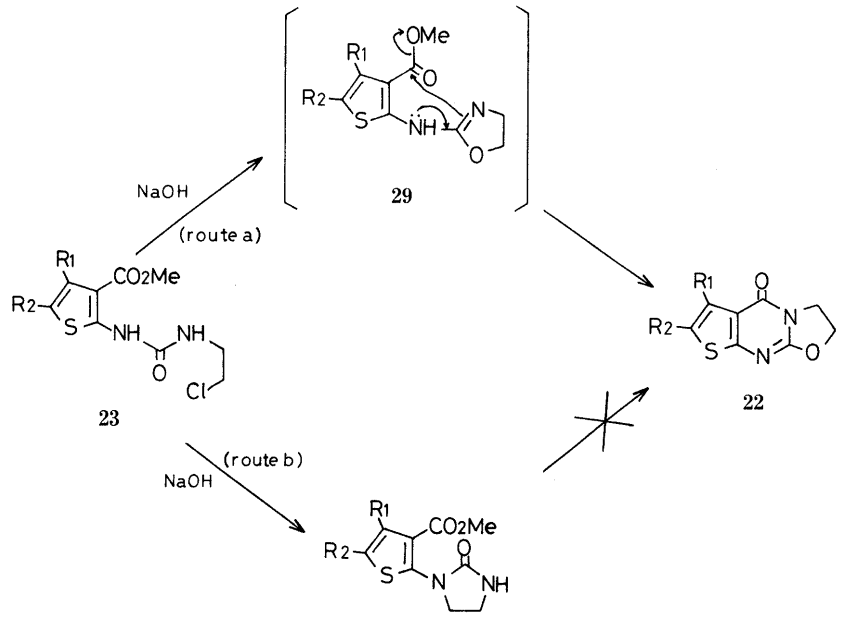
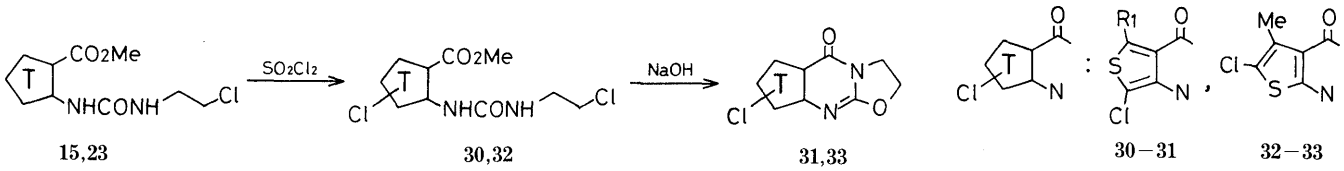
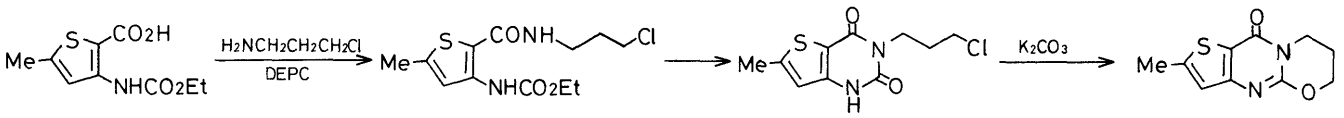


Chart 3



15,23 30,32 31,33 30–31 32–33

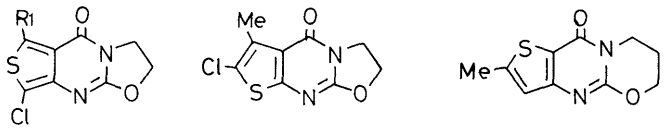
Chart 4



7e 34 35 36

Chart 5

TABLE II. Various 2,3-Dihydro-5*H*-oxazolothienopyrimidin-5-one Derivatives (**31**, **33**, and **36**)



31 **33** **36**

Compd. No.	R_1	Yield (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found)				
						C	H	Cl	N	S
31a	H	65	183—185	AcOEt	$C_8H_5ClN_2O_2S$	42.02	2.20	15.50	12.25	14.02
						(42.08	1.92	15.38	12.33	13.92)
31e	Me	60	221—223	AcOEt	$C_9H_7ClN_2O_2S$	44.54	2.91	14.61	11.54	13.21
						(44.52	2.99	14.75	11.41	13.15)
33		15	217—219	AcOEt	$C_9H_7ClN_2O_2S$	44.54	2.91	14.61	11.54	13.21
						(44.29	2.81	14.48	11.32	13.44)
36		87	165—166	AcOEt–hexane	$C_{10}H_{10}N_2O_2S$	54.04	4.53		12.60	14.43
						(54.01	4.40		12.61	14.31)

starting from aminothiophenecarboxylates (**10a**, **c**—**h** and **18a**—**g**, respectively). The physical properties of **1**, **14**, and **22** are summarized in Table I.

In method B, **22a**, **c**—**g** were obtained from **23** in only poor yields, different from the case of **1** or **14**, because of the formation of by-product. The ring closure reaction of **23c**, for example, afforded **22c** in 20% yield together with **24c** (Chart 2). The structure of **24c** was determined as follows. In the mass spectrum (MS), **24c** showed a molecular ion peak at *m/z* 302, indicating the elimination of hydrogen chloride from **23c**. The presence of an ester group in **24c** was confirmed by the absorption at 1705 cm^{-1} (C=O) in the infrared (IR) spectrum and the signal at δ 3.60 ppm (s, OCH_3) in the nuclear magnetic resonance spectrum (NMR). The structure of **24c** was confirmed to be methyl 2-(2-oxo-1-imidazolidinyl)-4-phenylthiophene-3-carboxylate by identification with a sample prepared by the alternative route shown in Chart 2.

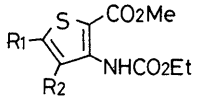
Treatment of **18c** with methyl chloroformate followed by reaction with *N*-(2-bromoethyl)phthalimide in the presence of sodium hydride (NaH) afforded the *N*-(2-phthalimidoethyl) derivative **26**. Reaction of **26** with hydrazine in methanol (MeOH) gave the amino compound **27**, which was treated with potassium hydroxide (KOH) in MeOH to obtain the desired cyclic compound **24c**, together with the decarboxylated product **28** as a by-product.

TABLE III. Gastric Antisecretory Activity of Tricyclic Thienopyrimidine Derivatives

Compd. No.	Gastric antisecretory activity (%, 50 mg/kg, i.d.)	Compd. No.	Gastric antisecretory activity (%, 50 mg/kg, i.d.)
1a	77	**14d**	56
1b	78	**14e**	61
1c	51	**14f**	68
1d	78	**14g**	25
1e	70	**14h**	75
1f	28	**22a**	44
1h	55	**22b**	39
1i	29	**22d**	28
1j	58	**22g**	30
1k	49	**31a**	82
1l	49	**31e**	64
1m	32	**33**	56
14a	78	**36**	38
14b	67	Cimetidine	46

Formation of **24** in the course of ring closure of **23** can be rationalized in terms of the reaction sequence outlined in Chart 3. The reaction is assumed to occur *via* route a or route b. Formation of **22** might proceed *via* the presumed oxazoline intermediate **29** (route a), which has not been isolated or detected. The same reaction mechanism was proposed for the synthesis of 2,3-dihydro-5*H*-oxazolo[2,3-

TABLE IV. 3-Aminothiophene-2-carboxylate Derivatives (**3**, **6**, **7** and **8**) and Thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Derivatives (**4** and **5**)



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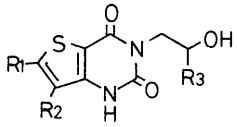

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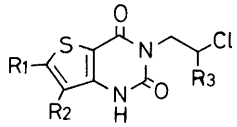

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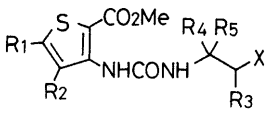

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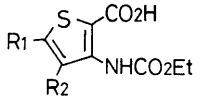

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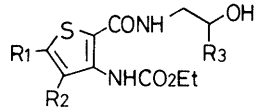

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Compd. No.	R_1	R_2	R_3	R_4	R_5	X	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	S	Cl (Br)
3a[b]	H	H						63—66	$C_9H_{11}NO_4S$					
3e	Me	H					96	49—51 (EA–H)	$C_{10}H_{13}NO_4S$	49.37 (49.29	5.39 5.41	5.76 5.76	13.18 13.27)	
3f	Et	H					81	Oil[c]	$C_{11}H_{15}NO_4S$	51.35 (51.13	5.88 5.93	5.44 5.51	12.46 12.76)	
3k	H	Me					94	81—83 (EA–H)	$C_{10}H_{13}NO_4S$	49.37 (49.09	5.39 5.29	5.76 5.63	13.18 13.37)	
4a[b]	H	H	H					261—262 (dec.)	$C_8H_8N_2O_3S$					
4b	H	H	Me				89	205—207 (M)	$C_9H_{10}N_2O_3S$	47.73 (47.63	4.46 4.34	12.38 12.44	14.17 14.35)	
4c	H	H	Et				85	187—188 (D–C)	$C_{10}H_{12}N_2O_3S$	50.00 (49.79	5.04 5.08	11.66 11.77	13.34 13.48)	
4e	Me	H	H				54	274—277 (dec.) (D–M)	$C_9H_{10}N_2O_3S$	47.78 (47.92	4.46 4.32	12.38 12.39	14.17 14.11)	
4f	Et	H	H				22	247—249 (dec.) (D–M)	$C_{10}H_{12}N_2O_3S$	49.99 (49.93	5.03 4.97	11.66 11.57	13.34 13.16)	
4h	Me	H	Me				69	236—239 (E)	$C_{10}H_{12}N_2O_3S$	50.00 (49.82	5.04 4.77	11.66 11.42	13.34 13.06)	
4k	H	Me	H				61	261—263 (dec.) (M)	$C_9H_{10}N_2O_3S$	47.78 (47.70	4.46 4.30	12.38 12.46	14.17 14.28)	
5a[b]	H	H	H					214—217 (dec.)	$C_8H_7ClN_2O_2S$					
5b	H	H	Me				83	192—194 (E)	$C_9H_9ClN_2O_2S$	44.18 (44.30	3.71 3.65	11.45 11.37	13.10 13.32	14.49 14.33)
5c	H	H	Et				90	197—198 (dec.) (E)	$C_{10}H_{11}ClN_2O_2S$	46.42 (46.17	4.29 4.16	10.83 10.84	12.39 12.48	13.70 13.72)
5e	Me	H	H				93	207—210 (EA)	$C_9H_9ClN_2O_2S$	44.18 (43.87	3.71 3.76	11.45 11.16	13.10 13.43	14.49 14.22)
5f	Et	H	H				83	239—241 (M–EA)	$C_{10}H_{11}ClN_2O_2S$	46.42 (46.67	4.29 4.35	10.83 10.65	12.39 12.74	13.70 13.37)
5h	Me	H	Me				75	214—217 (M–C)	$C_{10}H_{11}ClN_2O_2S$	46.42 (46.23	4.29 4.16	10.83 10.71	12.39 12.41	13.70 13.77)
5k	H	Me	H				95	248—251 (M–EA)	$C_9H_9ClN_2O_2S$	44.18 (44.12	3.71 3.76	11.45 11.43	13.10 13.02	14.49 14.40)
6a[b,d]	H	H	H	H	H	Cl		147—150	$C_9H_{11}ClN_2O_3S$	Lit.[d] mp 139—142 °C				
6d	H	H	H	Me	Me	Br	24	98—100 (EA–H)	$C_{11}H_{15}BrN_2O_3S$	39.41 (39.64	4.51 4.54	8.36 8.63	9.56 9.78	23.84 23.64)
6e	Me	H	H	H	H	Cl	89	130—131 (EA–H)	$C_{10}H_{13}ClN_2O_3S$	43.40 (43.04	4.74 4.64	10.12 10.04	11.59 11.86	12.81 12.86)
6g	Ph	H	H	H	H	Cl	83	157—159 (EA–H)	$C_{15}H_{15}ClN_2O_3S$	53.17 (53.17	4.46 4.40	8.27 8.33	9.46 9.37	10.46 10.52)
6i	Me	H	H	Et	H	Br	40	119—121 (EA–H)	$C_{12}H_{17}BrN_2O_3S$	41.27 (41.26	4.91 4.93	8.02 7.77	9.18 9.18	22.88 22.83)
6j	Me	H	H	Me	Me	Br	46	129—130 (dec.) (EA–H)	$C_{12}H_{17}BrN_2O_3S$	41.27 (41.15	4.91 5.06	8.02 7.88	9.18 9.48	22.88 22.73)
6l	H	Ph	H	H	H	Cl	58	118—120 (EA–H)	$C_{15}H_{15}ClN_2O_3S$	53.17 (53.33	4.46 4.35	8.27 8.50	9.46 9.59	10.46 10.23)
6m	Me	Me	H	H	H	Cl	77	198—199 (EA)	$C_{11}H_{15}ClN_2O_3S$	45.44 (45.44	5.20 5.19	9.63 9.70	11.03 11.26	12.19 12.43)
7a	H	H					77	154—156 (dec.) (EA–H)	$C_8H_9NO_4S$	44.65 (44.51	4.21 4.27	6.51 6.53	14.90 15.03)	
7e	Me	H					76	173—175 (dec.) (C–EA)	$C_9H_{11}NO_4S$	47.15 (46.74	4.84 4.82	6.11 6.09	13.98 14.36)	

TABLE IV. (continued)

Compd. No.	R_1	R_2	R_3	R_4	R_5	X	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd (Found)				
										C	H	N	S	Cl(Br)
8b	H	H	Me				63	108—110 (EA)	$C_{11}H_{16}N_2O_4S$	48.52 (48.22	5.92 5.94	10.29 10.07	11.77 11.84)	
8c	H	H	Et				65	110—112 (EA)	$C_{12}H_{18}N_2O_4S$	50.34 (50.46	6.34 6.55	9.78 9.73	11.20 11.37)	
8h	Me	H	Me				64	96—97 (EA–H)	$C_{12}H_{18}N_2O_4S$	50.34 (50.49	6.34 6.31	9.78 9.94	11.20 11.23)	

a) C, $CHCl_3$; D, DMF; E, EtOH; EA, AcOEt; H, hexane; M, MeOH. *b*) Ref. 2. *c*) bp 130 °C (5 mmHg). *d*) Ref. 8.

b]quinazolin-5-one by Kampe.[5] On the other hand, **24** was produced by intramolecular cyclization on the nitrogen atom (route b). Cyclization of **24** to the tricyclic compound **22** was not induced with a base under the same conditions. No corresponding imidazolidinone analogue was isolated in the course of tricyclic derivative formation from the isomeric ureas (**6** and **15**). It is not clear why compounds **24** are formed only in the case of the syntheses of the oxazolo[3,2-*a*]thieno[2,3-*d*]pyrimidin-5-one derivatives (**22**) from **23**. The different reactivities of **23** toward **6** or **15** might, however, be explained by the difference in basicity between **2** or **10** and **18**.[6]

Various R_3-substituted oxazolothienopyrimidines were synthesized by using method A, as it was hard to prepare 2-haloethyl isocyanates **9** bearing an alkyl-substituent at only the C-2 position ($R_4 = R_5 = H$). The absence of a ring closure product from carbamates **3** to **4** led us to investigate an alternative synthetic route. Carboxylic acids **7a**, **e** obtained by the hydrolysis of **3a**, **e** were condensed with alkyl-substituted ethanolamines to furnish **4b**, **c**, **h**.

Chloro-substituted compounds on the thiophene ring (**31a**, **e** and **33**) were synthesized as follows. Treatment of **15a**, **e** (**23b**) with sulfuryl chloride (SO_2Cl_2) in chloroform ($CHCl_3$) gave ureas **30a**, **e** (**32**), which were cyclized with NaOH to form the corresponding tricyclic compounds **31a**, **e** (**33**).

In order to compare the pharmacological activity with that of **1**, the thienopyrimidine derivative (**36**) containing an oxazine ring was synthesized according to the sequence illustrated in Chart 5. The data for these derivatives are summarized in Table II.

Pharmacology and Structure–Activity Relationships The biological results are listed in Table III. The tricyclic compounds prepared in the present study were evaluated for gastric antisecretory activity using pylorus-ligated rats. In the test, the compounds were administered at doses of 50 mg/kg by intraduodenal (i.d.) injection.

The structure–activity relationships in these compounds are as follows. These tricyclic compounds generally were more potent than cimetidine in gastric antisecretory activity. The oxazolothienopyrimidine **1e** exhibited more potent activity than the oxazinothienopyrimidine **36**. As for the positional isomers of the thiophene ring, oxazolo-[3,2-*a*]thieno[3,2-*d*]pyrimidines **1** and oxazolo[3,2-*a*]thieno-[3,4-*d*]pyrimidines **14** exhibited stronger activity than oxazolo[3,2-*a*]thieno[2,3-*d*]pyrimidines **22**. It was noted that the activity was strongly influenced by the substituents (R_1 and R_2) on the thiophene ring. Decreasing the number of substituents on the thiophene ring resulted in a marked increase of activity. A dialkyl-substituted derivative (**1m**) showed weak activity. Substituents (R_3, R_4, and R_5) on the oxazolidine ring had no significant influence on the activity (**1a**, **1b**, and **1d**). These compounds have no histamine H_2 receptor antagonist activity.[7]

The results of further investigation on the syntheses and structure–activity relationships of oxazolothienopyrimidine derivatives will be reported in a forthcoming paper.

Experimental

All melting points are uncorrected. IR spectra were measured on a JASCO A-102 spectrometer. NMR spectra were recorded with a Varian T-60A (60 MHz) or EM-390 (90 MHz) spectrometer and the chemical shifts are expressed in ppm from tetramethylsilane as an internal standard; s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets; m, multiplet; br, broad. MS were obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer. Merck silica gel (Kieselgel 60 Art. 7734) was employed for column chromatography.

Methyl 3-Ethoxycarbonylamino-5-methylthiophene-2-carboxylate (3e) General Procedure A solution of methyl 3-amino-5-methylthiophene-2-carboxylate (**2e**) (10.8 g) and ethyl chloroformate (8.2 g) in toluene (140 ml) was refluxed for 3 h. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel with AcOEt–hexane (3 : 1) as an eluent. Recrystallization from AcOEt–hexane gave **3e** (15.0 g, 98%) as colorless needles. Other compounds (**3**, **11**, and **19**) were similarly prepared. Other data are listed in Tables IV—IX.

3-(2-Hydroxyethyl)-6-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4e) General Procedure for 3-(2-Hydroxyethyl) Derivatives A mixture of **3e** (2.0 g) and ethanolamine (2.5 g) was stirred at 130—135 °C for 1 h and then cooled. Water was added to the mixture and the resulting crystalline solid was collected by filtration. Recrystallization from dimethylformamide (DMF)–MeOH afforded **4e** (1.0 g, 54%) as colorless needles. Other compounds (**4**, **12**, and **20**, except **4b**,**4c**, **4h**, and **12b**) were similarly prepared. Other data are listed in Tables IV—IX.

3-(2-Hydroxypropyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b) General Procedure for 4c, 4h, and 12b A solution of **8b** (4.45 g) in DMF (15 ml) was refluxed for 4 h. After evaporation of the solvent, $CHCl_3$ was added to the residue, and the resulting crystalline solid was collected by filtration. Recrystallization from MeOH afforded **4b** (3.28 g, 89%) as colorless needles. Other compounds were similarly prepared. Other data are listed in Tables IV—VII.

3-(2-Chloroethyl)-6-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione (5e) General Procedure A suspension of **4e** (1.0 g) in $CHCl_3$ (20 ml) was treated with $SOCl_2$ (0.7 g) and the whole was refluxed for 1 h. After cooling, the precipitate was collected, washed with water and $CHCl_3$, and recrystallized from AcOEt to obtain **5e** in 93% yield (1.0 g) as colorless needles. Other compounds (**5**, **13**, and **21**) were similarly prepared. Other data are listed in Tables IV—IX.

2,3-Dihydro-7-methyl-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one (1e) General Procedure Method A: Et_3N (0.9 g) was added to a stirred suspension of **5e** (0.9 g) in EtOH (15 ml) and the whole was refluxed for 2 h. After evaporation of the solvent, water was added to the residue and the resulting mixture was extracted with $CHCl_3$. A residue obtained from the $CHCl_3$ extracts was chromatographed on silica gel and eluted with AcOEt. Recrystallization from EtOH–AcOEt gave **1e** (0.6 g, 78%) as colorless

TABLE V. Spectral Data for 3-Aminothiophene-2-carboxylate Derivatives (**3**, **6**, **7** and **8**) and Thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Derivatives (**4** and **5**)

Compd. No.	IR	NMR	
	KBr, cm^{-1}	Solvent	δ: ppm
3e	1730, 1675[a)]	$CDCl_3$	1.30 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 2.47 (3H, s, $ArCH_3$), 3.84 (3H, s, OCH_3), 4.22 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 7.96 (1H, s, ArH), 9.3—9.7 (1H, br, NH)
3f	1730, 1675[a)]	$CDCl_3$	1.31 (6H, t, J=7.4 Hz, $OCH_2C\underline{H}_3$, $ArCH_2C\underline{H}_3$), 2.81 (2H, q, J=7.6 Hz, $ArC\underline{H}_2CH_3$), 3.85 (3H, s, OCH_3), 4.22 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.67 (1H, s, ArH), 9.4—9.7 (1H, br, NH)
3k	1735, 1690[a)]	$CDCl_3$	1.31 (3H, t, J=7.4 Hz, $OCH_2C\underline{H}_3$), 2.24 (3H, s, $ArCH_3$), 3.86 (3H, s, OCH_3), 4.21 (2H, q, J=7.4 Hz, $OC\underline{H}_2CH_3$), 7.13 (1H, s, ArH), 8.1—8.4 (1H, br, NH)
4b	1700 (sh), 1690, 1630	DMSO-d_6	1.06 (3H, br d, J=5.7 Hz, CH_3), 3.54—4.19 (3H, m, NCH_2CHO), 4.4—4.9 (1H, br, OH), 6.94 and 8.06 (each 1H, d, J=5.4 Hz, ArH×2)
4c	1705, 1660, 1645	DMSO-d_6	0.89 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.18—1.56 (2H, m, $C\underline{H}_2CH_3$), 3.58—4.07 (3H, m, NCH_2CHO), 4.5—4.7 (1H, br, OH), 6.93 and 8.05 (each 1H, d, J=4.8 Hz, ArH×2)
4e	1690, 1650 (sh), 1640	DMSO-d_6	2.53 (3H, s, $ArCH_3$), 3.58 (2H, t, J=6.8 Hz, $NCH_2C\underline{H}_2O$), 3.95 (2H, t, J=6.8 Hz, $NC\underline{H}_2CH_2O$), 6.71 (1H, s, ArH)
4f	1705, 1685, 1635 (sh), 1625	DMSO-d_6	1.25 (3H, t, J=7.5 Hz, $ArCH_2C\underline{H}_3$), 2.87 (2H, q, J=7.5 Hz, $ArC\underline{H}_2CH_3$), 3.55 (2H, t, J=6.5 Hz, $NCH_2C\underline{H}_2O$), 3.95 (2H, t, J=6.5 Hz, $NC\underline{H}_2CH_2O$), 6.71 (1H, s, ArH)
4h	1720 (sh), 1710, 1630	DMSO-d_6	1.03 (3H, br d, J=4.8 Hz, CH_3), 2.52 (3H, s, $ArCH_3$), 3.63—4.11 (3H, m, NCH_2CHO), 4.65 (1H, br d, J=4.2 Hz, OH), 6.71 (1H, s, ArH), 11.5—11.9 (1H, br, NH)
4k	1695, 1640 (sh), 1625	DMSO-d_6	2.22 (3H, s, $ArCH_3$), 3.60 (2H, t, J=6.8 Hz, $NCH_2C\underline{H}_2O$), 3.99 (2H, t, J=6.8 Hz, $NC\underline{H}_2CH_2O$), 4.73 (1H, br t, J=5.9 Hz, OH), 7.52 (1H, s, ArH), 11.5—11.8 (1H, br, NH)
5b	1710, 1650	DMF-d_7	1.53 (3H, d, J=6.0 Hz, CH_3), 3.97—4.73 (3H, m, NCH_2CHO), 7.08 and 8.15 (each 1H, d, J=4.8 Hz, ArH×2), 11.4—12.3 (1H, br, NH)
5c	1710, 1655	DMSO-d_6	1.01 (3H, t, J=7.4 Hz, $CH_2C\underline{H}_3$), 1.43—2.05 (2H, m, $C\underline{H}_2CH_3$), 3.99—4.51 (3H, m, NCH_2CHO), 6.95 and 8.07 (each 1H, d, J=4.8 Hz, ArH×2), 10.98 (1H, br s, NH)
5e	1710, 1660 (sh),[a)] 1650	$CDCl_3$	2.56 (3H, s, $ArCH_3$), 3.78 (2H, t, J=7.1 Hz, $NCH_2C\underline{H}_2Cl$), 4.41 (2H, t, J=7.1 Hz, $NC\underline{H}_2CH_2Cl$), 6.63 (1H, s, ArH), 10.3—10.6 (1H, br, NH)
5f	1715, 1695, 1640	DMSO-d_6	1.25 (3H, t, J=7.5 Hz, $ArCH_2C\underline{H}_3$), 2.88 (2H, q, J=7.5 Hz, $ArC\underline{H}_2CH_3$), 3.77 (2H, t, J=6.5 Hz, $NCH_2C\underline{H}_2Cl$), 4.20 (2H, t, J=6.5 Hz, $NC\underline{H}_2CH_2Cl$), 6.73 (1H, s, ArH), 10.95 (1H, br s, NH)
5h	1700, 1640	DMSO-d_6	1.47 (3H, d, J=6.3 Hz, CH_3), 2.52 (3H, s, $ArCH_3$), 3.86—4.60 (3H, m, NCH_2CHO), 6.72 (1H, s, ArH), 11.92 (1H, br s, NH)
5k	1705, 1635	DMSO-d_6	2.23 (3H, s, $ArCH_3$), 3.80 (2H, t, J=6.5 Hz, $NCH_2C\underline{H}_2Cl$), 4.23 (2H, t, J=6.5 Hz, $NC\underline{H}_2CH_2Cl$), 7.73 (1H, s, ArH), 10.84 (1H, br s, NH)
6d	1660	$CDCl_3$	1.49 (6H, s, CH_3×2), 3.80 (2H, s, $NCCH_2Br$), 3.86 (3H, s, OCH_3), 7.41 and 7.97 (each 1H, d, J=5.7 Hz, ArH×2), 4.7—5.0 and 9.2—9.6 (each 1H, br, NH×2)
6e	1700, 1665[a)]	$CDCl_3$	2.45 (3H, s, $ArCH_3$), 3.65 (4H, br s, NCH_2CH_2Cl), 3.82 (3H, s, OCH_3), 7.72 (1H, s, ArH), 5.2—5.5 and 9.4—9.7 (each 1H, br, NH×2)
6g	1695 (sh), 1670[a)]	DMSO-d_6	3.33—3.80 (4H, m, NCH_2CH_2Cl), 3.86 (3H, s, OCH_3), 7.40—7.85 (5H, m, PhH×5), 8.05 (1H, br t, J=5.3 Hz, $CONHCH_2$), 8.32 (1H, s, ArH), 9.38 (1H, br s, NH)
6i	1690, 1665[a)]	$CDCl_3$	0.98 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 1.50—1.92 (2H, m, $C\underline{H}_2CH_3$), 2.46 (3H, s, $ArCH_3$), 3.60 (2H, br t, J=3.2 Hz, $NCHC\underline{H}_2Br$), 3.83 (3H, s, OCH_3), 3.70—4.10 (1H, m, $NC\underline{H}CH_2Br$), 4.93 (1H, br d, J=9.0 Hz, NH), 7.73 (1H, s, ArH), 9.50 (1H, br s, NH)
6j	1660	$CDCl_3$	1.47 (6H, s, CH_3×2), 2.44 (3H, s, $ArCH_3$), 3.80 and 3.83 (5H, each s, OCH_3, $NCCH_2Br$), 7.70 (1H, s, ArH), 4.7—5.0 and 9.3—9.6 (each 1H, br, NH×2)
6l	1710, 1670[a)]	$CDCl_3$	3.17—3.35 (4H, m, NCH_2CH_2Cl), 3.89 (3H, s, OCH_3), 7.23—7.57 (6H, m, PhH×5, ArH), 5.1—5.3 and 8.2—8.3 (each 1H, br, NH×2)
6m	1695, 1645	DMSO-d_6	1.93 and 2.33 (each 3H, s, $ArCH_3$×2), 3.23—3.70 (4H, m, NCH_2CH_2Cl), 3.77 (3H, s, OCH_3), 7.17 (1H, br t, J=5.7 Hz, $N\underline{H}CH_2$), 8.40 (1H, br s, NH)
7a	1735, 1655[a)]	$CDCl_3$	1.34 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 4.26 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 7.54 and 7.96 (each 1H, d, J=5.4 Hz, ArH×2), 9.2—9.6 and 10.4—10.8 (each 1H, br, OH, NH)
7e	1740, 1635[a)]	DMSO-d_6	1.27 (3H, t, J=6.5 Hz, $OCH_2C\underline{H}_3$), 2.49 (3H, s, $ArCH_3$), 4.20 (2H, q, J=6.5 Hz, $OC\underline{H}_2CH_3$), 7.54 (1H, s, ArH), 9.61 (1H, br s, NH or OH)
8b	1730, 1620	$CDCl_3$	1.25 (3H, d, J=6.6 Hz, CH_3), 1.30 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 3.03—3.39 and 3.43—3.75 (each 1H, m, $NC\underline{H}_2CHO$), 3.82—4.31 (1H, m, $NCH_2C\underline{H}O$), 4.21 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 7.29 and 7.92 (each 1H, d, J=4.8 Hz, ArH×2), 2.5—2.9, 6.0—6.4 and 10.1—10.4 (each 1H, br, NH×2, OH)
8c	1730, 1605	DMSO-d_6	0.89 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 1.25 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.10—1.60 (2H, m, $C\underline{H}_2CH_3$), 2.92—3.73 (3H, m, NCH_2CHO), 4.15 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 4.65 (1H, br d, J=4.8 Hz, OH), 7.72 (2H, s, ArH×2), 8.03 (1H, br t, J=5.6 Hz, ArCONH), 10.4—10.7 (1H, br, $N\underline{H}CO_2Et$)
8h	1725, 1615[a)]	$CDCl_3$	1.23 (3H, d, J=6.6 Hz, CH_3), 1.29 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 2.47 (3H, s, $ArCH_3$), 3.03—3.38 and 3.42—3.81 (each 1H, m, $NC\underline{H}_2CHO$), 3.82—4.38 (1H, m, NCCHO), 4.20 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 7.64 (1H, s, ArH), 2.6—2.8, 5.8—6.2 and 10.1—10.5 (each 1H, br, NH×2, OH)

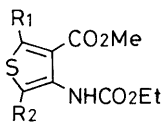
a) $CHCl_3$.

needles.

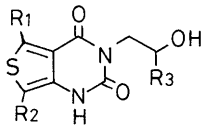
Method B: An aqueous 10% NaOH solution (4.4 ml) was added dropwise to a stirred solution of **6e** (3.0 g) in dioxane (5 ml) under reflux, and then the whole was stirred for 15 min at the same temperature. After evaporation of the solvent, water was added to the residue and the resulting mixture was extracted with $CHCl_3$. A residue obtained from the $CHCl_3$ extracts was recrystallized from EtOH–AcOEt to give **1e** (1.6 g, 71%). Other compounds (**1**, **14**, **22**, **31**, and **33**) were similarly prepared by the method indicated in Table I. Other data are listed in Tables I—II and X—XI.

Methyl 3-[*N'*-(2-Chloroethyl)ureido]-5-methylthiophene-2-carboxylate (6e) General Procedure A mixture of methyl 3-amino-5-methylthio-

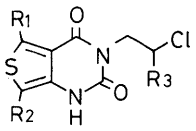
TABLE VI. 4-Aminothiophene-3-carboxylate Derivatives (**11**, **15**, **16** and **17**) and Thieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Derivatives (**12** and **13**)



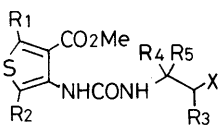
11



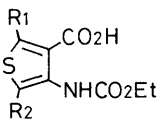
12



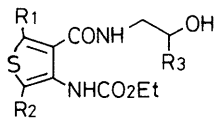
13



15



16



17

Compd. No.	R_1	R_2	R_3	R_4	R_5	X	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	S	Cl(Br)
11a	H	H					81	50—52 (EA–H)	$C_9H_{11}NO_4S$	47.15 (47.09	4.84 4.58	6.11 6.03	13.98 13.99)	
12a	H	H	H				39	247—248 (dec.) (M)	$C_8H_8N_2O_3S$	45.28 (45.21	3.80 3.72	13.20 13.21	15.11 14.97)	
12b	H	H	Me				16	184—186 (M)	$C_9H_{10}N_2O_3S$	47.73 (47.71	4.46 4.44	12.38 12.31	14.17 14.21)	
13a	H	H	H				69	205—208 (dec.) (D–M)	$C_8H_7ClN_2O_2S$	41.66 (41.49	3.06 2.90	12.14 12.10	13.90 14.17	15.37 15.45)
13b	H	H	Me				56	203—206 (E)	$C_9H_9ClN_2O_2S$	44.18 (44.39	3.71 3.58	11.45 11.38	13.10 13.40	14.49 14.13)
15a[b]	H	H	H	H	H	Cl		111—113	$C_9H_{11}ClN_2O_3S$	Lit.[b] mp 110—112 °C				
15c	H	H	H	Me	Me	Br	55	Oil[c]	$C_{11}H_{15}BrN_2O_3S$					
15d	H	H	Me	Me	Me	Br	61	Oil[c]	$C_{12}H_{17}BrN_2O_3S$					
15e[b]	Me	H	H	H	H	Cl	89	133—134	$C_{10}H_{13}ClN_2O_3S$	Lit.[b] mp 112—116 °C				
15f	H	Me	H	H	H	Cl	56	157—159 (EA–H)	$C_{10}H_{13}ClN_2O_3S$	43.40 (43.47	4.73 4.76	10.12 10.36	11.59 11.49	12.81 12.62)
15g	H	Et	H	H	H	Cl	45	151—153 (EA–H)	$C_{11}H_{15}ClN_2O_3S$	45.44 (45.46	5.20 5.17	9.63 9.49	11.03 11.26	12.19 12.20)
15h	Me	Me	H	H	H	Cl	83	165—167 (EA)	$C_{11}H_{15}ClN_2O_3S$	45.44 (45.34	5.20 5.20	9.63 9.61	11.03 11.11	12.19 12.39)
16a[d]	H	H						148—149	$C_8H_9NO_4S$	Lit.[d] mp 152—154 °C				
17b	H	H	Me				60	Oil[e]	$C_{11}H_{16}N_2O_4S$	48.52 (48.38	5.92 5.63	10.29 10.32	11.77 11.65)	

a) See footnote *a* in Table IV. *b*) Ref. 8. *c*) The material was used for the subsequent step without further purification. *d*) Ref. 9. *e*) bp 150 °C (0.01 mmHg).

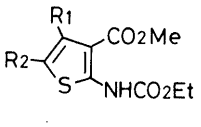
TABLE VII. Spectral Data for 4-Aminothiophene-3-carboxylate Derivatives (**11**, **15** and **17**) and Thieno[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Derivatives (**12** and **13**)

Compd. No.	IR	NMR	
	KBr, cm^{-1}	Solvent	δ: ppm
11a	1735, 1705	$CDCl_3$	1.31 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 3.89 (3H, s, OCH_3), 4.24 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 6.43 and 8.03 (each 1H, d, J=3.6 Hz, ArH×2), 8.9—9.7 (1H, br, NH)
12a	1690, 1650	DMSO-d_6	3.41—3.72 (2H, m, $NCH_2C\underline{H}_2O$), 3.96 (2H, t, J=5.1 Hz, $NC\underline{H}_2CH_2O$), 4.71 (1H, t, J=5.6 Hz, OH), 6.84 and 8.38 (each 1H, d, J=3.6 Hz, ArH×2), 11.0—11.4 (1H, br, NH)
12b	1725, 1640	DMSO-d_6	1.04 (3H, br d, J=5.7 Hz, CH_3), 3.61—4.13 (3H, m, NCH_2CHO), 4.64 (1H, br d, J=4.5 Hz, OH), 6.83 and 8.36 (each 1H, d, J=3.3 Hz, ArH×2), 11.0—11.4 (1H, br, NH)
13a	1720, 1665	DMSO-d_6	3.76 (2H, t, J=6.9 Hz, $NCH_2C\underline{H}_2Cl$), 4.18 (2H, t, J=6.9 Hz, $NC\underline{H}_2CH_2Cl$), 6.89 and 8.41 (each 1H, d, J=3.6 Hz, ArH×2), 11.2—11.4 (1H, br, NH)
13b	1720, 1660 (sh) 1640	DMSO-d_6	1.49 (3H, d, J=6.6 Hz, CH_3), 3.87—4.70 (3H, m, NCH_2CHO), 6.88 and 8.44 (each 1H, d, J=3.3 Hz, ArH×2), 11.2—11.5 (1H, br, NH)
15e	1690 (sh), 1680[a]	$CDCl_3$	2.64 (3H, s, $ArCH_3$), 3.56—3.73 (4H, m, NCH_2CH_2Cl), 3.90 (3H, s, OCH_3), 7.46 (1H, s, ArH), 4.9—5.3 and 9.3—9.5 (each 1H, br, NH×2)
15f	1705[a]	DMSO-d_6	2.21 (3H, s, $ArCH_3$), 3.23—3.86 (4H, m, NCH_2CH_2Cl), 3.76 (3H, s, OCH_3), 6.6—6.9 and 7.8—8.0 (each 1H, br, NH×2), 7.99 (1H, s, ArH)
15g	1715, 1645	DMSO-d_6	1.17 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.66 (2H, q, J=7.5 Hz, $C\underline{H}_2CH_3$), 3.17—3.80 (4H, m, NCH_2-CH_2Cl), 3.74 (3H, s, OCH_3), 8.04 (1H, s, ArH), 6.6—6.9 and 7.8—8.0 (each 1H, br, NH×2)
15h	1690[a]	$CDCl_3$	2.29 and 2.57 (each 3H, s, $ArCH_3$×2), 3.17—3.70 (4H, m, NCH_2CH_2Cl), 3.81 (3H, s, OCH_3), 5.1—5.3 and 7.0—7.2 (each 1H, br, NH×2)
17b	1720, 1645[a]	$CDCl_3$	1.17—1.46 (6H, m, $OCH_2C\underline{H}_3$, CH_3), 3.03—3.38 and 3.47—3.77 (each 1H, m, $NC\underline{H}_2CHO$), 3.83—4.13 (1H, m, $NCH_2C\underline{H}O$), 4.20 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.64 (2H, s, ArH×2), 2.0—2.4, 6.5—6.9 and 9.7—10.0 (each 1H, br, NH×2, OH)

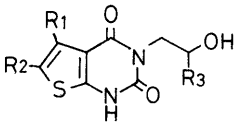
a) $CHCl_3$.

phene-2-carboxylate (**2e**) (3.5 g) and 2-chloroethyl isocyanate (4.0 g) in AcOEt (40 ml) was refluxed for 2 h and then cooled. The mixture was poured into water and extracted with AcOEt. A residue obtained from the AcOEt extracts was chromatographed on silica gel and eluted with AcOEt–hexane (1:4). Recrystallization from AcOEt–hexane gave **6e** (5.0 g, 89%) as colorless needles. Other compounds (**6**, **15**, and **23**) were

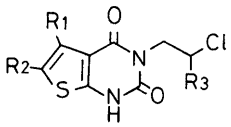
TABLE VIII. 2-Aminothiophene-3-carboxylate Derivatives (**19** and **23**) and Thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Derivatives (**20** and **21**)



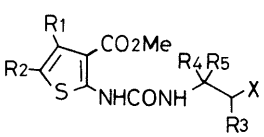
19



20



21



23

Compd. No.	R_1	R_2	R_3	R_4	R_5	X	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	S	Cl
19a	H	H					69	71—73 (EA–H)	$C_9H_{11}NO_4S$	47.15 (47.19)	4.84 (4.69)	6.11 (6.06)	13.98 (13.93)	
19d	H	Me					73	70—72 (EA–H)	$C_{10}H_{13}NO_4S$	49.37 (49.32)	5.39 (5.16)	5.76 (5.71)	13.18 (13.32)	
19e	H	Ph					72	106—107 (EA–H)	$C_{15}H_{15}NO_4S$	59.00 (59.11)	4.95 (4.99)	4.59 (4.73)	10.50 (10.42)	
20a	H	H	H				40	258—260 (dec.) (E)	$C_8H_8N_2O_3S$	45.28 (45.19)	3.80 (3.69)	13.20 (13.15)	15.11 (15.08)	
20d	H	Me	H				39	277—279 (dec.) (M)	$C_9H_{10}N_2O_3S$	47.78 (47.56)	4.46 (4.43)	12.38 (12.37)	14.17 (14.18)	
20e	H	Ph	H				34	281—284 (dec.) (D)	$C_{14}H_{12}N_2O_3S$	58.32 (58.02)	4.20 (4.18)	9.72 (9.84)	11.12 (11.15)	
21a	H	H	H				86	219—222 (dec.) (EA)	$C_8H_7ClN_2O_2S$	41.66 (41.55)	3.06 (3.09)	12.14 (12.00)	13.90 (14.01)	15.37 (15.12)
21d	H	Me	H				59	228—231 (dec.) (M)	$C_9H_9ClN_2O_2S$	44.18 (44.21)	3.71 (3.86)	11.45 (11.23)	13.10 (13.37)	14.49 (14.23)
21e	H	Ph	H				61	232—236 (dec.) (D–M)	$C_{14}H_{11}ClN_2O_2S \cdot 1/5\,H_2O$	54.18 (54.04)	3.70 (3.77)	9.03 (9.24)	10.33 (10.41)	11.42 (11.28)
23a[b,c]	H	H	H	H	H	Cl		86—88		Lit.[c] mp 85—87 °C				
23b	Me	H	H	H	H	Cl	97	121—122 (EA–H)	$C_{10}H_{13}ClN_2O_3S$	43.40 (43.53)	4.74 (4.63)	10.12 (10.28)	11.58 (11.83)	12.81 (13.03)
23c	Ph	H	H	H	H	Cl	56	118—120 (E)	$C_{15}H_{15}ClN_2O_3S$	53.18 (53.14)	4.46 (4.42)	8.27 (8.27)	9.46 (9.42)	10.46 (10.41)
23d	H	Me	H	H	H	Cl	94	112—114 (EA–H)	$C_{10}H_{13}ClN_2O_3S$	43.40 (43.45)	4.74 (4.69)	10.12 (10.19)	11.58 (11.86)	12.81 (12.86)
23e	H	Ph	H	H	H	Cl	59	143—146 (EA–H)	$C_{15}H_{15}ClN_2O_3S$	53.18 (53.02)	4.46 (4.41)	8.27 (8.36)	9.46 (9.38)	10.46 (10.77)
23f[b]	Et	Me	H	H	H	Cl	80	74—75 (EA–H)	$C_{13}H_{19}ClN_2O_3S$	48.97 (49.16)	6.01 (6.07)	8.79 (8.91)	10.06 (10.13)	11.12 (11.14)
23g[b]	$(CH_2)_4$		H	H	H	Cl	72	123—125 (EA–H)	$C_{14}H_{19}ClN_2O_3S$	50.83 (50.88)	5.79 (5.89)	8.47 (8.58)	9.69 (9.87)	10.72 (10.69)

a) See footnote *a* in Table IV. *b*) This material is the ethyl ester derivative because of the use of ethyl 2-aminothiophene-3-carboxylate as the starting material. *c*) Ref. 8.

similarly prepared. Other data are listed in Tables IV—IX.

3-Ethoxycarbonylaminothiophene-2-carboxylic Acid (7a) General Procedure A solution of **3a**[2] (2.00 g) and aqueous 10% NaOH solution (5 ml) in DMF (15 ml) was stirred at room temperature overnight, and then the reaction mixture was poured into ice water (*ca.* 200 ml). After the precipitate was filtered off, the filtrate was adjusted to pH 2.0 with aqueous 10% HCl solution and the resulting crystalline solid was collected by filtration. Recrystallization from AcOEt–hexane afforded **7a** (1.44 g, 77%) as colorless needles. Other compounds (**7e** and **16a**) were similarly prepared. Other data are listed in Tables IV—VII.

3-Ethoxycarbonylamino-*N*-(2-hydroxypropyl)thiophene-2-carboxamide (8b) General Procedure Diethyl phosphorocyanidate (DEPC, 90% purity) (5.98 g) and Et_3N (3.37 g) were added to a stirred solution of **7a** (6.88 g) and 1-amino-2-propanol (2.48 g) in DMF (15 ml) at room temperature. After being stirred for 5 h, the reaction mixture was poured into ice water and extracted with AcOEt. A residue obtained from the AcOEt extracts was chromatographed on silica gel and eluted with $CHCl_3$–AcOEt (3 : 1). Recrystallization from AcOEt gave **8b** (5.15 g, 63%) as colorless needles. Other compounds (**8** and **17**) were similarly prepared. Other data are listed in Tables IV—VII.

Methyl 5-Chloro-4-[*N'*-(2-chloroethyl)ureido]-2-methylthiophene-3-carboxylate (30e) General Procedure A mixture of **15e** (4.8 g) and SO_2Cl_2 (2.5 g) in $CHCl_3$ (55 ml) was refluxed for 1 h. A residue obtained by evaporation of the solvent was chromatographed on silica gel and eluted with CH_2Cl_2–AcOEt (10 : 1). Recrystallization of the product from AcOEt gave **30e** (3.4 g, 63%) as colorless needles. Other compounds (**30** and **32**) were similarly prepared. Other data are listed in Tables XII and XIII.

***N*-(3-Chloropropyl)-3-ethoxycarbonylamino-5-methylthiophene-2-carboxamide (34)** Et_3N (1.88 g) was added dropwise to a solution of **7e** (2.00 g), 3-chloropropylamine hydrochloride (1.20 g) and DEPC (90% purity) (1.58 g) in DMF (15 ml) at room temperature. After being stirred for 6 h, the reaction mixture was poured into ice water and extracted with AcOEt. A residue obtained from the AcOEt extracts was chromatographed on silica gel and eluted with AcOEt–hexane (1 : 3) to give **34** (1.50 g, 57%) as an oil. *Anal.* Calcd for $C_{12}H_{17}ClN_2O_3S$: C, 47.29; H, 5.62; Cl, 11.63; N, 9.19; S, 10.52. Found: C, 47.06; H, 5.75; Cl, 11.30; N, 8.93; S, 10.71. IR ($CHCl_3$): 1730, 1625 cm^{-1}. NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.07 (2H, quint, J=6.4 Hz, $NCH_2CH_2CH_2Cl$), 2.47 (3H, s, $ArCH_3$), 3.41—3.70 (4H, m, $NCH_2CH_2CH_2Cl$), 4.19 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.66 (1H, s, ArH), 5.6—5.9 and 10.2—10.4 (each 1H, br, NH × 2).

3-(3-Chloropropyl)-6-methylthieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (35) A solution of **34** (1.5 g) in DMF (6 ml) was refluxed for 3 h. After evaporation of the solvent, the residue was recrystallized from EtOH to give **35** (0.9 g, 70%) as colorless needles. mp 206—208 °C. *Anal.* Calcd for $C_{10}H_{11}ClN_2O_2S$: C, 46.42; H, 4.29; Cl, 13.70; N, 10.83; S, 12.39. Found: C, 46.53; H, 4.29; Cl, 13.47; N, 10.73; S, 12.60. IR ($CHCl_3$): 1705, 1655 (sh), 1650 cm^{-1}. NMR ($CDCl_3$) δ: 2.19 (2H, quint, J=6.8 Hz, $NCH_2CH_2CH_2Cl$), 2.56 (3H, s, $ArCH_3$), 3.62 (2H, t, J=6.8 Hz, CH_2Cl), 4.21 (2H, t, J=6.8 Hz, NCH_2), 6.66 (1H, s, ArH), 10.9—11.2 (1H, br, NH).

TABLE IX. Spectral Data for 2-Aminothiophene-3-carboxylate Derivatives (**19** and **23**) and Thieno[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Derivatives (**20** and **21**)

Compd. No.	IR	NMR	
	KBr, cm^{-1}	Solvent	δ: ppm
19a	1725, 1680	$CDCl_3$	1.33 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 3.87 (3H, s, OCH_3), 4.29 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 6.25 and 7.16 (each 1H, d, J=6.0 Hz, ArH×2), 10.0—10.4 (1H, br, NH)
19d	1720, 1680[a]	$CDCl_3$	1.33 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.34 (3H, d, J=1.8 Hz, $ArCH_3$), 3.83 (3H, s, OCH_3), 4.28 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 6.79 (1H, d, J=1.8 Hz, ArH), 9.8—10.3 (1H, br, NH)
19e	1720, 1685	$CDCl_3$	1.35 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 3.90 (3H, s, OCH_3), 4.32 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.15—7.67 (6H, m, PhH×5, ArH), 10.0—10.4 (1H, br, NH)
20a	1675, 1655 (sh), 1645	DMSO-d_6	3.54 (2H, t, J=6.5 Hz, $NCH_2C\underline{H}_2O$), 3.96 (2H, t, J=6.5 Hz, $NC\underline{H}_2CH_2O$), 7.10 and 7.16 (each 1H, d, J=6.0 Hz, ArH×2), 4.5—5.2 and 11.0—12.9 (each 1H, br, NH, OH)
20d	1690, 1625	DMSO-d_6	2.37 (3H, d, J=1.5 Hz, $ArCH_3$), 3.52 (2H, t, J=6.6 Hz, $NCH_2C\underline{H}_2O$), 3.95 (2H, t, J=6.6 Hz, $NC\underline{H}_2CH_2O$), 6.86 (1H, d, J=1.5 Hz, ArH), 4.4—5.2 and 10.8—11.4 (each 1H, br, NH, OH)
20e	1675, 1630	DMSO-d_6	3.58 (2H, t, J=6.5 Hz, $NCH_2C\underline{H}_2O$), 3.99 (2H, t, J=6.5 Hz, $NC\underline{H}_2CH_2O$), 7.29—7.80 (6H, m, ArH, PhH×5)
21a	1710, 1640	DMSO-d_6	3.78 (2H, t, J=6.9 Hz, $NCH_2C\underline{H}_2Cl$), 4.20 (2H, t, J=6.9 Hz, $NC\underline{H}_2CH_2Cl$), 7.15 and 7.20 (each 1H, d, J=5.7 Hz, ArH×2), 11.0—11.6 (1H, br, NH)
21d	1710, 1635	DMSO-d_6	2.39 (3H, d, J=0.9 Hz, $ArCH_3$), 3.76 (2H, t, J=6.9 Hz, $NCH_2C\underline{H}_2Cl$), 4.18 (2H, t, J=6.9 Hz, $NC\underline{H}_2CH_2Cl$), 6.87 (1H, d, J=0.9 Hz, ArH), 10.9—11.5 (1H, br, NH)
21e	1725, 1625	DMSO-d_6	3.80 (2H, t, J=6.8 Hz, $NCH_2C\underline{H}_2Cl$), 4.22 (2H, t, J=6.8 Hz, $NC\underline{H}_2CH_2Cl$), 7.22—7.76 (6H, m, PhH×5, ArH), 10.4—10.8 (1H, br, NH)
23b	1690, 1665[a]	$CDCl_3$	2.31 (3H, s, $ArCH_3$), 3.22—3.75 (4H, m, NCH_2CH_2Cl), 3.88 (3H, s, OCH_3), 6.27 (1H, s, ArH), 5.4—5.7 and 10.6—10.9 (each 1H, br, NH×2)
23c	1720, 1710, 1655	$CDCl_3$	3.56 (3H, s, OCH_3), 3.65—3.82 (4H, m, NCH_2CH_2Cl), 6.50 (1H, s, ArH), 7.33 (5H, s, PhH×5), 5.5—5.8 and 10.6—10.9 (each 1H, br, NH×2)
23d	1690 (sh), 1670[a]	$CDCl_3$	2.33 (3H, d, J=1.2 Hz, $ArCH_3$), 3.59—3.73 (4H, m, NCH_2CH_2Cl), 3.81 (3H, s, OCH_3), 6.76 (1H, d, J=1.2 Hz, ArH), 5.4—5.8 and 10.1—10.4 (each 1H, br, NH×2)
23e	1690, 1655	$CDCl_3$	3.56—3.80 (4H, m, NCH_2CH_2Cl), 3.87 (3H, s, OCH_3), 7.11—7.67 (6H, m, PhH×5, ArH), 5.70 and 10.36 (each 1H, br s, NH×2)
23f	1700, 1665,[b] 1645	$CDCl_3$	1.06 (3H, t, J=7.5 Hz, $ArCH_2C\underline{H}_3$), 1.37 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 2.21 (3H, s, $ArCH_3$), 2.71 (2H, q, J=7.5 Hz, $ArC\underline{H}_2CH_3$), 3.53—3.75 (4H, m, NCH_2CH_2Cl), 4.32 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 5.4—5.7 and 10.7—10.9 (each 1H, br, NH×2)
23g	1690, 1660[a]	$CDCl_3$	1.36 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 1.65—2.00 (4H, m, 5,6-CH_2×2), 2.43—2.92 (4H, m, 4,7-CH_2×2), 3.59—3.83 (4H, m, NCH_2CH_2Cl), 4.30 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.3—5.6 and 10.7—11.0 (each 1H, br, NH×2)

a) $CHCl_3$. *b*) Nujol.

TABLE X. Spectral Data for Alkyl Substituted 2,3-Dihydro-5*H*-oxazolothienopyrimidin-5-ones (**1**, **14** and **22**)

Compd. No.	IR	NMR	
	KBr, cm^{-1}	Solvent	δ: ppm
1b	1690, 1610[a]	$CDCl_3$	1.63 (3H, d, J=6.0 Hz, 2-CH_3), 3.89 (1H, dd, J=11.4, 8.1 Hz, 3-H), 4.48 (1H, dd, J=11.4, 8.4 Hz, 3-H), 4.95—5.40 (1H, m, 2-H), 7.14 and 7.73 (each 1H, d, J=4.8 Hz, ArH×2)
1c	1695, 1610	DMSO-d_6	0.98 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.67—2.08 (2H, m, $C\underline{H}_2CH_3$), 3.89 (1H, dd, J=11.1, 7.5 Hz, 3-H), 4.38 (1H, dd, J=11.1, 9.0 Hz, 3-H), 4.85—5.25 (1H, m, 2-H), 7.19 and 8.11 (each 1H, d, J=5.1 Hz, ArH×2)
1d	1670, 1605	$CDCl_3$	1.80 (6H, s, CH_3×2), 4.38 (2H, s, 2-H×2), 7.15 and 7.72 (each 1H, d, J=5.1 Hz, ArH×2)
1e	1680, 1610[a]	$CDCl_3$	2.57 (3H, s, $ArCH_3$), 4.22—4.43 (2H, m, $NC\underline{H}_2CH_2O$), 4.67—4.89 (2H, m, $NCH_2C\underline{H}_2O$), 6.83 (1H, s, ArH)
1f	1690 (sh), 1680, 1610	$CDCl_3$	1.35 (3H, t, J=7.5 Hz, $ArCH_2C\underline{H}_3$), 2.90 (2H, q, J=7.5 Hz, $ArC\underline{H}_2CH_3$), 4.25—4.44 (2H, m, $NC\underline{H}_2CH_2O$), 4.67—4.90 (2H, m, $NCH_2C\underline{H}_2O$), 6.87 (1H, s, ArH)
1g	1680, 1610[a]	DMSO-d_6	4.15—4.36 (2H, m, $NC\underline{H}_2CH_2O$), 4.65—4.86 (2H, m, $NCH_2C\underline{H}_2O$), 7.44—7.94 (6H, m, PhH×5, ArH)
1h	1680, 1605[a]	$CDCl_3$	1.62 (3H, d, J=5.7 Hz, 2-CH_3), 2.58 (3H, s, $ArCH_3$), 3.88 (1H, dd, J=11.4, 7.5 Hz, 3-H), 4.46 (1H, dd, J=11.4, 8.4 Hz, 3-H), 4.91—5.35 (1H, m, 2-H), 6.86 (1H, s, ArH)
1i	1690 (sh), 1680,[a] 1610	$CDCl_3$	0.95 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.57—2.24 (2H, m, $C\underline{H}_2CH_3$), 2.56 (3H, s, $ArCH_3$), 4.36—4.95 (3H, m, 2-H×2, 3-H), 6.84 (1H, s, ArH)
1j	1690, 1600	$CDCl_3$	1.77 (6H, s, CH_3×2), 2.54 (3H, s, $ArCH_3$), 4.33 (2H, s, 2-H×2), 6.82 (1H, s, ArH)
1k	1680, 1610[a]	DMSO-d_6	2.20 (3H, d, J=1.8 Hz, $ArCH_3$), 4.15—4.33 (2H, m, $NC\underline{H}_2CH_2O$), 4.66—4.88 (2H, m, $NCH_2C\underline{H}_2O$), 7.75 (1H, d, J=1.8 Hz, ArH)
1l	1685, 1615[a]	$CDCl_3$	4.26—4.45 (2H, m, $NC\underline{H}_2CH_2O$), 4.69—4.87 (2H, m, $NCH_2C\underline{H}_2O$), 7.25—7.90 (6H, m, PhH×5, ArH)
1m	1680, 1610[a]	$CDCl_3$	2.18 and 2.46 (each 3H, s, $ArCH_3$×2), 4.26—4.44 (2H, m, $NC\underline{H}_2CH_2O$), 4.66—4.89 (2H, m, $NCH_2C\underline{H}_2O$)
14a	1700, 1645	DMSO-d_6	4.06—4.24 (2H, m, $NC\underline{H}_2CH_2O$), 4.59—4.77 (2H, m, $NCH_2C\underline{H}_2O$), 7.36 and 8.41 (each 1H, d, J=3.0 Hz, ArH×2)

TABLE X. (continued)

Compd. No.	IR	NMR	
	KBr, cm^{-1}	Solvent	δ: ppm
14b	1690, 1640	$CDCl_3$	1.60 (3H, d, J=6.0 Hz, 2-CH_3), 3.77 (1H, dd, J=11.1, 7.5 Hz, 3-H), 4.37 (1H, dd, J=11.1, 8.1 Hz, 3-H), 4.83—5.27 (1H, m, 2-H), 7.18 and 8.18 (each 1H, d, J=3.3 Hz, ArH×2)
14c	1695, 1650[a]	$CDCl_3$	1.77 (6H, s, CH_3×2), 4.30 (2H, s, 2-H×2), 7.18 and 8.18 (each 1H, d, J=3.6 Hz, ArH×2)
14d	1700, 1690 (sh),[a] 1650	$CDCl_3$	1.44 (3H, d, J=6.3 Hz, 2-CH_3), 1.51 and 1.75 (each 3H, s, 3-CH_3×2), 4.47 (1H, q, J=6.3 Hz, 2-H), 7.15 and 8.15 (each 1H, d, J=3.0 Hz, ArH×2)
14e	1685, 1665[a]	$CDCl_3$	2.88 (3H, s, $ArCH_3$), 4.12—4.30 (2H, m, NCH_2CH_2O), 4.58—4.81 (2H, m, NCH_2CH_2O), 6.87 (1H, s, ArH)
14f	1690, 1660[a]	$CDCl_3$	2.53 (3H, s, $ArCH_3$), 4.14—4.33 (2H, m, NCH_2CH_2O), 4.57—4.80 (2H, m, NCH_2CH_2O), 7.95 (1H, s, ArH)
14g	1700, 1660	DMSO-d_6	1.22 (3H, t, J=7.5 Hz, CH_2CH_3), 2.90 (2H, q, J=7.5 Hz, CH_2CH_3), 4.04—4.26 (2H, m, NCH_2-CH_2O), 4.59—4.77 (2H, m, NCH_2CH_2O), 8.19 (1H, s, ArH)
14h	1695, 1660[a]	$CDCl_3$	2.42 and 2.80 (each 3H, s, $ArCH_3$×2), 4.09—4.27 (2H, m, NCH_2CH_2O), 4.56—4.74 (2H, m, NCH_2CH_2O)
22a	1690, 1680, 1610	DMSO-d_6	4.13—4.34 (2H, m, NCH_2CH_2O), 4.68—4.90 (2H, m, NCH_2CH_2O), 7.31 (2H, s, ArH×2)
22b	1695, 1600	DMSO-d_6	2.41 (3H, d, J=1.5 Hz, $ArCH_3$), 4.07—4.30 (2H, m, NCH_2CH_2O), 4.65—4.89 (2H, m, NCH_2-CH_2O), 6.85 (1H, d, J=1.5 Hz, ArH)
22c	1665	DMSO-d_6	4.05—4.28 (2H, m, NCH_2CH_2O), 4.68—4.90 (2H, m, NCH_2CH_2O), 7.24 (1H, s, ArH), 7.30—7.67 (5H, m, PhH×5)
22d	1690 (sh), 1680, 1600	DMSO-d_6	2.43 (3H, d, J=1.2 Hz, $ArCH_3$), 4.11—4.30 (2H, m, NCH_2CH_2O), 4.65—4.86 (2H, m, NCH_2CH_2-O), 6.96 (1H, d, J=1.2 Hz, ArH)
22e	1695, 1680 (sh), 1605	DMSO-d_6	4.15—4.33 (2H, m, NCH_2CH_2O), 4.70—4.91 (2H, m, NCH_2CH_2O), 7.31—7.84 (6H, m, ArH, PhH×5)
22f	1680, 1610[a]	$CDCl_3$	1.15 (3H, t, J=7.5 Hz, $ArCH_2CH_3$), 2.33 (3H, s, $ArCH_3$), 2.87 (2H, q, J=7.5 Hz, $ArCH_2CH_3$), 4.20—4.43 (2H, m, NCH_2CH_2O), 4.66—4.87 (2H, m, NCH_2CH_2O)
22g	1675, 1610[a]	$CDCl_3$	1.67—2.06 (4H, m, 7,8-CH_2×2), 2.92—3.06 (4H, m, 6,9-CH_2×2), 4.20—4.41 (2H, m, NCH_2CH_2-O), 4.67—4.88 (2H, m, NCH_2CH_2O)

a) $CHCl_3$.

TABLE XI. Spectral Data for Various 2,3-Dihydro-5*H*-oxazolothieno-pyrimidin-5-one Derivatives (**31**, **33** and **36**)

Compd. No.	IR	NMR	
	KBr, cm^{-1}	Solvent	δ: ppm
31a	1700, 1640	DMSO-d_6	4.05—4.19 (2H, m, NCH_2CH_2O), 4.63—4.79 (2H, m, NCH_2CH_2O), 8.34 (1H, s, ArH)
31e	1690, 1635	DMSO-d_6	2.77 (3H, s, $ArCH_3$), 4.00—4.21 (2H, m, NCH_2CH_2O), 4.61—4.80 (2H, m, NCH_2CH_2O)
33	1685	DMSO-d_6	2.39 (3H, s, $ArCH_3$), 4.11—4.32 (2H, m, NCH_2CH_2O), 4.69—4.90 (2H, m, NCH_2CH_2O)
36	1675[a]	$CDCl_3$	2.08—2.41 (2H, m, 3-H×2), 2.54 (3H, d, J=1.8 Hz, $ArCH_3$), 4.10 (2H, t, J=6.2 Hz, 4-H×2), 4.45 (2H, t, J=5.4 Hz, 2-H×2), 6.79 (1H, d, J=1.8 Hz, ArH)

a) $CHCl_3$.

3,4-Dihydro-8-methyl-[1,3]oxazino[3,2-*a*]thieno[3,2-*d*]pyrimidin-6-(2*H*)-one (36) A suspension of **35** (1.2 g) and K_2CO_3 (0.8 g) in Me_2CO (50 ml) was refluxed for 6 h. A precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in AcOEt. This solution was washed with water, dried over $MgSO_4$ and concentrated to dryness. The resulting crystalline product was recrystallized from AcOEt–hexane to afford **36** (0.9 g, 87%) as colorless needles. Other data are listed in Tables II and XI.

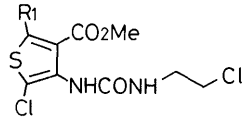
Formation of Methyl 2-(2-Oxo-1-imidazolidinyl)-4-phenylthiophene-3-carboxylate (24c) on a Synthesis of 22c An aqueous 10% NaOH solution (6.0 ml) was added dropwise to a stirred solution of **23c** (501 mg) in dioxane (2 ml) under reflux, and then the whole was stirred for 15 min at the same temperature. After evaporation of the solvent, water was added to the residue and the mixture was extracted with CH_2Cl_2. A residue obtained from the CH_2Cl_2 extracts was chromatographed on silica gel using AcOEt–hexane (2 : 1) as an eluent to give **22c** (78 mg, 20%) and **24c** (84 mg, 19%). **24c** was recrystallized from MeOH as colorless plates. mp 189—191 °C (dec.). *Anal.* Calcd for $C_{15}H_{14}N_2O_3S$: C, 59.59; H, 4.67; N, 9.27; S, 10.60. Found: C, 59.32; H, 4.56; N, 9.25; S, 10.46. IR (KBr): 1705 cm^{-1}. NMR (DMSO-d_6) δ: 3.26—3.97 (4H, m, NCH_2CH_2N), 3.60 (3H, s, OCH_3), 7.13 (1H, s, ArH), 7.18—7.47 (5H, m, PhH×5), 8.1—8.3 (1H, br, NH).

Methyl 2-Methoxycarbonylamino-4-phenylthiophene-3-carboxylate (25) Starting with **18c** and methyl chloroformate, the procedure described for the synthesis of **3e** afforded the desired product (**25**). Yield 83%. mp 104—105 °C. *Anal.* Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 57.80; H, 4.47; N, 4.86; S, 11.28. IR (KBr): 1731, 1659 cm^{-1}. NMR ($CDCl_3$) δ: 3.55 and 3.86 (each 3H, s, OCH_3×2), 6.54 (1H, s, ArH), 7.32 (5H, s, PhH×5), 10.56 (1H, br s, NH).

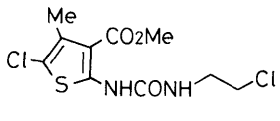
Methyl [*N*-Methoxycarbonyl-*N*-(2-phthalimidoethyl)amino]-5-phenylthiophene-3-carboxylate (26) A solution of **25** (5.00 g) in dry DMF (25 ml) was added dropwise to a suspension of NaH (55% dispersion in oil) (1.50 g) in dry DMF (50 ml) at 0 °C during 10 min under a nitrogen atmosphere and the whole was stirred at room temperature for 1 h. A solution of *N*-(2-bromoethyl)phthalimide (9.10 g) in dry DMF (50 ml) was added dropwise to the mixture and the resulting solution was stirred at 100 °C for 6.5 h. After evaporation of the solvent, water was added and the mixture was extracted with AcOEt. A residue obtained from the AcOEt extracts was chromatographed on silica gel and eluted with AcOEt–hexane (1 : 2). Recrystallization of the product from CH_2Cl_2–AcOEt gave **26** (1.18 g, 15%) as colorless needles. mp 149—151 °C. *Anal.* Calcd for $C_{24}H_{20}N_2O_6S$: C, 62.06; H, 4.34; N, 6.03; S, 6.90. Found: C, 62.24; H, 4.26; N, 6.33; S, 6.66. IR (KBr): 1716 cm^{-1}. NMR ($CDCl_3$) δ: 3.63 (5H, br s, OCH_3, NCH_2CH_2-Phth), 3.99—4.08 (5H, m, OCH_3, NCH_2CH_2-Phth), 6.95 (1H, s, ArH), 7.34 (5H, s, PhH×5), 7.65—7.96 (4H, m, PhthH×4).

Methyl 2-[*N*-(2-Aminoethyl)-*N*-methoxycarbonylamino]-5-phenylthiophene-3-carboxylate (27) A solution of **26** (1.12 g) and hydrazine monohydrate (0.25 g) in MeOH (20 ml) was refluxed for 3.5 h. A residue obtained from evaporation of the solvent was dissolved in water, and the solution was acidified with 10% HCl solution. The precipitate was filtered off, the

TABLE XII. Intermediates of Chloro-Substituted 2,3-Dihydro-5*H*-oxazolothienopyrimidin-5-ones (**30** and **32**)



30



32

Compd. No.	R_1	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd (Found)				
					C	H	Cl	N	S
30a[b]	H	91	163—165 (EA)	$C_9H_{10}Cl_2N_2O_3S$	36.38 (36.33	3.39 3.18	23.86 23.91	9.43 9.47	10.79 10.92)
30e	Me	63	165—167 (dec.) (EA)	$C_{10}H_{12}Cl_2N_2O_3S$	38.60 (38.54	3.89 3.76	22.79 22.98	9.00 8.94	10.30 10.37)
32		93	170—172 (dec.) (EA)	$C_{10}H_{12}Cl_2N_2O_3S$	38.60 (38.69	3.89 3.77	22.79 23.06	9.00 9.18	10.30 10.45)

a) See footnote *a* in Table IV. *b*) This compound was reported in ref. 8, but its physical data were not given.

TABLE XIII. Spectral Data for Intermediates of Chloro-Substituted 2,3-Dihydro-5*H*-oxazolothienopyrimidin-5-one (**30** and **32**)

Compd. No.	IR	NMR	
	KBr, cm^{-1}	Solvent	δ: ppm
30a	1645, 1715	DMSO-d_6	3.20—3.83 (7H, m, OCH_3, NCH_2-CH_2Cl), 6.76 (1H, br t, J=5.7 Hz, NH), 8.11 (1H, s, ArH), 8.14 (1H, br s, NH)
30e	1725, 1690	DMSO-d_6	2.50 (3H, s, $ArCH_3$), 3.20—3.79 (4H, m, NCH_2CH_2Cl), 3.71 (3H, s, OCH_3), 6.70 (1H, br t, J=5.4 Hz, NH), 8.17 (1H, br s, NH)
32	1714, 1653	DMSO-d_6	2.22 (3H, s, $ArCH_3$), 3.33—3.90 (4H, m, NCH_2CH_2Cl), 3.84 (3H, s, OCH_3), 8.32 (1H, br t, J=5.4 Hz, NH), 10.47 (1H, br s, NH)

filtrate was washed with AcOEt and the aqueous layer was basified with concentrated NH_4OH solution and extracted with AcOEt. The AcOEt extracts yielded a crystalline product. Recrystallization from AcOEt–hexane gave **27** (0.60 g, 75%) as colorless needles. mp 92—94 °C. *Anal.* Calcd for $C_{16}H_{18}N_2O_4S$: C, 57.47; H, 5.43; N, 8.38; S, 9.59. Found: C, 57.68; H, 5.33; N, 8.34; S, 9.67. IR (KBr): 1715 cm^{-1}. NMR ($CDCl_3$) δ: 1.50 (2H, br s, NH × 2), 2.93 (2H, t, J=6.0 Hz, CH_2NH_2), 3.63 and 3.69 (each 3H, s, OCH_3 × 2), 3.79 (2H, t, J=6.0 Hz, $NCH_2CH_2NH_2$), 7.02 (1H, s, ArH), 7.36 (5H, s, PhH × 5).

Preparation of 24c and 1-(4-Phenyl-2-thienyl)imidazolin-2-one (28) A solution of **27** (152 mg) and KOH (85% purity) (33 mg) in MeOH (4 ml) was stirred at room temperature for 6 h. A residue obtained from evaporation of the solvent was dissolved in water and the solution was extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated to dryness, and the product was separated by preparative thin layer chromatography on silica gel using AcOEt–hexane (3 : 1) as an eluent to give **24c** (38 mg, 28%) and **28** (10 mg, 9%). **24c**: mp 186—190 °C. The sample was identical with the specimen prepared *via* route b. **28**: mp 232—234 °C (dec.). *Anal.* Calcd for $C_{13}H_{12}N_2OS \cdot 1/3H_2O$: C, 62.38; H, 5.10; N, 11.19; S, 12.81. Found: C, 62.33; H, 4.90; N, 11.24; S, 12.92. IR (KBr): 1638 cm^{-1}. NMR (DMSO-d_6) δ: 3.33—3.47 (4H, m, NCH_2CH_2N), 6.28 (1H, s, ArH), 7.23 (6H, s, PhH × 5, ArH), 7.4—7.6 (1H, br, NH).

Gastric Secretion in Pylorus-Ligated Rats Sprague Dawley (Charles River Co., Ltd.) male rats, weighing 200—230 g, were divided into groups of four animals each and fasted for 24 h with free access to water before the experiment. The animals were anesthetized with ether and the pylorus was ligated by the method of Shay *et al.*[3] Fifty mg/kg of a test compound suspended in 0.5% carboxymethylcellulose solution was given intraduodenally immediately after ligation of the pylorus in a volume of 2 ml/kg of body weight. Four hours later the animals were sacrificed by carbon dioxide. The gastric contents were centrifuged at 3000 rpm for 10 min, after which the volume of the gastric juice was measured and expressed as ml/100 g body weight.

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