Condensed Thienopyrimidines. IV.[1] Synthesis and Gastric Antisecretory Activity of 2,3-Dihydro-5*H*-oxazolothienopyrimidine Derivatives

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2,3-Dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]-(2a—d), [3,4-*d*]-(2e—h), and [2,3-*d*]pyrimidine derivatives (2i, j) were synthesized and evaluated for gastric antisecretory activity. These analogues (2) were prepared stepwise starting from formylthiophenecarbamates (4). The structure–activity relationships of these compounds are discussed.

Keywords formylthiophenecarbamate; ethanolamine; Schiff's base; 5-deoxo analogue; gastric antisecretory activity; structure–activity relationship

Anti-ulcer agents, especially inhibitors of gastric acid secretion such as histamine H_2 receptor antagonists and anticholinergic agents, have been clinically used in the treatment of peptic ulcer. We have reported the syntheses of various 2,3-dihydro-5*H*-oxazolothienopyrimidin-5-one derivatives and their gastric antisecretory activity in pylorus-ligated rats.[1b] It was found that 2,3-dihydro-5*H*-oxazolo-[3,2-*a*]thieno[3,2-*d*]pyrimidin-5-one (**1a**) exhibited potent gastric antisecretory activity. Our continuing interest in the structure–activity relationships of **1** led us to attempt to eliminate the oxygen atom of the carbonyl group at C-5 on **1a**. In this paper, we describe the preparation and biological evaluation of 2,3-dihydro-5*H*-oxazolothienopyrimidine derivatives (**2**), which are 5-deoxo analogues of **1**.

Chemistry When 2,3-dihydro-5*H*-oxazolo[3,2-*a*]thieno-[3,2-*d*]pyrimidin-5-one (**1a**) was reduced with zinc in acetic acid, a ring-opening reaction occurred to give 3-(2-acetoxyethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione,[1c] and the reduced product (**2a**) could not be obtained. The 5-deoxo analogues **2a**—**j** were synthesized through the sequence of reactions outlined in Chart 1. Formylthiophenecarbamates (**4a**—**h**) were prepared according to the procedure reported by Binder *et al.*[2]

Reduction of the carbamates (**3a**—**h**)[1b] with lithium aluminum hydride (LAH) followed by oxidation with activated manganese(IV) oxide (MnO_2) gave the aldehydes (**4a**—**h**) in one pot, because the thiophenemethanol derivatives resulting from LAH reduction were too unstable for purification. In the case of preparation of *N*-(3-formyl-2-thienyl)carbamates (**4i, j**), no desired product was obtained under these oxidation conditions. Consequently, after testing of various oxidizing agents (pyridinium chlorochromate, pyridinium dichromate, pyridine–SO_3, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, *etc.*), **4i, j** were obtained by means of reduction of **3i, j** with LAH followed by oxidation with pyridinium dichromate (PDC) in poor yield (8—9%). The condensation of **4a**—**j** with ethanolamine by heating under reflux in ethanol (EtOH)[3] or by using molecular sieves 4A as a dehydrating agent yielded the Schiff's bases (**5a**—**j**). The reduction of **5a**—**j** with sodium borohydride

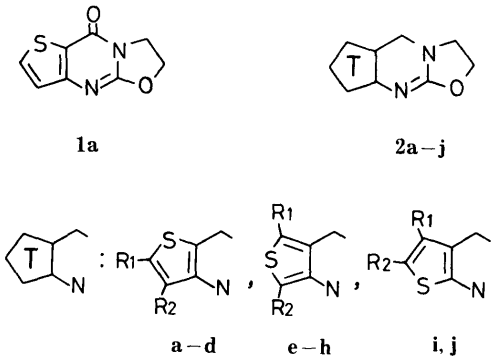


Fig. 1

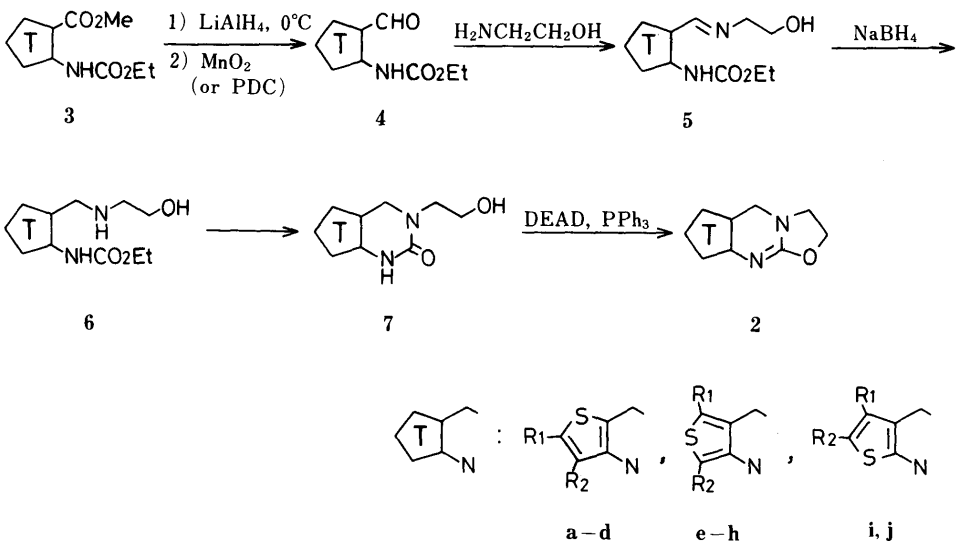
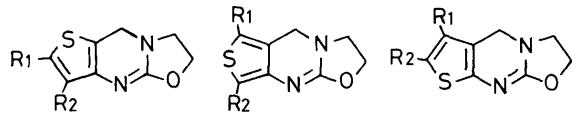


Chart 1

TABLE I. 2,3-Dihydro-5*H*-oxazolo[3,2-*a*]thienopyrimidines (**2a**—**j**)

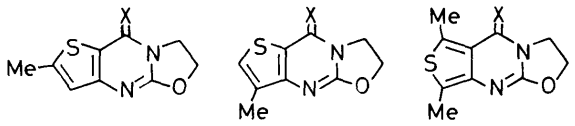


2a—**d** **2e**—**h** **2i, j**

Compd. No.	R_1	R_2	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd C	H	N	S	Found C	H	N	S
2a	H	H	73	>300 (EA)	$C_8H_8N_2OS$	53.32	4.47	15.54	17.79	53.11	4.42	15.69	17.78
2b	Me	H	76	>300 (C–H)	$C_9H_{10}N_2OS$	55.65	5.19	14.42	16.50	55.54	5.34	14.28	16.43
2c	Et	H	55	>300 (EA)	$C_{10}H_{12}N_2OS \cdot 1/3\,H_2O$	56.05	5.96	13.07	14.96	56.00	5.73	12.83	14.92
2d	H	Me	77	191—196 (dec.) (C–H)	$C_9H_{10}N_2OS$	55.65	5.19	14.42	16.50	55.40	5.21	14.34	16.48
2e	H	H	50	>300 (C)	$C_8H_8N_2OS$	53.32	4.47	15.54	17.79	53.23	4.59	15.38	17.87
2f	Me	H	62	>300 (EA)	$C_9H_{10}N_2OS \cdot 1/3\,H_2O$	53.98	5.20	13.99	16.01	53.97	5.28	13.93	16.25
2g	H	Et	75	>300 (EA)	$C_{10}H_{12}N_2OS \cdot 1/8\,H_2O$	57.05	5.87	13.31	15.23	57.20	5.84	13.05	14.84
2h	Me	Me	37	179—184 (dec.) (C)	$C_{10}H_{12}N_2OS$	57.67	5.81	13.45	15.39	57.42	5.67	13.30	15.25
2i	Me	H	34	>300 (EA)	$C_9H_{10}N_2OS \cdot 1/2\,H_2O$	53.18	5.46	13.78	15.77	53.35	5.25	14.08	14.91
2j	H	Me	52	>300 (EA)	$C_9H_{10}N_2OS$	55.65	5.19	14.42	16.50	55.57	5.25	14.37	16.35

a) C, $CHCl_3$; EA, AcOEt; H, hexane.

TABLE II. Gastric Antisecretory Activity of Various Oxazolothienopyrimidine Derivatives



1b, 2b **1c, 2d** **1d, 2h** 1 : X=O 2 : X=H_2

Compd. No.	*N*	Gastric secretion (ml/100 g body weight) Mean ± S.E.	Inhibition (%)	Compd.[a] No.	*N*	Gastric secretion (ml/100 g body weight) Mean ± S.E.	Inhibition (%)
2b	3	1.4 ± 0.35[b]	51	**1b**	3	0.85 ± 0.18[c]	70
Control	7	2.83 ± 0.27		Control	5	2.85 ± 0.26	
2d	3	2.2 ± 0.36	22	**1c**	4	2.26 ± 0.25[c]	49
Control	7	2.83 ± 0.27		Control	10	4.46 ± 0.33	
2h	3	1.47 ± 0.24	41	**1d**	4	0.7 ± 0.21[d]	75
Control	4	2.49 ± 0.4		Control	7	2.83 ± 0.27	
Cimetidine	5	1.23 ± 0.19[c]	46				
Control	5	2.26 ± 0.23					

a) Ref. 1*b*. *b*) $p<0.05$. *c*) $p<0.01$. *d*) $p<0.001$. Statistical analysis was performed using Student's *t* test.

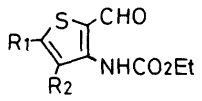
($NaBH_4$) in methanol (MeOH) gave the desired products, (2-hydroxyethyl)aminomethyl derivatives **6a**—**j**, in excellent yields. Heating of **6a**—**j** in *N*,*N*-dimethylformamide (DMF) afforded the pyrimidine derivatives, 3-(2-hydroxyethyl)-1,2,3,4-tetrahydrothienopyrimidin-2-ones (**7a**—**j**), in quantitative yields. Finally, intramolecular cyclization of **7a**—**j** by means of the Mitsunobu method[4] gave the oxazolothienopyrimidine derivatives (**2a**—**j**) in high yields. Physical data of **2a**—**j** prepared here are listed in Table I.

Pharmacology and Structure–Activity Relationships 5-Deoxo analogues (**2**) prepared in the present study were tested for gastric antisecretory activity using pylorus-ligated rats.[5] These results are included in Table II together with the comparative data for the corresponding 5-keto derivatives (**1**).[1b] In general, **2a**—**j** exhibited gastric antisecretory activity. The potencies of the activity of these derivatives were, however, somewhat lower than those of the previously reported 5-keto derivatives (right side in Table II). Thus, the carbonyl group at the C-5 position on compound **1** seems to play an important role in the stronger gastric antisecretory activity of **1** than the corresponding 5-deoxo analogues (**2**). Our research for superior gastric antisecretory agents is continuing on the basis of the present results.

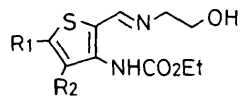
Experimental

All melting points were recorded on a Yamato melting point apparatus, model MP-21, and are uncorrected. Infrared (IR) spectra were measured on a JASCO A-102 spectrometer. Nuclear magnetic resonance (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. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-3100 spectrophotometer. Mass spectra (MS) were obtained with a JEOL JMS-01SG or JMS-G300 mass spectrometer. Merck silica gel

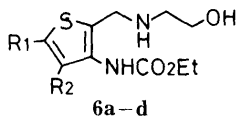
TABLE III. Intermediates (**4a—d**, **5a—d**, **6a—d**, and **7a—d**) for 2,3-Dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidines (**2a—d**)



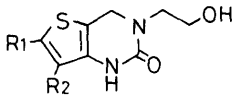
4a—d



5a—d



6a—d



7a—d

Compd. No.	R_1	R_2	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd C	H	N	S	Found C	H	N	S
4a	H	H	74	58—59 (EA–H)	$C_8H_9NO_3S$	48.23	4.55	7.03	16.09	48.17	4.56	7.32	15.71
4b	Me	H	60	54—56 (EA–H)	$C_9H_{11}NO_3S$	50.69	5.20	6.57	15.03	50.80	5.11	6.66	14.99
4c	Et	H	64	Oil	$C_{10}H_{13}NO_3S$	52.85	5.77	6.16	14.11	52.86	5.87	5.97	13.97
4d	H	Me	66	70—72 (EA–H)	$C_9H_{11}NO_3S$	50.69	5.20	6.57	15.03	50.63	5.09	6.48	15.11
5a	H	H	96	79—81 (EA–H)	$C_{10}H_{14}N_2O_3S$	49.57	5.82	11.56	13.23	49.34	5.68	11.49	13.25
5b	Me	H	87	81—82 (EA–H)	$C_{11}H_{16}N_2O_3S$	51.55	6.29	10.93	12.51	51.59	6.17	10.82	12.32
5c	Et	H	95	Oil[b]	$C_{12}H_{18}N_2O_3S$								
5d[c]	H	Me	90	98—100 (EA–H)	$C_{11}H_{16}N_2O_3S$	51.55	6.29	10.93	12.51	51.53	6.21	10.87	12.76
6a	H	H	96	97—99 (EA–H)	$C_{10}H_{16}N_2O_3S$	49.16	6.60	11.47	13.12	48.88	6.56	11.31	12.95
6b	Me	H	95	117—118 (EA–H)	$C_{11}H_{18}N_2O_3S$	51.14	7.02	10.84	12.41	51.01	7.09	10.80	12.67
6c	Et	H	85	108—111 (EA–H)	$C_{12}H_{20}N_2O_3S \cdot 1/5\,H_2O$	52.23	7.45	10.15	11.62	52.22	7.25	9.91	11.77
6d	H	Me	83	114—116 (EA–H)	$C_{11}H_{18}N_2O_3S$	51.14	7.02	10.84	12.41	51.03	6.88	10.76	12.41
7a	H	H	64	124—127 (dec.) (A)	$C_8H_{10}N_2O_2S \cdot 1/3\,H_2O$	47.05	5.26	13.72	15.70	47.16	5.13	13.47	15.47
7b	Me	H	74	120—124 (dec.) (E)	$C_9H_{12}N_2O_2S$	50.93	5.70	13.20	15.10	51.03	5.68	13.13	14.97
7c	Et	H	76	111—114 (E)	$C_{10}H_{14}N_2O_2S$	53.08	6.24	12.38	14.17	52.93	6.06	12.17	14.15
7d	H	Me	76	154—157 (M)	$C_9H_{12}N_2O_2S$	50.93	5.70	13.20	15.10	50.61	5.72	13.31	15.44

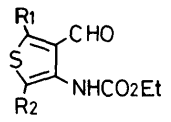
a) A, acetone; C, $CHCl_3$; D, DMF; E, EtOH; EA, AcOEt; H, hexane; M, MeOH. *b*) The material was used for the subsequent step without further purification. *c*) See Experimental.

TABLE IV. Spectral Data for **4a—d**, **5a**, **b**, **d**, **6a—d**, and **7a—d**

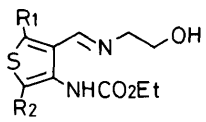
Compd. No.	IR KBr, cm^{-1}	NMR Solvent	δ: ppm
4a	1740, 1620	$CDCl_3$	1.32 (3H, t, J=7.0 Hz, OCH_2CH_3), 4.25 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.68 and 7.98 (each 1H, d, J=5.7 Hz, ArH×2), 9.75 (1H, s, CHO), 9.8—10.4 (1H, br, NH)
4b	1730, 1625	$CDCl_3$	1.30 (3H, t, J=7.0 Hz, OCH_2CH_3), 2.53 (3H, d, J=1.6 Hz, $ArCH_3$), 4.22 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.69 (1H, br s, ArH), 9.57 (1H, s, CHO), 9.8—10.3 (1H, br, NH)
4c	1740, 1635[a]	$CDCl_3$	1.32 and 1.33 (each 3H, t, J=7.5 Hz, CH_2CH_3×2), 2.85 (2H, q, J=7.5 Hz, $ArCH_2CH_3$), 4.23 (2H, q, J=7.5 Hz, OCH_2CH_3), 7.71 (1H, s, ArH), 9.57 (1H, s, CHO), 9.7—10.3 (1H, br, NH)
4d	1695, 1665	$CDCl_3$	1.30 (3H, t, J=7.0 Hz, OCH_2CH_3), 2.22 (3H, s, $ArCH_3$), 4.21 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.33 (1H, br s, ArH), 7.7—8.3 (1H, br, NH), 9.83 (1H, s, CHO)
5a	1700, 1615	$CDCl_3$	1.31 (3H, t, J=7.1 Hz, OCH_2CH_3), 3.60—4.01 (4H, m, NCH_2CH_2O), 4.22 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.35 and 7.87 (each 1H, d, J=5.4 Hz, ArH×2), 8.31 (1H, s, ArCH=N), 1.8—2.3 and 10.5—11.3 (each 1H, br, NH, OH)
5b	1705, 1610	$CDCl_3$	1.31 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.47 (3H, s, $ArCH_3$), 3.56—4.02 (4H, m, NCH_2CH_2O), 4.21 (2H, q, J=7.1 Hz, OCH_2CH_3), 7.59 (1H, br s, ArH), 8.23 (1H, s, ArCH=N), 9.9—11.4 (1H, br, NH or OH)
5d	1720 (sh), 1710, 1625	$CDCl_3$	1.30 (3H, t, J=7.0 Hz, OCH_2CH_3), 2.19 (3H, s, $ArCH_3$), 3.57—3.96 (4H, m, NCH_2CH_2O), 4.19 (2H, q, J=7.0 Hz, OCH_2CH_3), 7.00 (1H, br s, ArH), 1.7—2.4 and 7.5—8.1 (each 1H, br, NH, OH), 8.33 (1H, s, ArCH=N)
6a	1735	$CDCl_3$	1.29 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.77 (2H, t, J=4.5 Hz, NCH_2CH_2O), 3.72 (2H, t, J=4.5 Hz, NCH_2CH_2O), 3.93 (2H, s, $ArCH_2N$), 4.20 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.08 and 7.47 (each 1H, d, J=4.8 Hz, ArH×2), 1.9—2.4 (2H) and 8.2—8.6 (1H) (br, NH×2, OH)
6b	1740, 1600	$CDCl_3$	1.28 (3H, t, J=7.2 Hz, OCH_2CH_3), 2.38 (3H, s, $ArCH_3$), 2.74 (2H, t, J=4.8 Hz, NCH_2CH_2O), 3.68 (2H, t, J=4.8 Hz, NCH_2CH_2O), 3.82 (2H, s, $ArCH_2N$), 4.18 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.12 (1H, br s, ArH), 2.0—2.6 (2H) and 8.0—8.6 (1H) (br, NH×2, OH)
6c	1735	$CDCl_3$	1.26 and 1.29 (each 3H, t, J=7.2 Hz, CH_2CH_3×2), 2.59—3.01 (4H, m, $ArCH_2CH_3$, NCH_2CH_2O), 3.69 (2H, t, J=4.8 Hz, NCH_2CH_2O), 3.85 (2H, s, $ArCH_2N$), 4.18 (2H, q, J=7.2 Hz, OCH_2CH_3), 7.15 (1H, br s, ArH), 2.1—2.6 (2H) and 7.8—8.8 (1H) (br, NH×2, OH)
6d	1690	$CDCl_3$	1.28 (3H, t, J=6.9 Hz, OCH_2CH_3), 2.09 (3H, s, $ArCH_3$), 2.75 (2H, t, J=4.8 Hz, NCH_2CH_2O), 3.61 (2H, t, J=4.8 Hz, NCH_2CH_2O), 3.83 (2H, s, $ArCH_2N$), 4.17 (2H, q, J=6.9 Hz, OCH_2CH_3), 6.79 (1H, br s, ArH), 2.3—2.7 (2H) and 6.5—7.1 (1H) (br, NH×2, OH)
7a	1650, 1610	$CDCl_3$–DMSO-d_6	3.31—3.93 (4H, m, NCH_2CH_2O), 4.48 (1H, t, J=5.0 Hz, OH), 4.70 (2H, s, $ArCH_2N$), 6.62 and 7.14 (each 1H, d, J=5.0 Hz, ArH×2), 8.9—9.1 (1H, br, NH)
7b	1655, 1620	DMSO-d_6	2.35 (3H, s, $ArCH_3$), 3.05—3.83 (4H, m, NCH_2CH_2O), 4.54 (2H, s, $ArCH_2N$), 6.31 (1H, s, ArH), 4.2—5.0 and 8.8—9.2 (each 1H, br, NH, OH)
7c	1645, 1620	DMSO-d_6	1.18 (3H, t, J=7.5 Hz, $ArCH_2CH_3$), 2.70 (2H, q, J=7.5 Hz, $ArCH_2CH_3$), 3.10—3.81 (4H, m, NCH_2CH_2O), 4.56 (2H, s, $ArCH_2N$), 6.33 (1H, s, ArH), 4.3—5.1 and 8.9—9.2 (each 1H, br, NH, OH)
7d	1650	DMSO-d_6	2.05 (3H, s, $ArCH_3$), 3.15—3.90 (5H, m, NCH_2CH_2O, NH or OH), 4.59 (2H, s, $ArCH_2N$), 6.93 (1H, s, ArH), 8.8—9.1 (1H, br, NH or OH)

a) Liquid film.

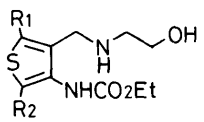
TABLE V. Intermediates (**4e—h**, **5e—h**, **6e—h**, and **7e—h**) for 2,3-Dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,4-*d*]pyrimidines (**2e—h**)



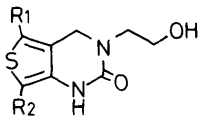
4e—h



5e—h



6e—h



7e—h

Compd. No.	R_1	R_2	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd C	H	N	S	Found C	H	N	S
4e	H	H	30	40—42 (EA–H)	$C_8H_9NO_3S$	48.23	4.55	7.03	16.09	48.40	4.45	7.14	15.99
4f	Me	H	53	58—60 (EA–H)	$C_9H_{11}NO_3S$	50.69	5.20	6.57	15.03	50.67	5.17	6.61	14.83
4g	H	Et	70	Oil	$C_{10}H_{13}NO_3S$	52.85	5.77	6.16	14.11	52.80	5.85	6.18	14.08
4h	Me	Me	58	73—74 (EA–H)	$C_{10}H_{13}NO_3S$	52.85	5.77	6.16	14.11	53.13	5.82	6.25	14.28
5e	H	H	Quant.	78—81 (EA–H)	$C_{10}H_{14}N_2O_3S$	49.57	5.82	11.56	13.23	49.24	5.93	11.52	13.27
5f	Me	H	95	86—87 (EA–H)	$C_{11}H_{16}N_2O_3S$	51.55	6.29	10.93	12.51	51.83	6.35	11.05	12.61
5g	H	Et	Quant.	Oil[b]	$C_{12}H_{18}N_2O_3S$								
5h	Me	Me	Quant.	64—66 (EA–H)	$C_{12}H_{18}N_2O_3S$	53.31	6.71	10.36	11.86	53.06	6.62	10.33	11.61
6e	H	H	Quant.	Oil	$C_{10}H_{16}N_2O_3S$	49.16	6.60	11.47	13.12	48.96	6.62	11.18	12.86
6f	Me	H	80	Oil	$C_{11}H_{18}N_2O_3S \cdot 1/3\,H_2O$	49.98	7.12	10.60	12.13	49.94	7.17	10.70	12.38
6g	H	Et	87	101—103 (EA–H)	$C_{12}H_{20}N_2O_3S$	52.92	7.40	10.29	11.77	52.78	7.35	10.14	11.82
6h	Me	Me	Quant.	92—94 (EA–H)	$C_{12}H_{20}N_2O_3S$	52.92	7.40	10.29	11.77	53.06	7.33	10.39	11.67
7e	H	H	55	131—135 (M)	$C_8H_{10}N_2O_2S \cdot 1/5\,H_2O$	47.61	5.19	13.88	15.88	47.93	5.20	13.96	15.56
7f	Me	H	84	159—162 (M)	$C_9H_{12}N_2O_2S$	50.93	5.70	13.20	15.10	51.19	5.66	13.34	15.06
7g	H	Et	76	124—127 (E)	$C_{10}H_{14}N_2O_2S$	53.08	6.24	12.38	14.17	52.87	6.03	12.36	13.95
7h	Me	Me	85	177—181 (M)	$C_{10}H_{14}N_2O_2S$	53.08	6.24	12.38	14.17	52.94	6.32	12.55	14.30

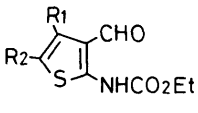
a) See footnote *a* in Table III. *b*) This material was used for the subsequent step without further purification.

TABLE VI. Spectral Data for **4e—h**, **5e, f, h**, **6e—h**, and **7e—h**

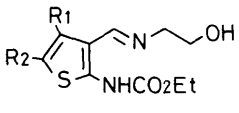
Compd. No.	IR KBr, cm^{-1}	NMR Solvent	NMR δ: ppm
4e	1730, 1660	$CDCl_3$	1.31 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 4.22 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.62 and 8.01 (each 1H, d, J=2.7 Hz, ArH × 2), 9.0—9.7 (1H, br, NH), 9.91 (1H, s, CHO)
4f	1715, 1650	$CDCl_3$	1.32 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 2.74 (3H, s, $ArCH_3$), 4.22 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.32 (1H, s, ArH), 9.2—9.8 (1H, br, NH), 10.07 (1H, s, CHO)
4g	1720, 1685[a]	$CDCl_3$	1.28 (6H, t, J=7.4 Hz, $CH_2C\underline{H}_3$ × 2), 2.83 (2H, q, J=7.4 Hz, $ArC\underline{H}_2CH_3$), 4.19 (2H, q, J=7.4 Hz, $OC\underline{H}_2CH_3$), 7.4—7.8 (1H, br, NH), 7.87 (1H, s, ArH), 9.81 (1H, s, CHO)
4h	1690	$CDCl_3$	1.30 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 2.30 and 2.67 (each 3H, s, $ArCH_3$ × 2), 4.18 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.5—8.1 (1H, br, NH), 10.00 (1H, s, CHO)
5e	1700, 1635	$CDCl_3$	1.31 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 3.53—4.00 (4H, m, NCH_2CH_2O), 4.20 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 7.40—7.65 (2H, m, ArH × 2), 8.39 (1H, s, ArCH=N), 2.33 and 10.71 (each 1H, br s, NH, OH)
5f	1700, 1633	$CDCl_3$	1.30 (3H, t, J=7.0 Hz, $OCH_2C\underline{H}_3$), 2.52 (3H, s, $ArCH_3$), 3.60—4.03 (4H, m, NCH_2CH_2O), 4.21 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.29 (1H, br s, ArH), 8.47 (1H, s, ArCH=N), 2.03 and 10.92 (each 1H, br s, NH, OH)
5h	1720, 1620	$CDCl_3$	1.28 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 2.31 and 2.47 (each 3H, s, $ArCH_3$ × 2), 3.53—3.95 (4H, m, NCH_2CH_2O), 4.17 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 8.38 (1H, s, ArCH=N), 2.15 and 9.14 (each 1H, br s, NH, OH)
6e	1725, 1710 (sh)[a]	$CDCl_3$	1.30 (3H, t, J=6.6 Hz, $OCH_2C\underline{H}_3$), 2.75 (2H, t, J=5.1 Hz, $NC\underline{H}_2CH_2O$), 3.74 (2H, t, J=5.1 Hz, $NCH_2C\underline{H}_2O$), 3.87 (2H, s, $ArCH_2N$), 4.21 (2H, q, J=6.6 Hz, $OC\underline{H}_2CH_3$), 6.95 and 7.43 (each 1H, br d, J=3.6 Hz, ArH × 2), 1.5—1.9 (2H) and 9.3—9.6 (1H) (br, NH × 2, OH)
6f	1725[a]	$CDCl_3$	1.30 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 2.33 (3H, s, $ArCH_3$), 2.75 (2H, t, J=6.6 Hz, $NC\underline{H}_2CH_2O$), 3.73 (2H, t, J=6.6 Hz, $NCH_2C\underline{H}_2O$), 3.79 (2H, s, $ArCH_2N$), 4.20 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.16 (1H, br s, ArH), 1.6—2.2 (2H) and 8.9—9.9 (1H) (br, NH × 2, OH)
6g	1695	$CDCl_3$	1.24 and 1.26 (each 3H, t, J=6.9 Hz, $CH_2C\underline{H}_3$), 2.12—2.96 (6H, m, $ArC\underline{H}_2CH_3$, $NC\underline{H}_2CH_2O$, NH or OH × 2), 3.55—3.75 (4H, m, $NCH_2C\underline{H}_2O$, $ArCH_2N$), 4.16 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 6.88 (1H, s, ArH), 7.0—7.7 (1H, br, NH or OH)
6h	1695	$CDCl_3$	1.27 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 2.24 and 2.30 (each 3H, s, $ArCH_3$ × 2), 2.70 (2H, t, J=4.8 Hz, $NC\underline{H}_2CH_2O$), 3.54—3.77 (4H, m, $ArCH_2N$, $NCH_2C\underline{H}_2O$), 4.16 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 1.8—2.6 (2H) and 7.1—7.9 (1H) (br, NH × 2, OH)
7e	1660, 1630	DMSO-d_6	3.07—3.77 (4H, m, NCH_2CH_2O), 4.50 (2H, s, $ArCH_2N$), 6.32 (1H, d, J=3.6 Hz, ArH), 7.10—7.26 (1H, m, ArH), 4.6—4.9 and 9.1—9.4 (each 1H, br, OH, NH)
7f	1660 (sh), 1640	DMSO-d_6	2.24 (3H, s, $ArCH_3$), 3.13—3.80 (4H, m, NCH_2CH_2O), 4.39 (2H, br s, $ArCH_2N$), 4.67 (1H, t, J=5.1 Hz, OH), 6.03 (1H, s, ArH), 9.0—9.3 (1H, br, NH)
7g	1680, 1660	DMSO-d_6	1.11 (3H, t, J=7.5 Hz, $ArCH_2C\underline{H}_3$), 2.69 (2H, q, J=7.5 Hz, $ArC\underline{H}_2CH_3$), 3.10—3.78 (4H, m, NCH_2CH_2O), 4.44 (2H, s, $ArCH_2N$), 6.93 (1H, s, ArH), 4.5—4.8 and 8.9—9.2 (each 1H, br, NH, OH)
7h	1660	DMSO-d_6	2.18 (6H, s, $ArCH_3$ × 2), 3.07—3.98 (4H, m, NCH_2CH_2O), 4.35 (2H, br s, $ArCH_2N$), 4.82 (1H, t, J=4.8 Hz, OH), 8.7—9.0 (1H, br, NH)

a) Liquid film.

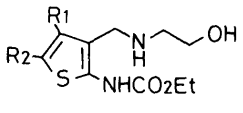
TABLE VII. Intermediates (**4i, j**, **5i, j**, **6i, j**, and **7i, j**) for 2,3-Dihydro-5*H*-oxazolo[3,2-*a*]thieno[2,3-*d*]pyrimidines (**2i, j**)



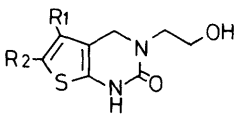
4i, j



5i, j



6i, j



7i, j

Compd. No.	R_1	R_2	Yield (%)	mp (°C) (Recryst. solv.)[a]	Formula	Analysis (%) Calcd C	H	N	S	Found C	H	N	S
4i	Me	H	8	78—80 (EA–H)	$C_9H_{11}NO_3S$	50.69	5.20	6.57	15.03	50.52	5.02	6.55	15.14
4j	H	Me	9	95—97 (EA–H)	$C_9H_{11}NO_3S$	50.69	5.20	6.57	15.03	50.78	5.23	6.59	15.26
5i	Me	H	72	Oil[b]	$C_{11}H_{16}N_2O_3S$								
5j	H	Me	86	97—98 (EA–H)	$C_{11}H_{16}N_2O_3S$	51.54	6.29	10.93	12.51	51.27	6.04	10.89	12.65
6i	Me	H	92	54—57 (dec.) (EA–H)	$C_{11}H_{18}N_2O_3S$	51.14	7.02	10.84	12.41	50.93	6.92	10.55	12.54
6j	H	Me	93	111—113 (dec.) (EA–H)	$C_{11}H_{18}N_2O_3S$	51.14	7.02	10.84	12.41	50.88	6.88	10.75	12.51
7i	Me	H	65	171—175 (dec.) (A)	$C_9H_{12}N_2O_2S \cdot 1/5\,H_2O$	50.08	5.79	12.98	14.85	50.17	5.78	12.92	14.94
7j	H	Me	66	115—119 (dec.) (A)	$C_9H_{12}N_2O_2S$	50.93	5.70	13.20	15.10	50.58	5.59	13.02	15.28

a) See footnote *a* in Table III. *b*) The material was used for the subsequent step without further purification.

TABLE VIII. Spectral Data for **4i, j**, **5j**, **6i, j**, and **7i, j**

Compd. No.	IR KBr, cm^{-1}	NMR Solvent	δ: ppm
4i	1725, 1640	$CDCl_3$	1.34 (3H, t, J=7.2 Hz, $OCH_2C\underline{H}_3$), 2.36 (3H, d, J=1.2 Hz, $ArCH_3$), 4.30 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 6.31 (1H, d, J=1.2 Hz, ArH), 9.87 (1H, s, CHO), 10.7—11.4 (1H, br, NH)
4j	1725, 1640	$CDCl_3$	1.34 (3H, t, J=7.5 Hz, $OCH_2C\underline{H}_3$), 2.38 (3H, d, J=1.8 Hz, $ArCH_3$), 4.29 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.74 (1H, d, J=1.8 Hz, ArH), 9.72 (1H, s, CHO), 10.3—11.1 (1H, br, NH)
5j	1694, 1625	$CDCl_3$	1.30 (3H, t, J=7.1 Hz, $OCH_2C\underline{H}_3$), 2.33 (3H, s, $ArCH_3$), 3.56—3.97 (4H, m, NCH_2CH_2O), 4.23 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 6.48 (1H, d, J=1.8 Hz, ArH), 8.22 (1H, d, J=1.8 Hz, ArCH=N), 6.3—7.6 (2H, br, NH, OH)
6i	1695	$CDCl_3$	1.29 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 2.09 (3H, s, $ArCH_3$), 2.74 (2H, t, J=4.5 Hz, $NC\underline{H}_2CH_2O$), 3.65—3.90 (4H, m, $ArC\underline{H}_2NCH_2C\underline{H}_2O$), 4.21 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 6.41 (1H, br s, ArH), 4.0—5.6 (3H, br, NH×2, OH)
6j	1700	DMSO-d_6	1.23 (3H, t, J=6.9 Hz, $OCH_2C\underline{H}_3$), 2.30 (3H, s, $ArCH_3$), 2.53 (2H, t, J=6.0 Hz, $NC\underline{H}_2CH_2O$), 3.35—3.65 (4H, m, $ArC\underline{H}_2NCH_2C\underline{H}_2O$), 4.11 (2H, q, J=6.9 Hz, $OC\underline{H}_2CH_3$), 6.50 (1H, br s, ArH), 3.7—5.0 (3H, br, NH×2, OH)
7i	1642, 1615	DMSO-d_6	2.00 (3H, s, $ArCH_3$), 3.14—3.78 (4H, m, NCH_2CH_2O), 4.43 (2H, s, $ArCH_2N$), 6.39 (1H, br s, ArH), 4.5—4.8 and 9.1—9.5 (each 1H, br, NH, OH)
7j	1650, 1620	DMSO-d_6	2.30 (3H, s, $ArCH_3$), 3.06—4.13 (5H, m, NCH_2CH_2O, NH or OH), 4.42 (2H, s, $ArCH_2N$), 6.34 (1H, br s, ArH), 9.0—9.5 (1H, br, NH or OH)

(Kieselgel 60 Art. 7734) was employed for column chromatography.

Ethyl *N*-(2-Formyl-3-thienyl)carbamate (4a) (General Procedure for 4b—h) LAH (0.5 g) was added portionwise to a solution of methyl 3-ethoxycarbonylaminothiophene-2-carboxylate (**3a**)[1b] (2.29 g) in dry Et_2O (40 ml) at 0 °C during 3 min under a nitrogen atmosphere and the whole was stirred for 30 min at the same temperature. A saturated NH_4Cl solution was carefully added to the reaction mixture, the precipitate was filtered through celite and the filtrate was washed with water. The aqueous layer was extracted with $CHCl_3$, and the extracts were combined, dried over $MgSO_4$, and filtered. MnO_2 (activated, 20.00 g) was added to the filtrate and the resulting reaction mixture was stirred at room temperature for 1 h. An insoluble material was filtered off, the filtrate was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel using AcOEt–hexane (1 : 9) as an eluent. Recrystallization from AcOEt–hexane gave **4a** (1.47 g, 74%) as colorless leaflets. Other data are listed in Tables III—VI.

Ethyl *N*-(3-Formyl-4-methyl-2-thienyl)carbamate (4i) (General Procedure for 4j) LAH (4.35 g) was added portionwise to a solution of methyl 2-ethoxycarbonylamino-4-methylthiophene-3-carboxylate (**3i**)[1b] (15.00 g) in dry Et_2O (220 ml) at −5 °C under a nitrogen atmosphere and the whole was stirred for 1 h at the same temperature. Saturated NH_4Cl solution was carefully added to the reaction mixture, the precipitate was filtered off through celite and the filtrate was washed with water. The residue obtained from the Et_2O extracts was dissolved in dry CH_2Cl_2 (70 ml) and PDC (23.00 g) was added. The mixture was stirred under a nitrogen atmosphere at room temperature for 3 h, Et_2O was added and the mixture was filtered through celite. Removal of the solvent gave an oily residue, which was chromatographed on a column of silica gel and eluted with AcOEt–hexane (1 : 9). Recrystallization from AcOEt–hexane afforded **4i** (1.02 g, 8%) as colorless needles. Other data are listed in Tables VII and VIII.

Ethyl *N*-[2-(2-Hydroxyethyl)iminomethyl-3-thienyl]carbamate (5a) (General Procedure for 5b, c and e—h) A solution of **4a** (9.00 g) and ethanolamine (13.7 ml) in EtOH (90 ml) was refluxed for 20 min. After evaporation of the solvent, water was added to the residue and the mixture was extracted with AcOEt. The residue obtained from the AcOEt extracts was recrystallized from AcOEt–hexane to give **5a** (10.54 g, 96%) as a white solid. Other data are listed in Tables III—VI.

Ethyl *N*-[2-(2-Hydroxyethyl)iminomethyl-4-methyl-3-thienyl]carbamate (5d) (General Procedure for 5i, j) A mixture of **4d** (1.19 g), ethanolamine (1.7 ml) and molecular sieves 4A (10.0 g) in CH_2Cl_2 (50 ml) was stirred at room temperature for 2 h. After removal of the molecular sieves 4A by filtration, the filtrate was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Recrystallization from AcOEt–hexane gave **5d** (1.24 g, 86%) as a white solid. Other data are listed in Tables III, IV, VII, and VIII.

Ethyl *N*-[2-(2-Hydroxyethyl)aminomethyl-3-thienyl]carbamate (6a) (General Procedure) $NaBH_4$ (3.29 g) was added to an ice-cooled solution of **5a** (10.54 g) in MeOH (200 ml) with stirring and then the whole was stirred at room temperature for 30 min. 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

TABLE IX. Spectral Data for **2a—j**

Compd. No.	IR	UV	NMR	
	KBr, cm^{-1}	$\lambda_{max}^{CH_3OH}$ nm (ε)	Solvent	δ: ppm
2a	1630	224 (15700) 288 (2800)	DMSO-d_6	3.40—3.58 (2H, m, NCH_2CH_2O), 4.35—4.52 (2H, m, NCH_2CH_2O), 4.67 (2H, s, $ArCH_2N$), 6.66 and 7.14 (each 1H, d, J=5.1 Hz, ArH×2)
2b	1630		CD_3OD	2.37 (3H, s, $ArCH_3$), 3.44—3.62 (2H, m, NCH_2CH_2O), 4.39—4.49 (2H, m, NCH_2CH_2O), 4.75 (2H, s, $ArCH_2N$), 6.36 (1H, s, ArH)
2c	1620		DMSO-d_6	1.18 (3H, t, J=7.2 Hz, $ArCH_2CH_3$), 2.67 (2H, q, J=7.2 Hz, $ArCH_2CH_3$), 3.38—3.55 (2H, m, NCH_2CH_2O), 4.31—4.49 (2H, m, NCH_2CH_2O), 4.58 (2H, br s, $ArCH_2N$), 6.39 (1H, s, ArH)
2d	1630	227 (15300) 287 (3200)	DMSO-d_6	2.00 (3H, s, $ArCH_3$), 3.40—3.57 (2H, m, NCH_2CH_2O), 4.34—4.51 (2H, m, NCH_2CH_2O), 4.64 (2H, br s, $ArCH_2N$), 6.89 (1H, br s, ArH)
2e	1660 (sh), 1640	233 (8100) 259 (9000)	DMSO-d_6	3.35—3.57 (2H, m, NCH_2CH_2O), 4.29—4.57 (4H, m, $ArCH_2NCH_2CH_2O$), 6.55 (1H, br d, J=3.0 Hz, ArH), 7.03—7.18 (1H, m, ArH)
2f	1640 (sh), 1630		DMSO-d_6	2.21 (3H, s, $ArCH_3$), 3.38—3.56 (2H, m, NCH_2CH_2O), 4.28—4.65 (4H, m, $ArCH_2NCH_2CH_2O$), 6.28 (1H, s, ArH)
2g	1660	238 (10400) 261 (10200)	DMSO-d_6	1.12 (3H, t, J=7.2 Hz, $ArCH_2CH_3$), 2.66 (2H, q, J=7.2 Hz, $ArCH_2CH_3$), 3.39—3.55 (2H, m, NCH_2CH_2O), 4.17—4.60 (4H, m, $ArCH_2NCH_2CH_2O$), 6.85 (1H, s, ArH)
2h	1640	240 (10600) 264 (9600)	CD_3OD	2.20 (6H, s, $ArCH_3$×2), 3.46—3.62 (2H, m, NCH_2CH_2O), 4.28 (2H, br s, $ArCH_2N$), 4.37—4.52 (2H, m, NCH_2CH_2O)
2i	1625		DMSO-d_6	1.99 (3H, d, J=1.8 Hz, $ArCH_3$), 3.38—3.59 (2H, m, NCH_2CH_2O), 4.35—4.54 (4H, m, $ArCH_2NCH_2CH_2O$), 6.40 (1H, d, J=1.8 Hz, ArH)
2j	1640 (sh), 1630		DMSO-d_6	2.28 (3H, s, $ArCH_3$), 3.38—3.56 (2H, m, NCH_2CH_2O), 4.35—4.51 (4H, m, $ArCH_2NCH_2CH_2O$), 6.33 (1H, br s, ArH)

AcOEt–hexane to give **6a** (10.18 g, 96%) as colorless needles. Other data are listed in Tables III—VIII.

3,4-Dihydro-3-(2-hydroxyethyl)thieno[3,2-*d*]pyrimidin-2(1*H*)-one (7a) (General Procedure) A solution of **6a** (14.50 g) in DMF (150 ml) was refluxed for 1.5 h. After evaporation of the solvent, water was added to the residue and the resulting precipitate was collected by filtration. Recrystallization from acetone afforded pure **7a** (7.76 g, 64%) as colorless prisms. Other data are listed in Tables III—VIII.

2,3-Dihydro-5*H*-oxazolo[3,2-*a*]thieno[3,2-*d*]pyrimidine (2a) (General Procedure) Diethyl azodicarboxylate (DEAD) (559 mg) and triphenylphosphine (PPh_3) (833 mg) were added to a stirred solution of **7a** (499 mg) in dry tetrahydrofuran (THF) (17 ml) under a nitrogen atmosphere at room temperature. After being stirred for 2.5 h, aqueous 10% citric acid solution was added to the reaction mixture and the solution was washed with AcOEt. The aqueous layer was neutralized with saturated $NaHCO_3$ solution, then extracted with AcOEt, and the dried extract was concentrated *in vacuo*. Recrystallization from AcOEt gave **2a** (322 mg, 73%) as colorless needles. Other data are listed in Tables I and IX.

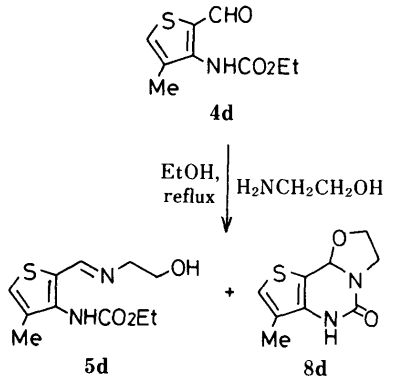
Gastric Secretion in Pylorus-Ligated Rats Sprague Dawley (Charles River Co., Ltd.) male rats, weighing 200—230 g, were divided into groups of three to ten animals each and fasted for 24 h with free access to water before the experiment. The animals were anesthetized with ether and the pylorus was ligated by the method of Shay *et al.*[5] 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 gastric juice was measured. The volume was then expressed as ml/100 g body weight.

References and Notes

1) *a*) Part III: M. Sugiyama, T. Sakamoto and H. Fukumi, *Heterocycles*, **29**, 985 (1989); *b*) Part I: M. Sugiyama, T. Sakamoto, K. Tabata, K. Endo, K. Ito, M. Kobayashi and H. Fukumi, *Chem. Pharm. Bull.*, **37**, 2091 (1989); *c*) H. Fukumi, M. Sugiyama and T. Sakamoto, *ibid.*, **37**, 1197 (1989).

2) D. Binder, C. R. Noe and M. Zahora, *Arch. Pharm.* (*Weinheim*), **314**, 557 (1981).

3) Some formylthiophenecarbamate derivatives (**4**) formed tricyclic oxazolothienopyrimidine derivatives (**8**) besides the Schiff's bases (**5**) under reflux in EtOH for longer than 30 min. For example:



Formation mechanisms of angular annelated tricyclic oxazolothienopyrimidine derivatives (**8**) will be described in detail elsewhere.

4) O. Mitsunobu, M. Wada and T. Sano, *J. Am. Chem. Soc.*, **94**, 679 (1972).

5) H. Shay, S. A. Komarov, S. S. Fels, D. Meranze, M. Gruenstein and H. Siplet, *Gastroenterology*, **5**, 43 (1945).