Studies on Gastric Antiulcer Active Agents. II.[1] Synthesis of Tetrazole Alkanamides and Related Compounds

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A series of tetrazole alkanamides was synthesized and tested for antiulcer activity against acetic acid-induced gastric ulcer in rats. These compounds were prepared by the reaction of tetrazole alkanoic acids and various amines by the mixed anhydride method or acid chloride method. Among them, 3-[(1-ethyl-5-tetrazolyl)methylthio]propionamide (IIn) was found to have the most potent activity. The structure–activity relationships are discussed.

Keywords tetrazole alkanamide; antiulcer activity; mucosal protective activity; structure–activity relationship; 3-[(1-ethyl-5-tetrazolyl)methylthio]propionamide

Introduction

We have been searching for compounds having gastric mucosal protective activity. In the preceding paper,[1] we reported that amino acid analogues of 2(1*H*)-quinolinones had potent antiulcer activity. As a continuation of our search for much more active compounds, we were again interested in cilostamide, having a butyramide moiety and antisecretory activity.[2] We have been attempting to find gastric antiulcer active agents among compounds bearing various nuclei.

On the other hand, tetrazoles are well known as bioisosters of the corresponding carboxylic acids, which are components of antibiotics, antiinflammatory agents and antiallergy agents.[3] We have been investigating the tetrazole derivatives and have developed a clinically useful blood platelet aggregation inhibitor.[4] Therefore, we were interested in synthesizing tetrazole alkanamides for testing of antiulcer activity against acetic acid-induced gastric ulcer in rats, as a model of chronic ulcer. We describe here the synthesis and antiulcer activity of tetrazole alkanamides and related compounds.

Synthesis Various tetrazole alkanamides (IIa—i, k—v) were prepared from tetrazole alkanoic acids and various amines by the mixed anhydride method using isobutyl chloroformate or by the acid chloride method using thionyl chloride. The acetamide derivative (IIj) was synthesized from 5-mercapto-1-methyltetrazole (IIIa) with *N*-cyclohexyl-*N*-ethyl chloroacetamide in the presence of potassium carbonate (Chart 1, Table I).

The preparation of the starting tetrazole alkanoic acids (Ia—j) is summarized in Charts 2 and 3 (methods A, B and C, Table II). The method was chosen based on the side chain present on the tetrazole ring.

Condensation of methyl 4-bromobutyrate with 5-mercapto-1-methyltetrazole (IIIa) or 5-hydroxy-1-mercaptotetrazole (IIIb)[5] in the presence of potassium carbonate or potassium hydroxide in acetone afforded the corresponding ester derivatives (Va, b), which were hydrolyzed with hydrochloric acid to give the tetrazole butyric acids (Ia, b) (method A, Chart 2).

The amide compound (VII) was prepared from methylamine and an acid chloride synthesized by treatment of adipic acid monomethyl ester (VI) with thionyl chloride. A benzene solution of VII was treated with phosphorus

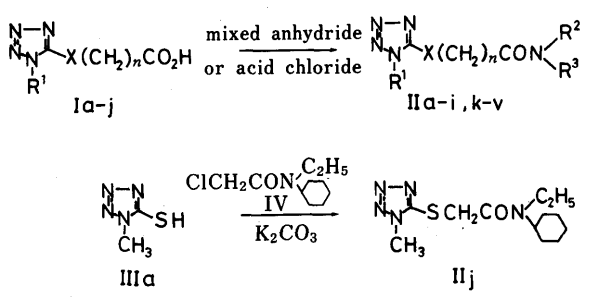


Chart 1

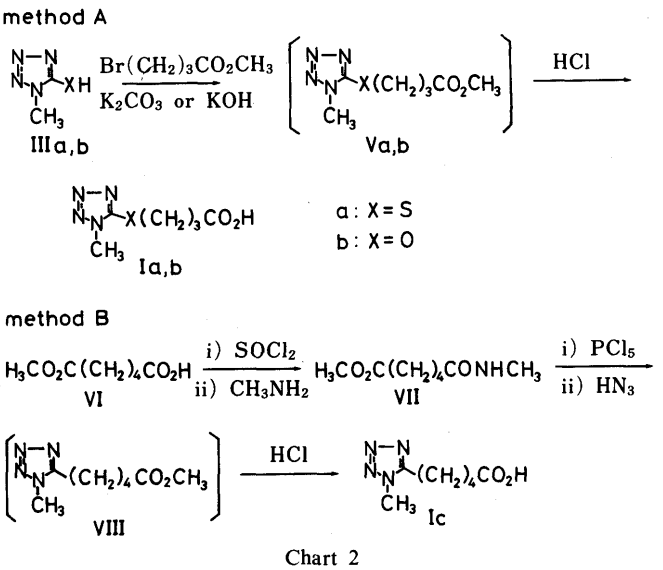


Chart 2

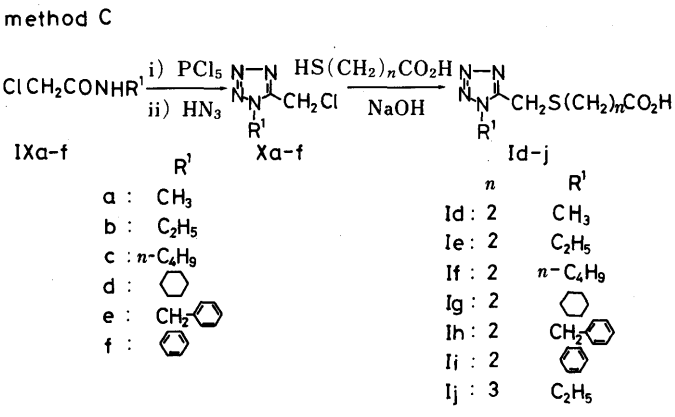
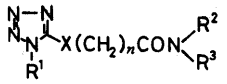
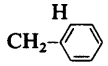
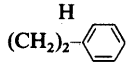
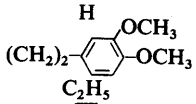
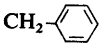


Chart 3

TABLE I. Tetrazole Alkanoic Acid Amide Derivatives



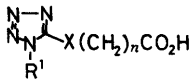
Compd. No.	X	n	R^1	R^2 R^3	Yield (%) (Method[a])	Activity[b]	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
IIa	S	3	CH_3	H H	75 (AC)	++	Colorless prisms (EtOH)	90—92	$C_6H_{11}N_5OS$	35.81 (35.66)	5.51 (5.40)	34.80 (34.63)
IIb	S	3	CH_3	H C_2H_5	16 (MA)	±	Oil		$C_8H_{15}N_5OS$	41.90 (41.57)	6.59 (6.63)	30.54 (30.26)
IIc	S	3	CH_3	H 	38 (MA)	±	Colorless needles (AcOEt–hexane)	116.5—117.5	$C_{12}H_{21}N_5OS$	50.86 (50.86)	7.47 (7.37)	24.71 (24.65)
IId	S	3	CH_3	H 	31 (MA)	±	Colorless needles (AcOEt–hexane)	65—66	$C_{13}H_{17}N_5OS$	53.59 (53.81)	5.88 (5.86)	24.03 (24.59)
IIe	S	3	CH_3	H 	28 (MA)	±	Colorless needles (AcOEt–hexane)	106—107	$C_{12}H_{15}N_5OS$	51.97 (52.06)	5.45 (5.39)	25.25 (25.82)
IIf	S	3	CH_3	H 	46 (MA)	±	Colorless needles (AcOEt–hexane)	58.5—60	$C_{14}H_{19}N_5OS$	55.06 (55.45)	6.27 (6.17)	22.93 (22.96)
IIg	S	3	CH_3	H 	41 (MA)	++	Colorless flakes (AcOEt–hexane)	70.5—71.5	$C_{16}H_{23}N_5O_3S$	52.59 (52.51)	6.34 (6.16)	19.16 (19.10)
IIh	S	3	CH_3	C_2H_5 	48 (MA)	++	Oil		$C_{14}H_{25}N_5OS$	53.99 (53.43)	8.03 (7.95)	22.49 (22.33)
IIi	S	3	CH_3	C_2H_5 C_2H_5	55 (MA)	±	Oil		$C_{10}H_{19}N_5OS \cdot 1/4H_2O$	45.87 (45.61)	7.51 (7.28)	26.74 (26.65)
IIj	S	1	CH_3	C_2H_5 	36	±	Colorless prisms (Et_2O–hexane)	69—71	$C_{12}H_{21}N_5OS$	50.86 (50.76)	7.47 (7.55)	24.71 (24.79)
IIk	O	3	CH_3	C_2H_5 	58 (MA)	±	Oil[c]		$C_{14}H_{25}N_5O_2$	295.2008[d] (295.1981)		
III	CH_2	3	CH_3	C_2H_5 	38 (MA)	±	Oil[c]		$C_{15}H_{27}N_5O$	293.2215[d] (293.2257)		
IIm	CH_2S	2	CH_3	H H	35 (AC)	+	White granules (EtOH)	105.5—108	$C_6H_{11}N_5OS$	35.81 (35.73)	5.51 (5.19)	34.80 (34.85)
IIn	CH_2S	2	C_2H_5	H H	46 (AC)	++	Colorless flakes (AcOEt)	72—75	$C_7H_{13}N_5OS$	39.06 (38.75)	6.09 (5.77)	32.53 (32.67)
IIo	CH_2S	2	n-C_4H_9	H H	33 (AC)	+	Colorless flakes (AcOEt)	79—81	$C_9H_{17}N_5OS$	44.43 (44.38)	7.04 (6.50)	28.78 (29.21)
IIp	CH_2S	2		H H	56 (AC)	±	Colorless needles (EtOH)	137—140	$C_{11}H_{19}N_5OS$	49.05 (48.99)	7.11 (6.92)	26.00 (26.06)
IIq	CH_2S	2	CH_2– 	H H	54 (AC)	±	Colorless needles (EtOH)	87—89.5	$C_{12}H_{15}N_5OS$	51.97 (51.85)	5.45 (5.36)	25.25 (25.46)
IIr	CH_2S	2		H H	69 (AC)	±	Colorless prisms (AcOEt)	91—92	$C_{11}H_{13}N_5OS$	50.18 (50.17)	4.98 (4.95)	26.60 (26.70)
IIs	CH_2S	3	C_2H_5	H H	40 (AC)	±	Colorless prisms (AcOEt–hexane)	72—73	$C_8H_{15}N_5OS$	41.90 (41.88)	6.59 (6.37)	30.54 (30.77)
IIt	CH_2S	2	C_2H_5	C_2H_5 C_2H_5	47 (MA)	±	Colorless needles (Et_2O)	58—59	$C_{11}H_{21}N_5OS$	48.68 (48.34)	7.80 (7.65)	25.81 (26.46)
IIu	CH_2S	2	C_2H_5	C_2H_5 	93 (MA)	±	Oil[c]		$C_{15}H_{27}N_5OS$	325.1936[d] (325.1931)		
IIv	CH_2S	2	CH_3	H C_2H_5	61 (MA)	±	Colorless flakes (AcOEt–hexane)	61.5—62.5	$C_8H_{15}N_5OS$	41.90 (41.72)	6.59 (6.24)	30.54 (30.80)

a) AC, acid chloride method; MA, mixed anhydride method. *b*) Statistically significant activity is assessed on the following scale: ±, 10—20% healing ratio at 10 mg/kg/d × 2; +, 20—30% healing ratio at 10 mg/kg/d × 2; ++, >30% healing ratio at 10 mg/kg/d × 2. For comparison: cimetidine healing ratio at 100 mg/kg/d × 2, +; sucralfate healing ratio at 1 g/kg/d × 2, ++. *c*) A sample sufficiently pure for analysis was not obtained. *d*) Determined by high-resolution mass spectrometry. Upper figure, calculated for M^+ and lower figure, found.

pentachloride, followed by addition of hydrogen azide. The solution was allowed to stand overnight at room temperature and then refluxed to give the ester derivative (VIII), which was hydrolyzed with hydrochloric acid to give Ic (method B, Chart 2).

Chloroacetamides (IXa—f)[6] were treated with phos-

TABLE II. (5-Tetrazolyl)alkanoic Acid Derivatives



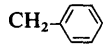
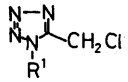
Compd. No.	n	X	R^1	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
Ia	3	S	CH_3	63	Colorless prisms (Et_2O)	40—42	$C_6H_{10}N_4O_2S$	35.63 (35.45	4.98 4.70	27.70 28.02)
Ib	3	O	CH_3	38	Colorless needles (AcOEt–hexane)	86.5—87.5	$C_6H_{10}N_4O_3$	38.71 (38.80	5.41 5.43	30.10 30.30)
Ic	3	CH_2	CH_3	76	Colorless prisms (EtOH–Et_2O)	107—109	$C_7H_{12}N_4O_2$	45.64 (45.87	6.57 6.53	30.42 30.65)
Id	2	CH_2S	CH_3	69	Colorless prisms (AcOEt–hexane)	80.5—82.5	$C_6H_{10}N_4O_2S$	35.63 (35.40	4.98 4.86	27.70 27.72)
Ie	2	CH_2S	C_2H_5	84	Colorless prisms (AcOEt–hexane)	128.5—130	$C_6H_{12}N_4OS$	38.88 (38.91	5.60 5.49	25.91 26.16)
If	2	CH_2S	n-C_4H_9	55	Pale yellow prisms (Et_2O–hexane)	33—35	$C_9H_{16}N_4O_2S$	44.25 (44.03	6.60 6.39	22.93 22.80)
Ig	2	CH_2S		92	Colorless needles (AcOEt)	108—110	$C_{11}H_{18}N_4O_2$	48.87 (48.72	6.71 6.49	20.72 20.86)
Ih	2	CH_2S		91	Colorless prisms (AcOEt)	142—143.5	$C_{12}H_{14}O_2S$	51.78 (51.86	5.07 4.89	20.13 20.19)
Ii	2	CH_2S		81	Colorless prisms (AcOEt–hexane)	102—103	$C_{11}H_{12}N_4O_2$	49.99 (49.91	4.56 4.48	21.20 21.26)
Ij	3	CH_2S	C_2H_5	19	Colorless prisms (Et_2O)	63—65	$C_8H_{14}N_4O_2S$	41.73 (41.57	6.13 6.04	24.33 24.49)

TABLE III. 5-Chloromethyl-1*H*-tetrazoles



Compd. No.	R^1	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
Xa	CH_3	57	Colorless needles (Et_2O)	62—63	$C_3H_5ClN_4$	27.18 (26.97	3.80 3.70	42.27 42.00)
Xb	C_2H_5	63	Oil[a]		$C_4H_7ClN_4$			
Xc	n-C_4H_9	87	Oil[a]		$C_6H_{11}ClN_4$			
Xd		54	Colorless needles (AcOEt–hexane)	106—107	$C_8H_{13}ClN_4$	47.88 (47.85	6.53 6.27	27.92 27.81)
Xe		61	Pale yellow needles (Et_2O–hexane)	62—63	$C_9H_9ClN_4$	51.81 (51.64	4.35 4.26	26.85 26.77)
Xf		67	Colorless plates (Et_2O–hexane)	71.5—73	$C_8H_7ClN_4$	49.37 (49.32	3.63 3.55	28.79 28.95)

a) A sample sufficiently pure for analysis was not obtained. MS *m/z* (%): Xb, 49 (100), 56 (53), 76 (19), 111 (18), 119 (10), 175 (M^+, 5); Xc, 55 (100), 76 (26), 83 (15), 103 (15), 104 (50), 106 (16), 147 (M^+, 54). ^{1}H-NMR δ ($CDCl_3$): Xa, 4.13 (3H, s), 4.85 (2H, s); Xb, 1.63 (3H, t, J=7.5 Hz), 4.48 (2H, q, J=7.5 Hz), 4.85 (2H, s); Xc, 0.97 (3H, t, J=7.5 Hz), 1.20—2.20 (4H, m), 4.40 (2H, t, J=7.5 Hz), 4.84 (2H, s); Xd, 1.20—2.30 (10H, m), 4.20—4.60 (1H, m), 4.97 (2H, s); Xe, 4.59 (2H, s), 5.63 (2H, s), 7.10—7.50 (5H, m); Xf, 4.78 (2H, s), 7.58 (5H, s).

phorus pentachloride, followed by addition of sodium azide to give 1-substituted 5-chloromethyltetrazoles (Xa—f) (Table III). Condensation of IXa—f with 3-mercaptopropionic acid in the presence of sodium hydroxide in the usual way gave IId—j (method C, Chart 3, Table II).

Structure–Activity Relationship The antiulcer activities of the synthesized compounds against acetic acid-induced gastric ulcer are summarized in Table I. The structure–activity relationships are discussed below.

First, the order as regards amide groups was primary (IIn), (IIa)≫secondary (IIv), tertiary (IIu). But, in the thiobutyramide series, the *N*-(3,4-dimethoxyphenethyl) and *N*-cyclohexyl-*N*-ethyl amide compounds (IIg, h) also showed high potency. The effect of substituents on the tetrazole ring at the 1-position was examined; it was found that the alkyl derivative (IIn) showed high potency, while the cyclohexyl and phenyl derivatives (IIp, r) were less active.

Next, when the effects of the linking group between the tetrazole and alkanamide were compared, the methylthio and sulfur compounds (IIn, h) showed high potency while the methylene and oxygen compounds (III, k) showed low activity. So, a sulfur group is essential for potent activity. The effect of the number of methylene groups in

$-CH_2S(CH_2)_nCONH_2$ was examined and the order of potency was found to be $n=2$ (IIn) $\gg n=3$ (IIs).

Among the compounds synthesized, 3-[(1-ethyl-5-tetrazolyl)methylthio]propionamide (IIn) and 4-[(1-methyl-5-tetrazolyl)thio]butyramide (IIa) were found to have the most potent activities. Compounds IIn and IIa were at least 10 times more potent than cimetidine and 100 times more potent than sucralfate. These compounds were selected for further pharmacological evaluation.

Experimental

All melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ on a Varian EM-390 NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained on a Varian MAT-312 instrument.

Preparation of Ia—j. Method A 4-[(1-Methyl-5-tetrazolyl)thio]butyric Acid (Ia): A mixture of 5-mercapto-1-methyltetrazole (11.6 g, 0.1 mol), methyl 4-bromobutyrate (21.7 g, 0.12 mol) and K_2CO_3 (15.0 g, 0.11 mol) in acetone (100 ml) was refluxed for 4 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was refluxed in 20% HCl (150 ml) for 2 h, then cooled. The resulting solution was extracted with $CHCl_3$. The extract was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from Et_2O to give Ia (10.0 g, 63%) as colorless prisms, mp 40—42 °C. IR ν (KBr): 3100, 2950, 1720, 1410, 1390, 1230, 1170 cm^{-1}. The elemental analysis and spectral data are give in Tables II and IV.

4-[(1-Methyl-5-tetrazolyl)oxy]butyric Acid (Ib): Compound Ib (7.0 g, 24%) was prepared by a synthetic procedure similar to that used for Ia, with 5-hydroxy-1-methyltetrazole[5] (13.0 g, 0.13 mol), methyl 4-bromobutyrate (25.9 g, 0.14 mol) and KOH (10.0 g, 0.18 mol). Colorless needles from AcOEt–hexane, mp 86.5—87.5 °C. The elemental analysis and spectral data are given in Tables II and IV.

Method B *N*-Methyladipamic Acid Methyl Ester (VII): A mixture of adipic acid monomethyl ester (17.0 g, 106 mmol) and thionyl chloride (20 ml) was refluxed for 1 h. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in acetone (100 ml). The solution was added dropwise to a stirred and ice-cooled solution of 40% methylamine (25 ml) and K_2CO_3 (8.2 g, 59 mmol) in acetone (100 ml) and water (15 ml). The mixture was stirred at room temperature for 2 h. After removal of the solvent, the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with water and saturated NaCl solution and dried over

TABLE IV. Spectral Data for (5-Tetrazolyl)alkanoic Acids

Compd. No.	IR ν[a] cm^{-1} (C=O)	^{1}H-NMR δ ($CDCl_3$)
Ia	1720	1.90—2.80 (4H, m), 3.42 (2H, t, J=6 Hz), 3.97 (3H, s), 11.18 (1H, s)
Ib	1725	1.90—2.80 (4H, m), 3.58 (3H, s), 3.97 (2H, t, J=6 Hz), 10.68 (1H, brs)
Ic	1720	1.50—2.10 (4H, m), 2.30 (2H, t, J=6 Hz), 2.88 (2H, t, J=6 Hz), 4.02 (3H, s), 10.20—10.70 (1H, brs)[b]
Id	1725	2.40—2.80 (4H, m), 3.93 (2H, s), 4.00 (3H, s), 8.86 (1H, brs)
Ie	1730	1.46 (3H, t, J=7.5 Hz), 2.30—2.80 (4H, m), 4.15 (2H, s), 4.41 (2H, q, J=7.5 Hz)
If	1720	0.97 (3H, t, J=6.5 Hz), 1.10—2.10 (4H, m), 2.40—2.90 (4H, m), 3.98 (2H, s), 4.30 (2H, t, J=6.5 Hz), 10.27 (1H, brs)
Ig	1720	1.20—1.60 (3H, m), 1.70—2.20 (7H, m), 2.60—2.90 (4H, m), 3.99 (2H, s), 4.10—4.30 (1H, m)
Ih	1710	2.40—2.60 (2H, m), 2.60—2.80 (2H, m), 3.85 (2H, s), 5.66 (2H, s), 7.10—7.60 (5H, m)
Ii	1710	2.60—2.80 (2H, m), 2.80—3.10 (2H, m), 3.96 (2H, s), 7.60 (5H, brs), 9.30—10.00 (1H, brs)[b]
Ij	1710	1.56 (3H, t, J=7.5 Hz), 1.70—2.00 (2H, m), 2.20—2.60 (4H, m), 3.90 (2H, s), 4.34 (2H, q, J=7.5 Hz), 10.43 (1H, brs)

a) The spectra of Ia—j were taken in KBr. b) In DMSO-d_6.

TABLE V. Spectral Data for Tetrazole Alkanamides

Compd. No.	IR ν[a] cm^{-1} (C=O)	^{1}H-NMR δ ($CDCl_3$)
IIa	1690	1.90—2.50 (4H, m), 3.30 (2H, t, J=6 Hz), 3.84 (3H, s), 5.80—6.60 (2H, brs)
IIb	1640	1.14 (3H, t, J=7.5 Hz), 2.00—2.60 (4H, m), 3.26 (2H, q, J=7.5 Hz), 3.36 (2H, t, J=6 Hz), 3.90 (3H, s), 6.40 (1H, brs)
IIc	1640	1.00—2.50 (14H, m), 3.30 (2H, t, J=6 Hz), 3.50—4.00 (1H, m), 3.86 (3H, s), 5.90 (1H, brs)
IId	1640	1.90—2.50 (4H, m), 3.31 (2H, t, J=6.5 Hz), 3.83 (3H, s), 4.38 (2H, d, J=6 Hz), 7.24 (5H, s), 6.40 (1H, brs)
IIe	1690	2.00—2.70 (4H, m), 3.40 (2H, t, J=6.5 Hz), 3.86 (3H, s), 7.00—7.80 (5H, m), 8.40 (1H, brs)
IIf	1640	1.90—2.50 (4H, m), 2.78 (2H, t, J=7.5 Hz), 3.23 (2H, t, J=7.5 Hz), 3.30—3.60 (2H, m), 3.80 (3H, s), 6.30 (1H, brs), 6.90—7.30 (5H, m)
IIg	1640	1.90—2.40 (4H, m), 2.72 (2H, t, J=6.5 Hz), 3.10—3.50 (4H, m), 3.76 (6H, s), 3.82 (3H, s), 6.20 (1H, brs), 6.50—6.80 (3H, m)
IIh	1630	0.90—2.00 (13H, m), 2.00—2.70 (4H, m), 3.00—3.60 (4H, m), 3.90 (3H, s), 4.00—4.50 (1H, m)
IIi	1630	1.13 (3H, t, J=7.5 Hz), 1.18 (3H, t, J=7.5 Hz), 1.80—2.50 (4H, m), 3.20—3.60 (6H, m), 3.90 (3H, s)
IIj	1625	1.00—2.00 (13H, m), 3.10—3.70 (2H, m), 3.96 (3H, s), 4.42 (2H, d, J=4 Hz), 4.00—4.50 (1H, m)
IIk	1640	1.00—2.00 (13H, m), 2.00—2.50 (4H, m), 3.00—3.50 (2H, m), 3.59 (3H, s), 4.02 (2H, t, J=6 Hz), 3.80—4.50 (1H, m)
IIl	1630	0.90—2.10 (17H, m), 2.36 (2H, t, J=6 Hz), 2.87 (2H, t, J=6 Hz), 3.23 (2H, q, J=6 Hz), 4.00 (3H, s)
IIm	1670	2.30—2.80 (4H, m), 3.96 (2H, s), 4.00 (3H, s), 6.10 (1H, brs), 6.90 (1H, brs)
IIn	1660	1.55 (3H, t, J=7.5 Hz), 2.30—2.80 (4H, m), 3.94 (2H, s), 4.34 (2H, q, J=7.5 Hz), 6.00—6.60 (2H, brs)
IIo	1650	0.94 (3H, t, J=6.5 Hz), 1.10—2.10 (4H, m), 2.30—2.80 (4H, m), 3.91 (2H, s), 4.27 (2H, t, J=7.5 Hz), 5.60—6.30 (2H, brs)
IIp	1660	1.20—2.20 (10H, m), 2.30—2.80 (4H, m), 3.93 (2H, s), 4.00—4.40 (1H, m), 5.70—6.40 (2H, brs)
IIq	1650	2.30—2.80 (4H, m), 3.72 (2H, s), 5.57 (2H, s), 5.80—6.20 (2H, brs), 7.00—7.40 (5H, m)
IIr	1660	2.30—3.00 (4H, m), 3.91 (2H, s), 5.80—6.40 (2H, brs), 7.50 (5H, s)
IIs	1650	1.55 (3H, t, J=7.5 Hz), 1.60—2.60 (6H, m), 3.86 (2H, s), 4.32 (2H, q, J=7.5 Hz), 5.95 (2H, brs)
IIt	1640	1.10—1.30 (6H, m), 1.58 (3H, t, J=7.5 Hz), 2.40—3.00 (4H, m), 3.10—3.50 (4H, m), 3.97 (2H, s), 4.39 (2H, q, J=7.5 Hz)
IIu	1630	0.90—1.90 (13H, m), 1.47 (3H, t, J=6.5 Hz), 2.30—2.90 (4H, m), 2.90—3.30 (2H, m), 3.20—3.50 (1H, m), 3.88 (2H, s), 4.30 (2H, q, J=6.5 Hz)
IIv	1640	1.12 (3H, t, J=7.5 Hz), 1.58 (3H, t, J=7.5 Hz), 2.30—2.90 (2H, m), 3.00—3.40 (2H, m), 3.98 (2H, s), 4.39 (2H, q, J=7.5 Hz), 6.50 (1H, brs)

a) The spectra of IIa, c—g, j, m—t, v were taken in KBr. The spectra of IIb h—i, k, l, u were taken neat. MS m/z (%): IIb, 44 (65), 72 (69), 87 (100), 114 (44), 143 (45), 229 (M^+, 2), 230 (20); IIh, 41 (48), 55 (37), 69 (45), 84 (38), 114 (29), 126 (100), 185 (21), 312 (M^++1, 7); IIi, 43 (41), 58 (32), 69 (29), 72 (100), 100 (46), 115 (32), 128 (20), 142 (36), 257 (M^+, 2), 258 (11); IIk, 41 (89), 55 (63), 56 (23), 69 (38), 84 (65), 112 (56), 126 (100), 127 (32), 169 (40), 295 (M^+, 32), 296 (36); IIl, 41 (31), 55 (58), 56 (23), 82 (38), 84 (38), 126 (100), 167 (38), 293 (M^+, 7), 294 (23); IIu, 41 (46), 55 (100), 56 (29), 83 (51), 84 (36), 126 (47), 154 (37), 182 (32), 214 (23), 325 (M^+, 32), 326 (62).

$MgSO_4$. After removal of the $CHCl_3$, the residue was distilled *in vacuo* to give VII (13.0 g, 76%), bp 160—165 °C (0.7 mmHg). NMR δ: 1.40—1.80 (4H, m), 2.00—2.40 (4H, m), 2.70 (3H, d, J=7 Hz), 3.62 (3H, s), 7.20—7.50 (1H, br s). IR ν (neat): 3300, 2950, 1730, 1650, 1460, 1440, 1200, 1170 cm^{-1}. *Anal.* Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.17; H, 8.44; N, 7.95.

Methyl 5-(1-Methyl-5-tetrazolyl)valerate (VIII): A stirred and ice-cooled solution of VII (13 g, 75 mmol) in benzene (150 ml) was treated with PCl_5 (17.7 g, 85 mmol). The reaction mixture was stirred at room temperature for 1.5 h, then a 1.6 M benzene solution (87 ml, 148 mmol) of HN_3 was added with stirring at room temperature. The reaction mixture was stirred overnight and then refluxed for 2 h. After removal of the solvent under reduced pressure, the residue was poured into ice-water and extracted with $CHCl_3$. The extract was washed successively with water, aqueous NaOH solution and water, dried over $MgSO_4$ and concentrated to give VIII (9 g, 60%) as an oil. NMR δ: 1.50—2.20 (4H, m), 2.38 (2H, t, J=6 Hz), 2.90 (2H, t, J=6 Hz), 3.65 (3H, s), 4.05 (3H, s). IR ν (neat): 2950, 1730, 1460, 1440, 1200, 1170 cm^{-1}.

5-(1-Methyl-5-tetrazolyl)valeric Acid (Ic): A solution of VIII (6.0 g, 30 mmol) in 20% HCl (100 ml) was stirred at 85—90 °C for 2 h, and then cooled. The mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from EtOH–water to give IIc (3.7 g, 66%) as colorless prisms, mp 107—109 °C. IR ν (KBr): 3050, 2960, 1720, 1180 cm^{-1}. The elemental analysis and spectral data are listed in Tables II and IV.

Method C *N*-Monosubstituted Chloroacetamides (IXa—f): All of the amides employed as intermediates for the preparation of 1-substituted 5-chloromethyltetrazoles are described in the literature.[6]

5-Chloromethyl-1-ethyltetrazole (Xb): PCl_5 (351.0 g, 1.69 mol) was added slowly to a solution of *N*-ethylchloroacetamide (186.0 g, 1.53 mol) in benzene (1.9 l) under cooling with ice-water. The mixture was stirred at room temperature for 2 h, then NaN_3 (150.0 g, 2.31 mol) was added with stirring at room temperature. The reaction mixture was stirred at the same temperature for 30 min, water (12 ml) was added dropwise and the whole was refluxed for 5 h, then was poured into water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed successively with water, NaOH solution and saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with AcOEt as a solvent to give pure Xb as an oily material (142.0 g, 63%). NMR δ: 1.63 (3H, t, J=7 Hz), 4.45 (2H, q, J=7 Hz), 4.87 (2H, s).

Compounds Xa and Xc—f were obtained by the same procedure as described for Xb; the yields and physical data are listed in Table III.

3-[(1-Ethyl-5-tetrazolyl)methylthio]propionic Acid (Ie): A solution of Xb (44.0 g, 0.3 mol) in acetone (50 ml) was added dropwise to an ice-cooled solution of 3-mercaptopropionic acid (31.8 g, 0.3 mol) in 1 N NaOH. The mixture was stirred at 5—10 °C for 3 h. After removal of the acetone, the residue was acidified with HCl and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel using $CHCl_3$–MeOH (10:1) as an eluent to give a solid, which was recrystallized from AcOEt–hexane to give Ie (53.0 g, 82%) as colorless prisms, mp 80.5—82.5 °C. IR ν (KBr): 3000, 1730, 1410, 1220, 1190, 1170 cm^{-1}. The elemental analysis and spectral data are given in Tables II and IV.

Compounds Id and If—j were obtained by the same procedure as described for Ie; the yields and physical data are listed in Tables II and IV.

Preparation of IIa—i, k—v. Mixed Anhydride Method *N*-(3,4-Dimethoxyphenethyl)-4-[(1-methyl-5-tetrazolyl)thio]butyramide (IIg): Isobutyl chloroformate (4.5 g, 33 mmol) was added dropwise to a stirred and ice-cooled solution of Ia (6.1 g, 30 mmol) and Et_3N (3.3 g, 33 mmol) in tetrahydrofuran (THF) (80 ml) and the reaction mixture was stirred at room temperature for 30 min. Then, 3,4-dimethoxyphenethylamine (6.5 g, 36 mmol) was added dropwise with stirring at room temperature. The mixture was stirred at the same temperature for 3 h, poured into water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed successively with dilute HCl, aqueous $NaHCO_3$ solution and saturated NaCl solution and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, $CHCl_3$:MeOH=100:1) and recrystallized from AcOEt–hexane to give IIg (4.5 g, 41%) as colorless flakes, mp 70.5—71.5 °C. IR ν (KBr): 3300, 1640, 1540, 1515, 1140 cm^{-1}. The elemental analysis and spectral data are given in Tables I and V.

Compounds IIa—f, h, i, k, l and IIt—v were obtained by the same procedure as described for IIg; the yields, melting points, elemental analyses and spectral data are given in Tables I and V.

Acid Chloride Method 3-[(1-Ethyl-5-tetrazolyl)methylthio]propionamide (IIn): A mixture of Ia (20 g, 93 mmol) and thionyl chloride (30 ml) was stirred at 40—50 °C for 30 min. The mixture was evaporated to dryness *in vacuo*. The residue was added dropwise to a stirred and ice-cooled mixture of 25% aqueous ammonia (20 ml) and K_2CO_3 (12.8 g) in acetone (150 ml) and water (30 ml). After being stirred at the same temperature for 2 h, the mixture was concentrated *in vacuo* and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from AcOEt to give IIn (9.2 g, 46%) as colorless flakes, mp 72—75 °C. IR ν (KBr): 3350, 3175, 1660, 1630 cm^{-1}. The elemental analysis and spectral data are given in Tables I and V.

Compounds IIa, m and IIo—s were obtained by the same procedure as described for IIn; yields, melting points, elemental analyses and spectral data are given in Tables I and V.

Preparation of IIj. *N*-Cyclohexyl-*N*-ethylchloroacetamide (IV) Chloroacetyl chloride (2.6 g, 23 mmol) was added to a stirred solution of *N*-ethylcyclohexylamine (2.6 g, 20 mmol) and triethylamine (2.4 g, 24 mmol) in benzene (20 ml). The reaction mixture was stirred at room temperature for 1 h, poured into water and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give IV (3.0 g, 74%), bp 118—120 °C (0.2 mmHg), n_D^{26} 1.4975.

***N*-Cyclohexyl-*N*-ethyl-2-[(1-methyl-5-tetrazolyl)thio]acetamide (IIj)** A mixture of IV (3.0 g, 15 mmol), 5-mercapto-1-methyltetrazole (1.8 g, 16 mmol) and K_2CO_3 (2.4 g, 17 mmol) in acetone (50 ml) was refluxed for 3 h, then poured into water and extracted with Et_2O. The extract was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was recrystallized from Et_2O–petroleum ether to give IIj (1.5 g, 36%) as colorless prisms, mp 69—71 °C. IR ν (KBr): 2930, 1630, 1430, 700 cm^{-1}. The elemental analysis and spectral data are listed in Tables I and V.

Biological Method Antiulcer activity against acetic acid-induced gastric ulcer in rats was tested by the reported method.[1]

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