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Monitored Aminolysis of 3-Acyl-1,3-thiazolidine-2-thiones: Synthesis of Amides and Amide Alkaloids[1,2]

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A functional heterocycle, 3-acyl-1,3-thiazolidine-2-thione [ATT (**1**)] has been shown to be effective as an acylating reagent for the amino group. ATT (**1**) was readily prepared by several methods, and reacted with various amino compounds in $CHCl_3$, CH_2Cl_2, THF, EtOH, THF–H_2O, or sulfolane to afford the corresponding amides, **2a**—**w** and **3**—**10** in very high yields within a short time. This reagent exhibits high chemo-selectivity. Its reaction with the diamines **13** and **15** and the triamine **29**, which include a primary amino group(s) and a secondary amino group, gave the products acylated only at the primary amino group(s), **14**, **16**, and **30**, respectively, in high yields. Aminoalcohols and aminophenols were chemoselectively converted into acylaminoalcohols and acylaminophenols, respectively, by ATT (**1**). By utilizing this method, several amide alkaloids (**26**, **28**, **30**, and **34**) were efficiently synthesized. This new aminolysis can be monitored by the disappearance of the yellow color of the starting materials, ATT (**1**); it is remarkably characteristic of this reaction.

Keywords——monitored aminolysis; 3-acyl-1,3-thiazolidine-2-thione; high chemo-selectivity; amide synthesis; fagaramide; dolichotheline; spermidine; maytenine; *N*-ferulyltryptamine

Our recent synthetic target compounds have been focused on the naturally occurring amide compounds,[3] especially macrocyclic spermidine alkaloids,[4] spermidine siderophores,[5] macrocyclic lactone lactams,[6] peptides, enzymes, and nucleic acids. We are also carrying out the systematic development of new reactions which should be practically applicable for the synthesis of our target compounds, utilizing sulfur-containing leaving groups.[7] We have also reported the monitored reduction of carboxylic acid into aldehyde or into alcohol *via* 3-acyl-1,3-thiazolidine-2-thione (ATT).[8]

We wish to report herein the full details of our amide synthesis and its application to the synthesis of some acylic amide alkaloids utilizing the monitored aminolysis of ATT.

ATT (**1**) is easily prepared by four methods (A—D[9]) as shown in Chart 1.[8b,10] On treatment with amines under mild conditions, ATT gave amides in high yields through aminolysis (Chart 2). This reaction can be monitored by following the disappearance of the original yellow color of the starting material [**1**: $R^1 = -(CH_2)_{14}Me$: λ_{max}^{hexane} 415 nm (ε 61) ($n \rightarrow \pi^*$ of $>C=S$)].

In a general procedure exemplified by the reaction of 3-hexadecanoyl-1,3-thiazolidine-2-thione, [**1**: $R^1 = -(CH_2)_{14}Me$], a solution of amine (1.1 mol eq) in CH_2Cl_2 was added dropwise to a solution of **1** (1.0 mol eq) in CH_2Cl_2 with stirring. When the yellow color of the reaction mixture disappeared, the reaction ended and the solvent was evaporated off *in vacuo*. The residue was dissolved in $CHCl_3$, and the solution was passed through a short silica gel column impregnated with 10% silver nitrate; the 1,3-thiazolidine-2-thione (TT) was removed by adsorption on the column. The eluate was evaporated to dryness to provide the desired amide **2** as a pure product in a very high yield. Some results of aminolyses of 3-hexadecanoyl-, 3-

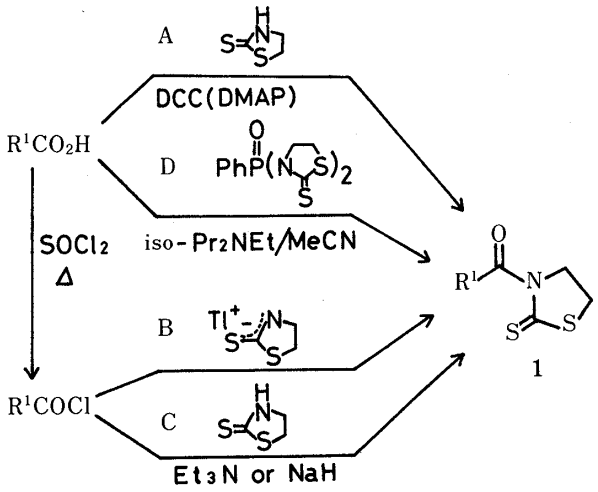


Chart 1

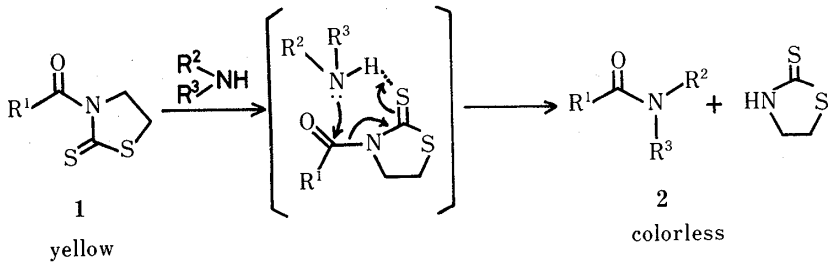


Chart 2

TABLE I. Aminolysis of 3-Hexadecanoyl-1,3-thiazolidine-2-thione[a)]

Amine: R^2–NH–R^3 R^2	R^3	Reaction time	Yield % of **2** $Me(CH_2)_{14}CONR^2R^3$
n-Bu	H	1 min	**2a** 96
sec-Bu	H	30 min	**2b** 97
tert-Bu	H	70 h	**2c** 98
Cyclohexyl	H	5 min	**2d** 92
$PhCH_2$	H	2 min	**2e** 96
Ph	H	95 h	**2f** 91
n-Bu	Me	5 min	**2g** 98
n-Bu	*n*-Bu	15 min	**2h** 99
Cyclohexyl	Me	10 min	**2i** 99
$PhCH_2$	Me	8 min	**2j** 95
$-(CH_2)_4-$		1 min	**2k** 98
$-(CH_2)_5-$		1 min	**2l** 99
$-(CH_2)_6-$		1 min	**2m** 99

a) All reactions were carried out in CH_2Cl_2 at room temperature.

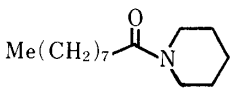
benzoyl-, and 3-phenacyl-TT with several amines are summarized in Tables I and II.

The rate of the aminolysis was found to depend upon the electron density on the nitrogen atom of the amine and its steric surroundings. Comparison of the reaction rates of amines gave the following sequence: aliphatic amine > aromatic amine; $RCH_2NH_2 > R_2CHNH_2 \gg R_3CNH_2$; $RNH_2 \geq RR'NH$; $\overbrace{(CH_2)_nNH}$ ($n=4$—6) > R_2NH (see Table I). Aminolyses

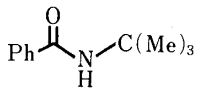
TABLE II. Aminolysis of 3-Benzoyl- and 3-Phenacyl-1,3-thiazolidine-2-thione[a]

1	Amine: R^2–NH–R^3 R^2	R^3	Reaction time	Yield % of **2** $R^1CONR^2R^3$
Ph	*n*-Bu	H	5 min	**2n** 99
Ph	*sec*-Bu	H	3 h	**2o** 99
Ph	Cyclohexyl	H	40 min	**2p** 96
Ph	$PhCH_2$	H	30 min	**2q** 98
Ph	*n*-Bu	Me	6 min	**2r** 99
Ph	$-(CH_2)_5-$		1 min	**2s** 99
$PhCH_2$	Cyclohexyl	H	4 min	**2t** 99
$PhCH_2$	$PhCH_2$	H	2 min	**2u** 100
$PhCH_2$	Cyclohexyl	Me	2 min	**2v** 100
$PhCH_2$	$PhCH_2$	Me	1 min	**2w** 100

a) All reactions were carried out in CH_2Cl_2 at room temperature.



3 97%



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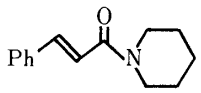

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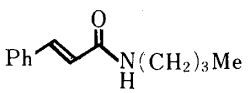

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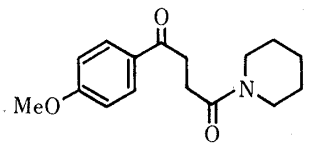

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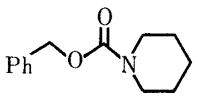

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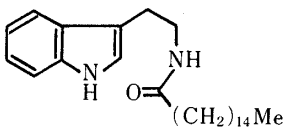
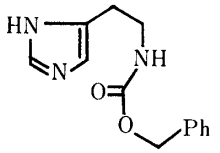


9 93%



10 98%

of various ATTs with several amines proceeded similarly; amides **3**—**10** were obtained in high yields.

ATT (**1**) can recognize the five- or six-membered intramolecular hydrogen-bonding between a primary amino group and a secondary amino group. Treatment of ATT (**1**) [$R^1 = (CH_2)_{14}Me$] with an equimolar mixture of butylamine (**11**) and *N*-methylbutylamine (**12**) gave a mixture of the corresponding hexadecanoyl amines **2a** and **2g** in a ratio of 1 : 1 (nuclear magnetic resonance (NMR) analysis) showing almost the same aminolysis rate for the primary amine and the secondary amine (see also Table I). When ATT (**1**) [$R^1 = (CH_2)_{14}Me$] was similarly treated with a diamine **13** or **15** containing a primary amino group and a secondary amino group, however, the hexadecanoyl amine **14** or **16**, respectively, was obtained chemoselectively in high yield, the secondary amino group being kept intact (Chart 3). This may be due to a potential intramolecular hydrogen-bonding (**17** and **18** in Fig. 1) which must enhance the reactivity of the primary amino group. A similar result was observed in the aminolysis of ATT with spermidine **29** (*vide post*).

Subsequently, the reactions of 3-hexadecanoyl-1,3-thiazolidine-2-thione [**1**: $R^1 = -(CH_2)_{14}Me$] (1 mol eq) with several aminoalcohols or aminophenols (1.1 mol eq) were carried out at room temperature to give chemoselectively only the desired amide (**19a**—**h**) having a free hydroxyl group(s) in satisfactory yield (Table III). ATT (**1**) does not react with the SH group either. Thus, the reaction of **1** [$R^1 = C_6H_4$–Me(*p*)] with ethanethiol resulted in the

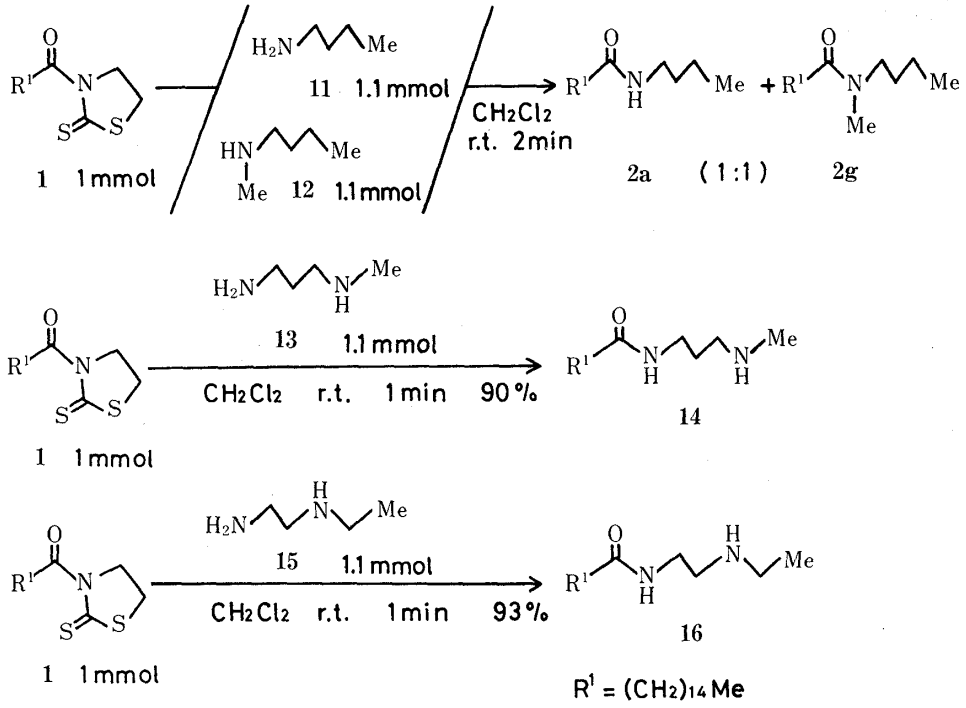
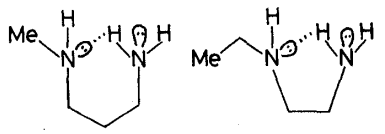


Chart 3



17 18

Fig. 1

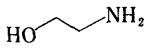
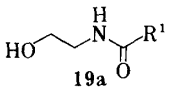
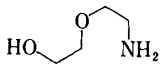
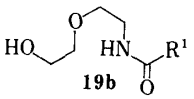
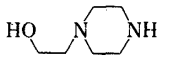
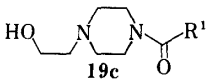
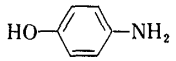
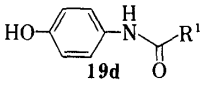
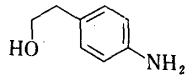
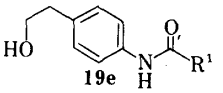
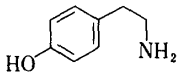
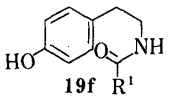
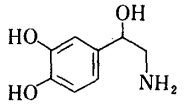
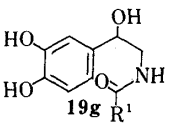
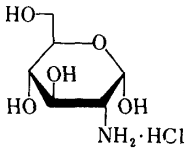
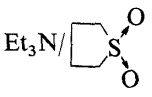
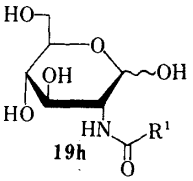
recovery of the starting compound (68%), and a competitive reaction between **1** (R^1 = Ph) and three kinds of nucleophilic compounds (butylamine, butane-1-thiol, and butan-1-ol) afforded only the amide **2n** in 95% yield (Chart 4). This high chemoselectivity of ATT is useful for peptide synthesis and for protecting the ω-amino group of lysine.[11] In order to obtain the thioesters **20** and **21** and esters **22**—**24**, the reaction in the presence of NaH is effective.[12] Some examples are shown in Chart 4; the procedure of successive aminolysis and esterification of aminoethyl hydroxyethyl ether was successfully used to synthesize the desired *N*,*O*-diacylated ether **22**.

Finally this aminolysis was applied to the syntheses of some amide alkaloids. Fagaramide (**26**,[13] obtained from *Fagara macrophylla*), dolichotheline (**28**,[14] from *Dolichothele sphaerica*), and maytenine (**30**,[15] from *Maytenus chuchuhuasha*) were synthesized in good yields (Chart 5).

The selective cinnamoylation of primary amino groups of spermidine (**29**) may be due to deactivation of the secondary amino group based on a potential intramolecular hydrogen-bonding (Fig. 2). This was very useful for the total synthesis of spermidine siderophores, parabactin and parabactin A.[5,16] Although maytenine (**30**) has been synthesized,[17] our method gave a better yield under milder conditions.

N-Ferulyltryptamine[18] (**34**), a very minor component (40 μg/kg) isolated from aqueous acetone extracts of ground kernels of *Zea mays*, was also synthesized through the sequence of reactions shown in Chart 6; aminolysis of ATT **32** with tryptamine was the main step.

TABLE III. Aminolysis of 3-Hexadecanoyl-1,3-thiazolidine-2-thione with Aminoalcohols and Aminophenols

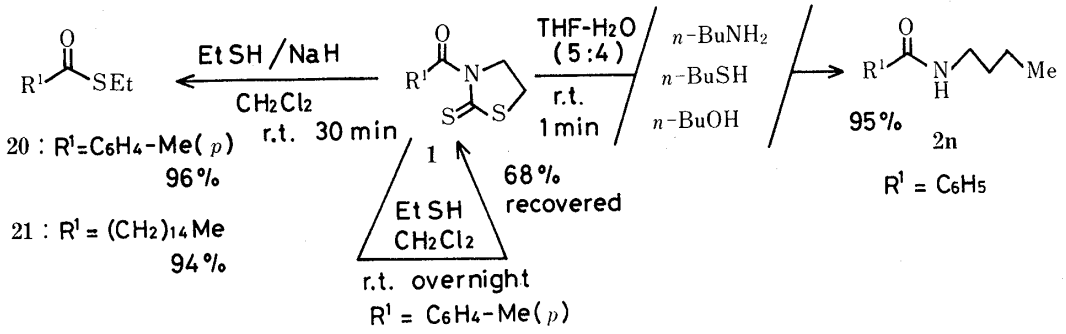
Aminoalcohol aminophenol	Solvent	Reaction time	Product **19** [$R^1=(CH_2)_{14}Me$]	Yield %
	CH_2Cl_2	20 min	 **19a**	91
	CH_2Cl_2	30 min	 **19b**	75
	CH_2Cl_2	3 min	 **19c**	95
	THF	7 d	 **19d**	63
	THF	7 d	 **19e**	61
	EtOH–THF	3 min	 **19f**	95
	EtOH–THF	5 h	 **19g**	51
		2 d	 **19h**	74

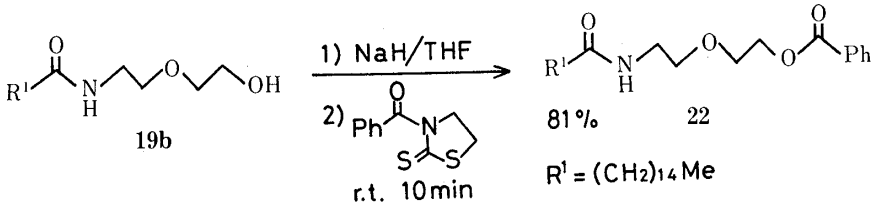
The reason why ATT is so highly reactive toward such nucleophiles as amines and hydride ion was clarified by the X-ray analysis[10,19] of compounds **35** and **36**. It was found that they were not the usual type of amide[20] (*e.g.* **37**) but rather could be regarded as activated carbonyl compounds having a good leaving group, that is, the 2-thiono-1,3-thiazolidino group. Both **35** and **36** had a longer amide C–N bond than that of the usual amide **37**, while both had a C(2)–N(3) bond that was shorter than their N(3)–C(4) bond or the C(2)–N(3) bond in **37**. This means that the lone pair electron on the amide nitrogen atom in the **35** and **36** conjugates with the thiocarbonyl group rather than with the carbonyl group. In other words, the contribution of the canonical formula **38** must be large (Fig. 3).

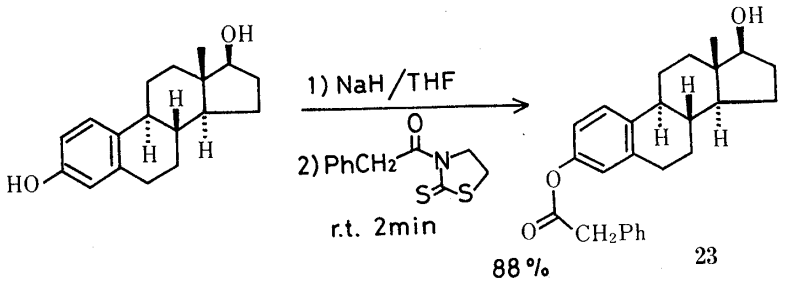
There have been many reports on amide bond formation, but no other method which can be so conveniently monitored has been described.

Experimental

Melting points were determined on a Yanagimoto microapparatus. Infrared (IR) spectra were measured on JASCO A-202 and Hitachi EPI-S2 spectrophotometers. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were







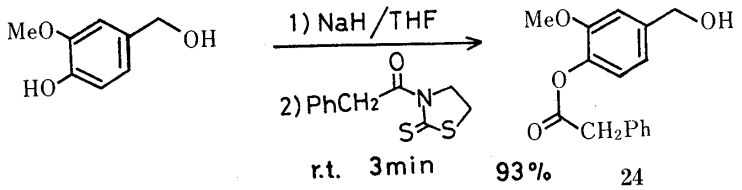


Chart 4

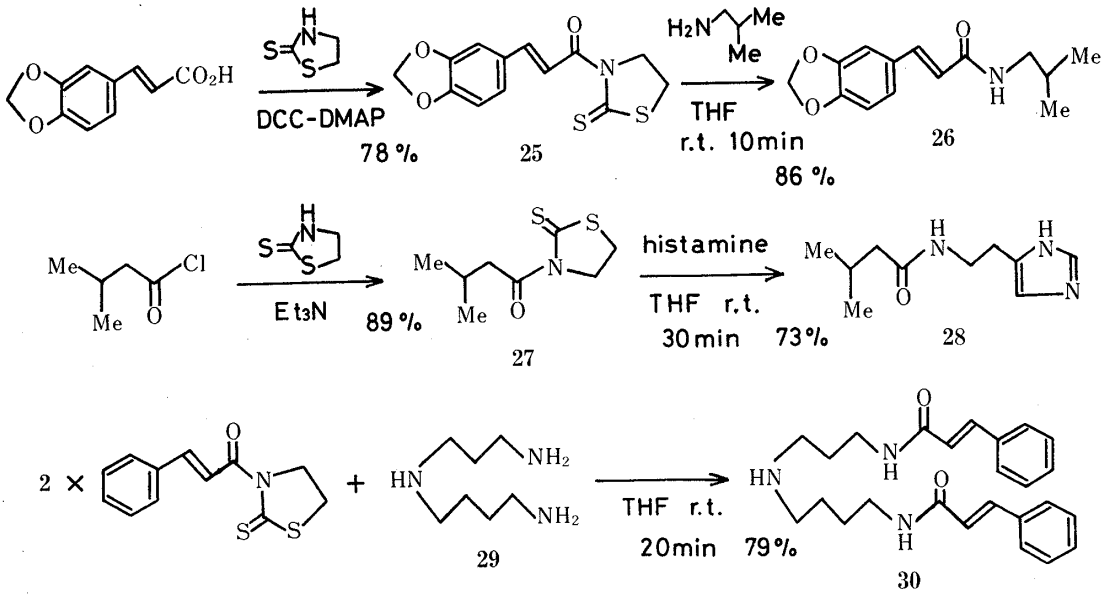


Chart 5

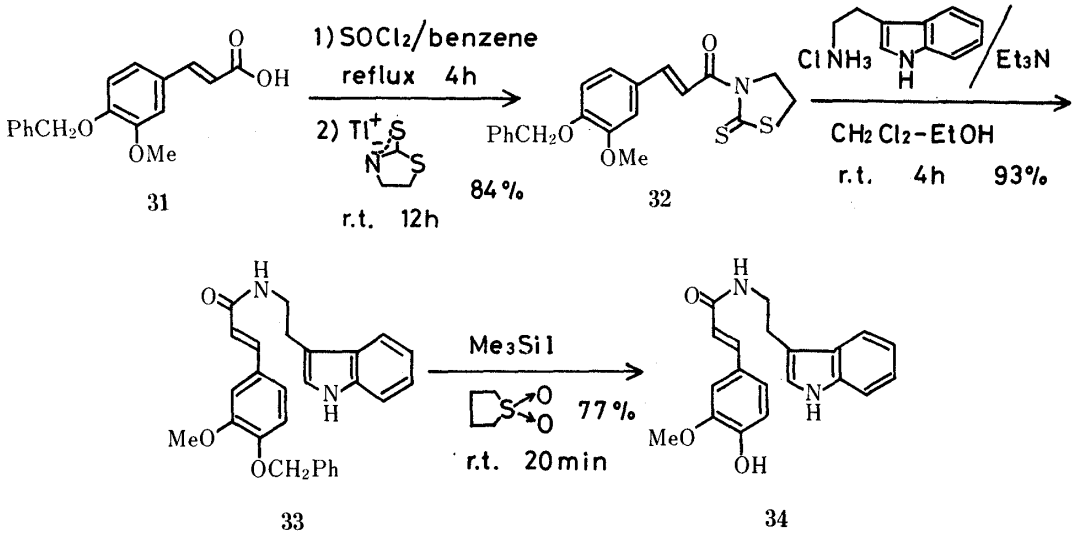


Chart 6

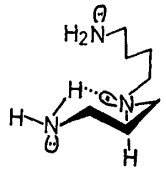


Fig. 2

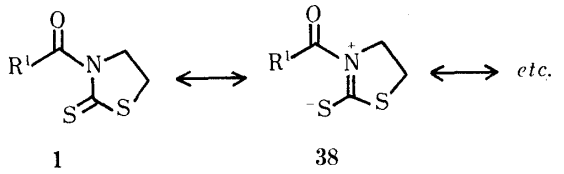
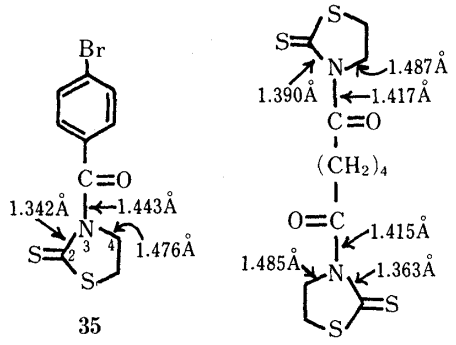
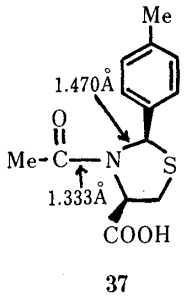


Fig. 3





taken with Varian T-60, JEOL JNM-PMX 60, and JEOL JNM-FX 100 instruments; signals are given in ppm from $SiMe_4$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-OISG double-focusing mass spectrometer. Extracts were dried over anhydrous Na_2SO_4. A mixture of Kieselgel 60 (70—230 mesh) (Merck) and silicic acid (Mallinckrodt) (4 : 1), Kieselgel 60 (70—230 mesh) (Merck) impregnated with 10% $AgNO_3$, and Sephadex LH-20 (Pharmacia Fine Chemicals) were used for column chromatography.

3-Acyl-1,3-thiazolidine-2-thione (1)——General procedures for synthesis of ATT (**1**) have been reported by us[8b,10] and the physical data for 3-hexadecanoyl-, 3-benzoyl-, 3-cinnamoyl-, and 3-benzyloxycarbonyl-1,3-thiazolidine-2-thiones were also published.[8b,10]

3-Nonanoyl-1,3-thiazolidine-2-thione——This compound was prepared by method C in Chart 1. 99% yield; yellow oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=7 Hz), 1.32 (12H, br s), 3.25 (2H, t, J=7 Hz), 3.32 (2H, t, J=7 Hz), 4.58 (2H, t, J=7 Hz). IR ($CHCl_3$): 1700 cm^{-1}. Mol. wt. Calcd for $C_{12}H_{21}NOS_2$: 259.106. Found: MS m/z: 259.104 (M^+).

3-Phenacyl-1,3-thiazolidine-2-thione——This compound was prepared by method C in Chart 1. 76% yield; yellow prisms, mp 84—85 °C ($CHCl_3$–hexane). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 3.24 (2H, t, J=7.6 Hz), 4.55 (2H, t, J=7.6 Hz), 4.64 (2H, s), 7.28 (5H, m). IR (KBr): 1700 cm^{-1}. MS m/z: 237 (M^+). *Anal.* Calcd for $C_{11}H_{11}NOS_2$: C,

55.69; H, 4.67; N, 5.91. Found: C, 55.77; H, 4.58; N, 5.63.

3-(3′-*p*-Anisoyl)propanoyl-1,3-thiazolidine-2-thione——This compound was prepared by method A in Chart 1. 71% yield; yellow amorphous powder. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.17—3.63 (6H, m), 3.87 (3H, s), 4.57 (2H, t, J=8 Hz), 6.93, 7.95 (each 2H, AB type, J=9 Hz). Mol. wt. Calcd for $C_{14}H_{15}NO_3S_2$: 309. Found: MS m/z: 309 (M^+).

A Typical Example of the Aminolyses of 3-Acyl-1,3-thiazolidine-2-thiones (1) with Amines——A solution of *sec*-butylamine (80 mg, 1.1 mmol) in CH_2Cl_2 (1 ml) was added to a yellow solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (357 mg, 1 mmol) in CH_2Cl_2 (4 ml). After being stirred at room temperature for 30 min (the yellow color of the reaction mixture disappeared), the reaction mixture was concentrated *in vacuo* to give an oily residue, which was dissolved in a minimum amount of $CHCl_3$. The solution was passed through a short silica gel column impregnated with 10% $AgNO_3$, and elution with $CHCl_3$ afforded *N-sec*-butylhexadecanamide (**2b**) (303 mg, 97% yield) as colorless needles from hexane.

Physical Data for Each Amide——*N*-Butylhexadecanamide (**2a**): Colorless needles, mp 70—71 °C (hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.78—1.05 (6H, m), 1.27 (30H, br), 2.15 (2H, t, J=6 Hz), 3.23 (2H, q, J=6 Hz), 5.67 (1H, br). IR (KBr): 3300, 1635, 1555 cm^{-1}. MS m/z: 311 (M^+). *Anal.* Calcd for $C_{20}H_{41}NO$: C, 77.10; H, 13.27; N, 4.50. Found: C, 76.88; H, 13.58; N, 4.30.

N-sec-Butylhexadecanamide (**2b**): Colorless needles, mp 71—72.7 °C (hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.90 (6H, t, J=6 Hz), 1.12 (3H, d, J=6 Hz), 1.28 (28H, br), 2.17 (2H, t, J=6 Hz), 3.93 (1H, m), 5.43 (1H, br). IR (KBr): 3300, 1640, 1550 cm^{-1}. MS m/z: 311 (M^+). *Anal.* Calcd for $C_{20}H_{41}NO$: C, 77.10; H, 13.27; N, 4.50. Found: C, 77.02; H, 13.21; N, 4.46.

N-tert-Butylhexadecanamide (**2c**): Colorless needles, mp 67.5—68 °C (hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.87 (3H, t, J=6 Hz), 1.27 (26H, br), 1.33 (9H, s), 2.07 (2H, t, J=6 Hz), 5.33 (1H, br). IR (KBr): 3350, 1645, 1555 cm^{-1}. MS m/z: 311 (M^+). *Anal.* Calcd for $C_{20}H_{41}NO$: C, 77.10; H, 13.27; N, 4.50. Found: C, 77.04; H, 13.20; N, 4.45.

N-Cyclohexylhexadecanamide (**2d**): Colorless needles, mp 92—93 °C (hexane). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.86 (3H, t, J=5.6 Hz), 1.0—2.0 (36H, br), 2.11 (2H, t, J=7 Hz), 3.70 (1H, m), 5.21 (1H, br). IR (KBr): 3300, 1635, 1550 cm^{-1}; MS m/z: 337 (M^+). *Anal.* Calcd for $C_{22}H_{43}NO$: C, 78.27; H, 12.84; N, 4.15. Found: C, 78.13; H, 12.71; N, 4.04.

N-Benzylhexadecanamide (**2e**): Colorless needles, mp 93—94 °C (CH_2Cl_2–hexane). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=5.5 Hz), 1.26 (24H, br), 1.69 (2H, m), 2.21 (2H, t, J=6 Hz), 4.44 (2H, d, J=7 Hz), 5.78 (1H, br), 7.29 (5H, s). IR (KBr): 3270, 1630, 1545 cm^{-1}. MS m/z: 345 (M^+). *Anal.* Calcd for $C_{23}H_{39}NO$: C, 79.94; H, 11.38; N, 4.05. Found: C, 79.89; H, 11.07; N, 4.02.

N-Phenylhexadecanamide (**2f**): Colorless needles, mp 88—89 °C (CH_2Cl_2–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 1.27 (26H, br), 2.32 (2H, t, J=6 Hz), 7.1—7.7 (5H, m); IR (KBr): 3300, 1660, 1545 cm^{-1}. MS m/z: 331 (M^+). *Anal.* Calcd for $C_{22}H_{37}NO$: C, 79.70; H, 11.25; N, 4.23. Found: C, 79.95: H, 11.03; N, 4.20.

N-Butyl-*N*-methylhexadecanamide (**2g**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.8—1.1 (6H, m), 1.27 (30H, br), 2.30 (2H, t, J=6 Hz), 2.90, 2.97 (3H, each s), 3.30 (2H, m). IR ($CHCl_3$): 1625 cm^{-1}. Mol. wt. Calcd for $C_{21}H_{43}NO$: 325.334. Found: MS m/z: 325.337 (M^+).

N,N-Dibutylhexadecanamide (**2h**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.8—1.1 (9H, m), 1.27 (34H, br), 2.27 (2H, t, J=6 Hz), 3.27 (4H, m). IR ($CHCl_3$): 1620 cm^{-1}; Mol. wt. Calcd for $C_{24}H_{49}NO$: 367.381. Found: MS m/z: 367.382 (M^+).

N-Cyclohexyl-*N*-methylhexadecanamide (**2i**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 1.0—2.0 (36H, br), 2.28 (2H, t, J=6 Hz), 2.82 (3H, br s), 3.47 (1H, m). IR ($CHCl_3$): 1625 cm^{-1}; Mol. wt. Calcd for $C_{23}H_{45}NO$: 351.350. Found: MS m/z: 351.349 (M^+).

N-Benzyl-*N*-methylhexadecanamide (**2j**): Colorless needles, mp 47—48 °C (hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 1.28 (26H, br), 2.37 (2H, t, J=6 Hz), 2.73 (3H, br s), 4.52, 4.57 (2H, each s), 7.22 (5H, br s). IR (KBr): 1645 cm^{-1}. MS m/z: 359 (M^+). *Anal.* Calcd for $C_{24}H_{41}NO$: C, 80.15; H, 11.49; N, 3.90. Found: C, 79.91; H, 11.53; N, 3.82.

N-Hexadecanoylpyrrolidine (**2k**): Colorless needles, mp 43.5—44 °C (hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 1.28 (26H, br), 1.90 (4H, m), 2.27 (2H, t, J=6 Hz), 3.43 (4H, m). IR (KBr): 1635, 1620 cm^{-1}. MS m/z: 309 (M^+). *Anal.* Calcd for $C_{20}H_{39}NO$: C, 77.60; H, 12.70; N, 4.53. Found: C, 77.42; H, 12.69; N, 4.59.

N-Hexadecanoylpiperidine (**2l**): Colorless needles, mp 38—38.5 °C (hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 1.27 (26H, br), 1.5—1.9 (6H, m), 2.30 (2H, t, J=6 Hz), 3.47 (4H, m). IR ($CHCl_3$): 1620 cm^{-1}. MS m/z: 323 (M^+). *Anal.* Calcd for $C_{21}H_{41}NO$: C, 77.95; H, 12.77; N, 4.33. Found: C, 77.96; H, 12.74; N, 4.31.

N-Hexadecanoylhexamethyleneimine (**2m**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.90 (3H, t, J=6 Hz), 1.28 (26H, br), 1.5—2.0 (8H, br), 2.33 (2H, t, J=7 Hz), 3.50 (4H, m). IR ($CHCl_3$): 1620 cm^{-1}. Mol. wt. Calcd for $C_{22}H_{43}NO$: 337.334. Found: MS m/z: 337.332 (M^+).

N-Butylbenzamide (**2n**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.90 (3H, t, J=6 Hz), 1.1—1.8 (4H, m), 3.37 (2H, q, J=6 Hz), 7.0—7.9 (6H, m). IR ($CDCl_3$): 3450, 1655, 1530 cm^{-1}. Mol. wt. Calcd for $C_{11}H_{15}NO$: 177.119. Found: MS m/z: 177.117 (M^+).

N-sec-Butylbenzamide (**2o**): Colorless needles, mp 85—85.5 °C (hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.92 (3H, t, J=6 Hz), 1.18 (3H, d, J=6 Hz), 1.53 (2H, quintet, J=6 Hz), 4.13 (1H, m), 6.50 (1H, br), 7.2—7.9 (5H, m). IR ($CHCl_3$): 3450, 1650, 1525 cm^{-1}. MS *m/z*: 177 (M^+). *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.66; H, 8.63; N, 8.01.

N-Cyclohexylbenzamide (**2p**): Colorless needles, mp 149—150 °C ($CHCl_3$–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.0—2.3 (10H, m), 3.93 (1H, m), 6.27 (1H, br), 7.2—7.9 (5H, m). IR (KBr): 3350, 3250, 1625, 1540 cm^{-1}. MS *m/z*: 203 (M^+). *Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.93; H, 8.61; N, 6.94.

N-Benzylbenzamide (**2q**): Colorless needles, mp 102.5—104 °C ($CHCl_3$–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 4.55 (2H, d, J=6 Hz), 6.82 (1H, br), 7.27 (5H, s), 7.3—7.9 (5H, m). IR (KBr): 3300, 1640, 1550 cm^{-1}. MS *m/z*: 211 (M^+). *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.50, H, 6.20; N, 6.48.

N-Benzoyl-*N*-methyl-butylamine (**2r**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.87 (3H, t like, J=6 Hz), 1.0—1.9 (4H, m), 2.97 (3H, br s), 3.67 (2H, m), 7.37 (5H, s). IR ($CHCl_3$): 1620 cm^{-1}. Mol. wt. Calcd for $C_{12}H_{17}NO$: 191.131. Found: MS *m/z*: 191.128 (M^+).

N-Benzoylpiperidine (**2s**): Colorless prisms, mp 45—46 °C (CH_2Cl_2–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.60 (6H, br), 3.48 (4H, br), 7.35 (5H, s); IR ($CHCl_3$): 1615 cm^{-1}. MS *m/z*: 189 (M^+). *Anal.* Calcd for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.03; H, 8.17; N, 7.40.

(*N*-Cyclohexyl)phenylacetamide (**2t**): Colorless needles, mp 137—138 °C ($CHCl_3$–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.6—2.1 (10H, m), 3.52 (2H, s), 3.70 (1H, m), 5.75 (1H, br), 7.32 (5H, s). IR ($CHCl_3$): 3410, 1655, 1520 cm^{-1}. MS *m/z*: 217 (M^+). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.33; H, 8.97; N, 6.29.

N-Phenacylbenzylamine (**2u**): Colorless needles, mp 120.5—121 °C ($CHCl_3$–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.55 (2H, s), 4.35 (2H, d, J=6 Hz), 6.00 (1H, br), 7.20 (5H, br s), 7.25 (5H, s). IR ($CHCl_3$): 3430, 1660, 1520 cm^{-1}. MS *m/z*: 225 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.74; H, 6.91; N, 6.14.

N-Cyclohexyl-*N*-methylphenylacetamide (**2v**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.8—1.9 (10H, m), 2.74, 2.77 (3H, each s), 3.68, 3.73 (2H, each s), 4.38 (1H, m), 7.24 (5H, s). IR ($CHCl_3$): 1620 cm^{-1}. Mol. wt. Calcd for $C_{15}H_{21}NO$: 231.162. Found: MS *m/z*: 231.162 (M^+).

N-Benzyl-*N*-methylphenylacetamide (**2w**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.83, 2.91 (3H, each s), 3.73 (2H, s), 4.47, 4.57 (2H, each s), 7.23 (5H, s), 7.26 (5H, s). IR ($CHCl_3$): 1640 cm^{-1}. Mol. wt. Calcd for $C_{16}H_{17}NO$: 239.131. Found: MS *m/z*: 239.128 (M^+).

N-Nonanoylpiperidine (**3**): Reaction time = 1 min; colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.88 (3H, t, J= 5 Hz), 1.30 (12H, br), 1.60 (6H, br), 2.32 (2H, t, J=7 Hz), 3.50 (4H, br). IR ($CHCl_3$): 1620 cm^{-1}. Mol. wt. Calcd for $C_{14}H_{27}NO$: 225.209. Found: MS *m/z*: 225.213 (M^+).

N-tert-Butylbenzamide (**4**): Reaction time = 19 h; colorless needles, mp 134—135 °C (CH_2Cl_2–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.46 (9H, s), 5.08 (1H, br), 7.2—7.8 (5H, m). IR (KBr): 3350, 1640, 1530, 1520 cm^{-1}. MS *m/z*: 177 (M^+). *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.30; H, 8.55; N, 7.71.

N-Cinnamoylpiperidine (**5**): Reaction time = 1 min; colorless needles, mp 119—120 °C (Et_2O). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.60 (6H, br), 3.58 (4H, br), 6.87, 7.58 (each 1H, AB type), 7.1—7.6 (5H, m). IR (KBr): 1645, 1590 cm^{-1}. MS *m/z*: 215 (M^+); *Anal.* Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.91; N, 6.51. Found: C, 78.07; H, 7.99; N, 6.24.

N-Cinnamoylbutylamine (**6**): Reaction time = 1 min; colorless needles, mp 78—79 °C (hexane–ether). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.90 (3H, t, J=6 Hz), 1.2—1.8 (4H, m), 3.38 (2H, q, J=6 Hz), 6.55, 7.59 (each 1H, AB type, J= 15.5 Hz), 6.77 (1H, br), 7.1—7.6 (5H, m). IR (KBr): 3300, 1665, 1615, 1560 cm^{-1}. MS *m/z*: 203 (M^+). *Anal.* Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.62; H, 8.55; N, 6.53.

(*N*-3-(*p*-Anisoyl)propanoyl)piperidine (**7**): Reaction time = 1 min; colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.60 (6H, br), 2.75 (2H, t, J=6 Hz), 3.30 (2H, t, J=6 Hz), 3.50 (4H, m), 3.87 (3H, s), 6.91, 7.97 (each 2H, AB type, J= 9 Hz). IR ($CHCl_3$): 1675, 1625 cm^{-1}. Mol. wt. Calcd for $C_{16}H_{26}NO_3$: 275. Found: MS *m/z*: 275 (M^+).

N-Benzyloxycarbonylpiperidine (**8**): Reaction time = 3 min; colorless oil. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 1.56 (6H, br), 3.44 (4H, br), 5.12 (2H, s), 7.32 (5H, s). IR ($CHCl_3$): 1688 cm^{-1}. Mol. wt. Calcd for $C_{13}H_{17}NO_2$: 219. Found: MS *m/z*: 219 (M^+).

N-Hexadecanoyltryptamine (9)——A solution of tryptamine hydrochloride (147 mg, 0.746 mmol) and Et_3N (82.5 mg, 0.817 mmol) in EtOH (5 ml) was added to a yellow solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (243 mg, 0.681 mmol) in THF (5 ml). The mixture was stirred at room temperature for 1 h; the original yellow color disappeared. The solvent was evaporated off *in vacuo* to leave an oily residue. Purification of the residue on a silica gel column afforded the amide **9** (253 mg) as colorless needles from $CHCl_3$–hexane. mp 115.5—116 °C. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 1.26 (24H, br), 1.59 (2H, m), 2.12 (2H, t, J=7 Hz), 2.98 (2H, t, J=6 Hz), 3.63 (2H, q, J=6 Hz), 5.51 (1H, br), 8.10 (1H, br), 7.04—7.68 (5H, m). IR (KBr): 3380, 3260, 1645, 1625, 1555 cm^{-1}. MS *m/z*: 398 (M^+). *Anal.* Calcd for $C_{26}H_{42}N_2O$: C, 78.34; H, 10.62; N, 7.03. Found: C, 78.31; H, 10.88; N, 6.71.

N-Benzyloxycarbonylhistamine (10)——Histamine (100 mg, 0.9 mmol) was added to a suspension of 3-benzyloxycarbonyl-1,3-thiazolidine-2-thione (207 mg, 0.82 mmol) in THF (20 ml). The mixture was refluxed under N_2

for 15 min. Usual work-up gave compound **10** (196 mg) as colorless flakes from MeOH–$CHCl_3$. mp 127—128 °C. ^{1}H-NMR (100 MHz, $CDCl_3$–CD_3OD) δ: 2.76 (2H, t, J=7.5 Hz), 3.33—3.48 (2H, m), 5.65 (2H, s), 6.75 (1H, br s), 7.30 (5H, s), 7.47 (1H, d, J=1.5 Hz). IR (KBr): 3200, 3050—2850, 1680 cm^{-1}. MS m/z: 245 (M^+). *Anal.* Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.89; H, 6.22; N, 17.55.

Treatment of 3-Hexadecanoyl-1,3-thiazolidine-2-thione with an Equimolar Mixture of Butylamine (11) and *N*-Methylbutylamine (12)——An equimolar amount of butylamine (**11**) (80 mg, 1.1 mmol) and *N*-methylbutylamine (**12**) (96 mg, 1.1 mmol) was added to a solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (357 mg, 1 mmol) in CH_2Cl_2 (5 ml) with stirring at room temperature. The whole was stirred for 2 min, and usual work-up of the reaction mixture gave the amide fraction (310 mg). On the basis of the ^{1}H-NMR data, this fraction was estimated to be a 1 : 1 mixture of **2a** and **2b**.

Treatment of 3-Hexadecanoyl-1,3-thiazolidine-2-thione with *N*-Methyl-1,3-propanediamine——*N*-Methyl-1,3-propanediamine (**13**) (96.8 mg, 1.1 mmol) was added to a solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (357 mg, 1 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature for 1 min and the solvent was evaporated off *in vacuo* to give an oily residue, which was chromatographed on a Sephadex LH-20 column with MeOH–$CHCl_3$ (4 : 1) to afford the amide **14** (293 mg) as colorless fine prisms from $CHCl_3$–hexane. mp 67—68 °C. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.87 (3H, t, J=6 Hz), 1.25 (26H, br), 1.67 (2H, quint., J=6.5 Hz), 2.16 (2H, t, J=6.5 Hz), 2.42 (3H, s), 2.67 (2H, t, J=6.5 Hz), 3.33 (2H, q, J=6.5 Hz), 6.83 (1H, br). IR (KBr): 3300, 1630, 1550 cm^{-1}. Mol. wt. Calcd for $C_{20}H_{42}N_2O$: 326. Found: MS m/z: 326 (M^+).

Treatment of 3-Hexadecanoyl-1,3-thiazolidine-2-thione with *N*-Ethylethylenediamine——*N*-Ethylethylenediamine (**15**) (96.8 mg, 1.1 mmol) was added to a solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (357 mg, 1 mmol) in CH_2Cl_2 (5 ml). The whole was stirred at room temperature for 1 min, and usual work-up of the reaction mixture gave the amide **16** (303 mg) as colorless plates from $CHCl_3$–hexane. mp 66.5—67 °C. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.87 (3H, t, J=6 Hz), 1.10 (3H, t, J=7 Hz), 1.25 (24H, br), 1.61 (2H, m), 2.18 (2H, t, J=7 Hz), 2.18 (1H, s), 2.66 (2H, q, J=7 Hz), 2.75 (2H, t, J=5.5 Hz), 3.35 (2H, q, J=5.5 Hz), 6.39 (1H, br). IR (KBr): 3300, 1635, 1550 cm^{-1}. MS m/z: 326 (M^+). *Anal.* Calcd for $C_{20}H_{42}N_2O$: C, 73.56; H, 12.96; N, 8.58. Found: C, 73.38; H, 13.05; N, 8.45.

Examples of the Treatment of 3-Hexadecanoyl-1,3-thiazolidine-2-thione with Aminoalcohols or Aminophenols——(1) A solution of 2-aminoethanol (67 mg, 1.1 mmol) in CH_2Cl_2 (2 ml) was added to a solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (357 mg, 1 mmol) in CH_2Cl_2 (3 ml). The reaction mixture was stirred at room temperature for 20 min, then concentrated *in vacuo* to give an oily residue. This residue was chromatographed on a silica gel column impregnated with 10% $AgNO_3$ and elution with $CHCl_3$ afforded the amide **19a** (271 mg) as colorless needles from $CHCl_3$. The amides **19b**, **19c**, **19f** and **19g** were similarly prepared. However, in the cases of **19c** and **19g**, the usual silica gel without $AgNO_3$ was used for column chromatography.

(2) A solution of *p*-aminophenol (120 mg, 1.1 mmol) in THF (2 ml) was added to a solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (357 mg, 1 mmol) in THF (3 ml). After being stirred at room temperature for 7 d, the solution was evaporated *in vacuo* to give a solid residue. The residue was washed with a little ether and the crude crystals were repeatedly recrystallized from $CHCl_3$ to give the amide **19d** (227 mg) as colorless needles. Compound **19e** was also obtained in the same manner as described for **19d**.

(3) A solution of 3-hexadecanoyl-1,3-thiazolidine-2-thione (330 mg, 0.924 mmol), D-glucosamine hydrochloride (200 mg, 0.930 mmol), and Et_3N (224 mg, 2.18 mmol) in sulfolane (20 ml) was stirred at 35 °C for 2 d, then 200 ml of CH_2Cl_2 was added to the colorless mixture and the whole was left at room temperature for a day to give a colorless precipitate. This precipitate was filtered off and washed with hot $CHCl_3$, MeOH, and ether successively to afford the amide **19h** (287 mg) as a colorless crystalline powder.

Physical Data for Each Amide——*N*-(2-Hydroxyethyl)hexadecanamide (**19a**): Colorless needless, mp 115.5—116 °C ($CHCl_3$–hexane). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=7 Hz), 1.25 (24H, br), 1.62 (2H, m), 2.20 (2H, t, J=7 Hz), 2.64 (1H, br), 3.44 (2H, q, J=7 Hz), 3.70 (2H, m), 5.90 (1H, br). IR (KBr): 3300, 1640, 1555 cm^{-1}. MS m/z: (M^+). *Anal.* Calcd for $C_{18}H_{37}NO_2$: C, 72.19; H, 12.45; N, 4.68. Found: C, 72.05; H, 12.63; N, 4.66.

N-(*w*-Hydroxyethoxyethyl)hexadecanamide (**19b**): Colorless needles, mp 83—83.5 °C ($CHCl_3$–hexane). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=5.6 Hz), 1.26 (24H, br), 1.62 (2H, m), 2.19 (2H, t, J=7 Hz), 2.38 (1H, s), 3.34—3.84 (8H, m), 6.09 (1H, br). IR (KBr): 3340, 1645, 1575 cm^{-1}: MS m/z: 343 (M^+). *Anal.* Calcd for $C_{20}H_{41}NO_3$: C, 69.92; H, 12.03; N, 4.08. Found: C, 69.92; H, 12.20; N, 3.96.

N-Hexadecanoyl-*N'*-hydroxyethylpiperazine (**19c**): Colorless prisms, mp 61.5—62 °C (hexane). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=6 Hz), 1.26 (24H, br), 1.61 (2H, m), 2.14 (1H, br s), 2.34 (2H, t, J=7 Hz), 2.50 (2H, t, J=5 Hz), 2.58 (4H, t, J=5 Hz), 3.51 (2H, t, J=5 Hz), 3.67 (4H, t, J=5 Hz). IR (KBr): 3430, 1630 cm^{-1}. MS m/z: 368 (M^+). *Anal.* Calcd for $C_{22}H_{44}N_2O_2$: C, 71.68: H, 12.03; N, 7.60. Found: C, 71.34; H, 12.04; N, 7.53.

N-(*p*-Hydroxyphenyl)hexadecanamide (**19d**): Colorless needles, mp 134—135 °C ($CHCl_3$). ^{1}H-NMR [100 MHz, $CDCl_3$–CD_3OD (3 : 2)] δ: 0.88 (3H, t, J=6 Hz), 1.26 (24H, br), 1.70 (2H, m), 2.33 (2H, t, J=7.5 Hz), 6.77, 7.32 (each 2H, AB type, J=9 Hz). IR (KBr): 3320, 1650, 1550 cm^{-1}. MS m/z: 347 (M^+). *Anal.* Calcd for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73; N, 4.03. Found: C, 76.06; H, 10.56; N, 4.03.

N-(*p*-Hydroxyethylphenyl)hexadecanamide (**19e**): Colorless needles, mp 131—132 °C ($CHCl_3$). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=6 Hz), 1.25 (26H, br), 2.35 (2H, t, J=7 Hz), 2.84 (2H, t, J=7 Hz), 3.68 (2H, t,

$J=7$ Hz), 7.20, 7.47 (each 2H, AB type, $J=9$ Hz). IR (KBr): 3325, 1660, 1535 cm^{-1}. MS *m/z*: 375 (M^+). *Anal.* Calcd for $C_{24}H_{41}NO_2$: C, 76.75; H, 11.00; N, 3.73. Found: C, 76.52; H, 11.02; N, 3.92.

N-[2-(4-Hydroxyphenyl)ethyl]hexadecanamide (**19f**): Colorless needles, mp 104—105 °C ($CHCl_3$). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6$ Hz), 1.25 (26H, br), 2.13 (2H, t, $J=7$ Hz), 2.74 (2H, t, $J=7$ Hz), 3.49 (2H, q, $J=7$ Hz), 5.41 (1H, br), 6.79, 7.06 (each 2H, AB type, $J=9$ Hz). IR (KBr): 3310, 1640, 1555 cm^{-1}. MS *m/z*: 375 (M^+). *Anal.* Calcd for $C_{24}H_{41}NO_2$: C, 76.75; H, 11.00; N, 3.73. Found: C, 76.72; H, 10.90; N, 3.81.

N-Hexadecanoyl-L-noradrenaline (**19g**): Colorless fine prisms, mp 104—105.5 °C ($CHCl_3$–MeOH). ^{1}H-NMR [100 MHz, CD_3OD–$CDCl_3$ (4:1)] δ: 0.88 (3H, t, $J=6$ Hz), 1.26 (24H, br), 1.60 (2H, m), 2.19 (2H, t, $J=6$ Hz), 3.36 (2H, m), 4.60 (1H, m), 6.65—6.85 (3H, m). IR (KBr): 3450, 3350, 3180, 1640, 1545 cm^{-1}. MS *m/z*: 389 ($M^+ - H_2O$). *Anal.* Calcd for $C_{24}H_{41}NO_4$: C, 70.72; H, 10.14; N, 3.44. Found: C, 70.71; H, 9.92; N, 3.46.

N-Hexadecanoyl-α-D-glucosamine (**19h**): Colorless crystalline powder, mp 198—202 °C (dec.). ^{1}H-NMR (100 MHz, C_5D_5N) δ: 0.88 (3H, t, $J=6$ Hz), 1.26 (24H, br), 1.87 (2H, m), 2.54 (2H, t, $J=7$ Hz), 4.1—5.0 (6H, m), 6.05 (1H, d, $J=3$ Hz). IR (KBr): 3300 (br), 1640, 1550 cm^{-1}. Mol. wt. Calcd for $C_{22}H_{43}NO_6$: 417. Found: FD-MS *m/z*: 440 $(M+Na)^+$.

Preparations of Thioesters 20 and 21——Ethanethiol (85 mg, 1.37 mmol) was added to a suspension of 47% NaH (67 mg) in CH_2Cl_2 (2 ml). The mixture was stirred for 10 min and then a yellow solution of 3-(*p*-methylbenzoyl)-1,3-thiazolidine-2-thione (237 mg, 1 mmol) in CH_2Cl_2 (3 ml) was added. After being stirred at room temperature for 30 min (the original yellow color disappeared), the reaction mixture was poured into water. The mixture was extracted with CH_2Cl_2. The extract was treated as usual to give the thioester **20** (172 mg) as a colorless oil. The thioester **21** was similarly prepared.

Physical Data for Thioesters——*S*-Ethyl *p*-Methylbenzenethioate (**20**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.35 (3H, t, $J=7.5$ Hz), 2.40 (3H, s), 3.07 (2H, q, $J=7.5$ Hz), 7.20, 7.85 (each 2H, AB type, $J=8$ Hz). IR ($CHCl_3$): 1650 cm^{-1}. Mol. wt. Calcd for $C_{10}H_{12}OS$: 180. Found: MS *m/z*: 180 (M^+).

S-Ethyl Hexadecanethioate (**21**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.90 (3H, t, $J=5$ Hz), 1.25 (26H, br), 1.30 (3H, t, $J=7$ Hz), 2.55 (2H, t, $J=7$ Hz), 2.90 (2H, q, $J=7$ Hz). IR ($CHCl_3$): 1680 cm^{-1}. Mol. wt. Calcd for $C_{18}H_{36}OS$: 300. Found: MS *m/z*: 300 (M^+).

Competitive Reaction of Amine, Thiol, and Alcohol with 3-Benzoyl-1,3-thiazolidine-2-thione——A solution of 3-benzoyl-1,3-thiazolidine-2-thione (223 mg, 1 mmol) in THF (4 ml) was added to the reagent solution [a mixture of butylamine (1.1 mmol), butane-1-thiol (1.1 mmol), butan-1-ol (1.1 mmol), THF (1 ml), and water (4 ml)]. After being stirred at room temperature for 1 min, the reaction mixture was treated as usual to give only the amide **2n** in 95% yield.

Preparations of Esters 22, 23, and 24——A mixture of 50% NaH (116 mg, 2.4 mmol), the amide **19b**, and THF (10 ml) was stirred at room temperature for 10 min, then a yellow solution of 3-benzoyl-1,3-thiazolidine-2-thione (223 mg, 1 mmol) in THF (10 ml) was added. After being stirred at room temperature for 10 min, the reaction mixture was poured into cold 5% HCl and extracted with EtOAc. The organic layer was washed with brine, dried, and evaporated *in vacuo* to give an oily residue. Purification of the residue on a Sephadex LH-20 column with MeOH and on a silica gel column with $CHCl_3$ gave the ester **22** (364 mg). The esters **23** and **24** were also similarly prepared, except that 1.1 mmol of 50% NaH was used.

N-Benzoyloxyethoxyethylhexadecanamide (**22**): Colorless fine needles, mp 66.5—67 °C (hexane). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.88 (3H, t, $J=6$ Hz), 1.25 (24H, br), 1.55 (2H, m), 2.13 (2H, t, $J=7$ Hz), 3.45 (2H, q like, $J=4$ Hz), 3.60 (2H, t, $J=4$ Hz), 3.80 (2H, t, $J=4.5$ Hz), 4.50 (2H, t, $J=4.5$ Hz), 5.96 (1H, br), 7.26—7.70 (3H, m), 8.02—8.22 (2H, m). IR (KBr): 3320, 1715, 1630, 1550 cm^{-1}. MS *m/z*: 447 (M^+). *Anal.* Calcd for $C_{27}H_{45}NO_4$: C, 72.44; H, 10.13; N, 3.13. Found: C, 72.55; H, 10.11; N, 3.15.

3-*O*-Phenacyl-β-estradiol (**23**): Colorless plates mp 122—123 °C ($CHCl_3$–hexane). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.72 (3H, s), 1.0—2.5 (12H, m), 2.6—3.0 (2H, m), 2.87 (1H, s), 3.60 (1H, d, $J=6$ Hz), 3.77 (2H, s), 6.60—6.73 (2H, m), 7.03—7.50 (6H, m). IR (KBr): 3560, 3500, 1755 cm^{-1}. MS *m/z*: 390 (M^+). *Anal.* Calcd for $C_{26}H_{30}O_3$: C, 79.96; H, 7.74. Found: C, 79.95; H, 7.59.

2-Methoxy-4-hydroxymethylphenyl Phenylacetate (**24**): Colorless oil. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.58 (3H, s), 3.80 (2H, s), 4.27 (1H, s), 4.40 (2H, s), 6.60—7.00 (2H, m), 7.10—7.50 (6H, m). IR ($CHCl_3$): 3600, 3545, 1750 cm^{-1}. Mol. wt. Calcd for $C_{16}H_{16}O_4$: 272. Found: MS *m/z*: 272 (M^+).

3-(3,4-Methylenedioxycinnamoyl)-1-3-thiazolidine-2-thione (25)——DCC (680 mg, 3.3 mmol) was added to a suspension of 3,4-methylenedioxycinnamic acid (576 mg, 3 mmol), 4-dimethylaminopyridine (36.6 mg, 0.3 mmol), and 1,3-thiazolidine-2-thione (357 mg, 3 mmol) in CH_2Cl_2 (5 ml) at 0 °C with stirring. After 5 min at 0 °C, the mixture was further stirred at room temperature for 30 min. The precipitate was filtered off and the filtrate was evaporated *in vacuo* to give a yellow residue, which was chromatographed on a silica gel column to afford the amide **25** (684 mg) as yellow prisms from CH_2Cl_2–C_6H_6. mp 156—158 °C. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 3.36 (2H, t, $J=8$ Hz), 4.58 (2H, t, $J=8$ Hz), 6.00 (2H, s), 6.76—7.10 (3H, m), 7.60, 7.72 (each 1H, AB type, $J=16$ Hz). IR (KBr): 1665 cm^{-1}. MS *m/z*: 293 (M^+). *Anal.* Calcd for $C_{13}H_{11}NO_3S_2$: C, 53.24; H, 3.78; N, 4.78. Found: C, 53.11; H, 3.70; N, 4.56.

Fagaramide (26)——The usual aminolysis of **25** (293 mg, 1 mmol) with isobutylamine (0.11 ml, 1.1 mmol) in CH_2Cl_2 (12 ml) gave fagaramide (**26**) (212 mg) as colorless needles, mp 118—119 °C (MeOH) (lit.[13] 119—120 °C). ^{1}H-

NMR (100 MHz, $CDCl_3$) δ: 0.93 (6H, d, J=6.5 Hz), 1.70—2.04 (2H, m), 3.20 (2H, t, J=6.5 Hz), 5.95 (2H, s), 6.26, 7.50 (each 1H, AB type, J=16 Hz), 6.75 (1H, d, J=8 Hz), 6.95 (1H, d-like, J=8 Hz), 6.97 (1H, br s). IR (KBr): 3300, 1650, 1615, 1533 cm^{-1}. MS m/z: 247.122 (M^+). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.76; H, 6.99; N, 5.61. This synthetic fagaramide was shown to be identical (TLC, IR, ^{1}H-NMR, and mixed melting point) with the natural product.

3-(3-Methylbutanoyl)-1,3-thiazolidine-2-thione (27)——The usual treatment of 1,3-thiazolidine-2-thione with isovaleryl chloride in the presence of Et_3N gave **27** as a yellow oil. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 0.96 (3H, d, J=7 Hz), 2.22 (1H, quint., J=7 Hz), 3.15 (2H, d, J=7 Hz), 3.29 (2H, t, J=8 Hz), 4.58 (2H, t, J=8 Hz).

Dolichotheline (28)——Histamine (100 mg, 0.901 mmol) was added to a solution of the amide **27** (165 mg, 0.813 mmol) in THF (10 ml). After being stirred at room temperature for 30 min, the reaction mixture was treated as usual to give dolichotheline (**28**) (115 mg) as colorless needles from $CHCl_3$. mp 129—130 °C (lit.[14] 130—131 °C). ^{1}H-NMR (100 MHz, CD_3OD–$CDCl_3$) δ: 0.91 (6H, d, J=6 Hz), 2.04 (3H, br), 2.77 (2H, t, J=7.5 Hz), 6.80 (1H, s), 7.53 (1H, s). IR (KBr): 3240, 3130, 3050, 1635, 1570 cm^{-1}. Mol. wt. Calcd for $C_{10}H_{17}N_3O$: 195.137. Found: MS m/z: 195.136 (M^+). This synthetic dolichotheline was shown to be identical (IR and ^{1}H-NMR spectra) with natural dolichotheline.

Maytenine (30)——A solution of spermidine (**29**) (160 mg, 1.1 mmol) in THF (10 ml) was added to a solution of 3-cinnamoyl-1,3-thiazolidine-2-thione[8] (498 mg, 2 mmol) in THF (3 ml). After being stirred at room temperature for 20 min, the reaction mixture was treated as usual to give maytenine (**30**) (391 mg) as colorless prisms from Et_2O–MeOH. mp 161—162 °C (lit.[15] 158 °C). ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 1.32—1.90 (7H, m), 2.50—2.88 (4H, m), 3.23—3.60 (4H, m), 6.25 (1H, br), 6.37 (1H, d, J=16 Hz), 6.40 (1H, d, J=16 Hz), 6.94 (1H, br), 7.20—7.59 (10H, m), 7.60 (2H, d, J=16 Hz). IR (KBr): 3440, 3300, 1650, 1620, 1545 cm^{-1}. This synthetic maytenine (**30**) was shown to be identical (TLC, IR, ^{1}H-NMR, and mixed melting point) with natural maytenine.

***O*-Benzylferulic Acid (31)**——Benzyl *O*-benzylferulate (1.453 g, 3.9 mmol) (derived from ferulic acid by benzylation) was hydrolyzed by heating with 40% KOH (40 ml) in THF (5 ml). The usual work-up gave the acid **31** (1.1 g) as colorless needles. mp 264—265 °C. ^{1}H-NMR (100 MHz, acetone-d_6) δ: 3.92 (3H, s), 5.19 (2H, s), 6.42, 7.62 (each 1H, AB type, J=16 Hz), 7.03—7.50 (8H, m). IR (KBr): 1670 cm^{-1}. MS m/z: 284 (M^+). *Anal.* Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.45; H, 5.73.

3-(*O*-Benzylferulyl)-1,3-thiazolidine-2-thione (32)——Thionyl chloride (335 mg, 2.8 mmol) was added to a suspension of *O*-benzylferulic acid (**31**) (400 mg, 1.4 mmol) in benzene (10 ml). After being refluxed for 4 h, the reaction mixture was evaporated *in vacuo* to give an oily residue. This residue was taken up in THF (15 ml) and the thallium (I) salt of 1,3-thiazolidine-2-thione (681 mg, 2.1 mmol) was added to the solution. The mixture was stirred at room temperature for 12 h and treated as usual[8] to give the amide **32** (455 mg) as yellow needles. mp 140—141 °C. ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 3.35 (2H, t, J=7 Hz), 3.91 (3H, s), 4.58 (2H, t, J=7 Hz), 5.20 (2H, s), 6.88 (1H, d, J=8.5 Hz), 7.09 (1H, dd, J=8.5 and 2.0 Hz), 7.09 (1H, d, J=2.0 Hz), 7.39 (5H, m). IR (KBr): 1670 cm^{-1}. MS m/z: 358 (M^+). *Anal.* Calcd for $C_{20}H_{19}NO_3S_2$: C, 62.31; H, 4.97; N, 3.63. Found: C, 62.26; H, 4.88; N, 3.62.

***O*-Benzyl-*N*-ferulyltryptamine (33)**——A solution of tryptamine hydrochloride (217 mg, 1.1 mmol) and Et_3N (152 mg, 1.5 mmol) in CH_2Cl_2 (30 ml) was added to a solution of the amide **32** (385 mg, 1 mmol) in CH_2Cl_2 (15 ml). The mixture was stirred at room temperature for 4 h. The solvent was evaporated off *in vacuo* to give an oily residue, which was chromatographed on a Sephadex LH-20 column with MeOH to afford tryptamine amide **33** (396 mg) as pale yellow plates from MeOH. mp 91—92 °C. ^{1}H-NMR [100 MHz, DMSO-d_6–$CDCl_3$ (1:1)+D_2O] δ: 3.00 (2H, t, J=7 Hz), 3.62 (2H, t, J=7 Hz), 3.88 (3H, s), 5.13 (2H, s), 6.47, 7.47 (each 1H, AB type, J=15.6 Hz), 6.80—7.60 (13H, m). IR (KBr): 3410, 3200, 1665, 1540, 1520 cm^{-1}. MS m/z: 426 (M^+). *Anal.* Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.15; N, 6.57. Found: C, 75.93; H, 6.04; N, 6.42.

***N*-Ferulyltryptamine (34)**——Trimethylsilyl iodide (240 mg, 2 mmol) was added to a solution of the amide **33** (213 mg, 0.5 mmol) in sulfolane (4 ml). The mixture was stirred at room temperature under N_2 for 20 min, then poured into MeOH. After addition of water, the mixture was extracted with a large amount of Et_2O. The extract was evaporated *in vacuo* to give an oily residue, which was purified on a Sephadex LH-20 column with MeOH to afford *N*-ferulyltryptamine (**34**) (142 mg) as pale yellow needles from MeOH–$CHCl_3$–Et_2O. mp 163—165 °C. ^{1}H-NMR (100 MHz, CD_3OD) δ: 3.00 (2H, t, J=7.3 Hz), 3.61 (2H, t, J=7.3 Hz), 3.81 (3H, s), 6.42, 7.47 (each 1H, AB type, J=15.6 Hz), 6.75—7.81 (8H, m). IR (KBr): 3400, 1650, 1520 cm^{-1}. Mol. wt. Calcd for $C_{20}H_{20}N_2O_3$: 336. Found: MS m/z: 336 (M^+).

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References and Notes

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