the latter tests, it was given orally to rats, and their brain MAO became inhibited. It therefore passes through both the gut wall and the "blood-brain barrier". Since 7 has a nonmetabolizable group para to the amide nitrogen, it was sent for mutagenicity testing; 7 was found to be mutagenic in the Ames test with activation, performed by three different laboratories independently. It should be noted that 7 has been reported to give a slight incidence of tumors in 8-month rat carcinogenicity testing.[10]

The effect of electron withdrawal on mutagenicity was checked by preparing and subjecting to the Ames test the thioxanthen-9-one 10,10-dioxide analogue 8. This compound has two strongly electron-withdrawing groups and was found nonmutagenic with strains in which 7 was mutagenic (Table I). However, octanol-water partition coefficients [log P = log (concentration in octanol/concentration in water)][11] showed that 8 has a lower log P value (i.e., is less lipophilic) than 7. The 7-methyl, 7-ethyl, and 7-propyl homologues of 8, i.e., 9, 10, and 11,[12] were therefore prepared to ensure a lipophilicity range including that of 7 and subjected to the Ames test. The log P values of these[13] were shown (see Table I) to straddle that of 7, and all were found nonmutagenic in the systems in which 7 was mutagenic. To ensure that nonmutagenicity was not causally related specifically to the thioxanthone dioxide ring system present in 8-11, 2-(acetylamino)dibenzothiophene 9,9-dioxide (12) was also subjected to the Ames test and also was found to show no mutagenicity. This compound was negative in limited carcinogenicity testing.[10] Compounds 8-11 were found to be inhibitors of the MAO in mouse brains after intraperitoneal administration and so penetrated the "blood-brain barrier". Of course this does not prove their penetration into microsomes or into the strains of *Salmonella typhimurium* used in the mutagenicity testing. However, since penetration into the brain appears more restricted than microsomal oxidation in general, it is likely that these compounds would penetrate into the microsomal oxidation region.[14] Penetration of 7 into the test strains of *Salmonella* obviously occurs as shown by dose-related toxicity. Penetration of 8-12 was not proved, since toxicity due to these compounds did not occur at the highest dosage used. Penetration is commonly assumed in the Ames test; the tester strains have genetically defective cell walls, to ensure permeability to chemicals which are tested.

The results reported are in agreement with our theory that mutagenicity can be removed from an otherwise mutagenicity-causing pharmacophore by reducing the electron availability. Proof that this phenomenon is general for aryl amide carcinogens and that it can be generalized to functionalities other than aryl amide and from mutagenicity to carcinogenicity awaits further studies.

A recent publication[15] has reported a lowered rate of enzymatic N-hydroxylation of *p*-(substituted styryl)acetanilides due to an electron-withdrawing nitrile group, as anticipated. Another[16] has a regression curve in which σ^+ (i.e., electron input) correlates with increased Ames test mutagenicity and L1210 leukemia for 1-(substituted phenyl)-3,3-dialkyltriazines. These are probably carcinogenic and mutagenic after mono-N-dealkylation followed by N-N cleavage and ultimately carbonium ion formation, a complex situation to interpret but at least in agreement with our results despite the differing ultimate carcinogen.

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Articles

Thrombin Inhibitors. 1. Ester Derivatives of N^{α}-(Arylsulfonyl)-L-arginine

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A series of N^{α}-(arylsulfonyl)-L-arginine esters was prepared and tested as inhibitors of the clotting activity of thrombin. N^{α}-Dansyl-L-arginine methyl ester was the most inhibitory of the N^{α}-(arylsulfonyl)-L-arginine methyl esters. The most potent inhibitors were the *n*-propyl and *n*-butyl esters of N^{α}-dansyl-L-arginine with an I_{50} of 2×10^{-6} M. Esters of unsaturated straight-chain alcohols with a chain length of four carbons were also as inhibitory as the *n*-butyl ester. The inhibitors were hydrolyzed by thrombin and trypsin more slowly than N^{α}-tosyl-L-arginine methyl ester.

Thrombin catalyzes the formation of fibrin and stimulates the aggregation of platelets. Synthetic inhibitors of this enzyme are of interest as potential therapeutic and prophylactic agents for thrombotic diseases as well as re-

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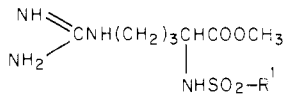
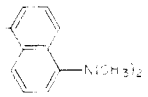
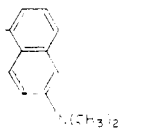
Table I. N^{α}-(Arylsulfonyl)-L-arginine Methyl Esters



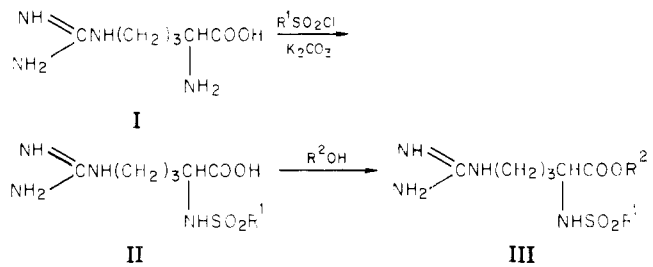
no.	R^1	mp,[a] °C	formula[b]	I_{50},[c] M
1[d]	p-CH_3-C_6H_4-			1.0×10^{-3}
2	p-Cl-C_6H_4-	e	$C_{13}H_{19}ClN_4O_4S \cdot HCl$	2.7×10^{-3}
3	p-OCH_3-C_6H_4-	145-147	$C_{14}H_{22}N_4O_5S \cdot HCl$	1.0×10^{-4}
4	m-NO_2-C_6H_4-	e	$C_{13}H_{19}N_5O_6S \cdot HCl$	2.9×10^{-3}
5	p-NH_2-C_6H_4-	e	$C_{13}H_{21}N_5O_4S \cdot HCl$	4.8×10^{-3}
6	p-NO_2-C_6H_4-	e	$C_{13}H_{19}N_5O_6S \cdot HCl$	2.4×10^{-3}
7	p-F-C_6H_4-	143-145	$C_{13}H_{19}FN_4O_4S \cdot HCl$	5.2×10^{-3}
8	-α-naphthyl	e	$C_{17}H_{22}N_4O_4S \cdot HCl$	5.2×10^{-4}
9	-β-naphthyl	183-186	$C_{17}H_{22}N_4O_4S \cdot HCl$	1.3×10^{-4}
10		145-150	$C_{19}H_{27}N_5O_4S \cdot HCl \cdot H_2O$	2.0×10^{-5}
11		e	$C_{19}H_{27}N_5O_4S \cdot 2HCl$	1.0×10^{-4}

[a] Melting points are uncorrected. [b] All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% of the theoretical values. [c] I_{50} was defined as the concentration at which the clotting time was prolonged by twice the control. [d] This compound is commercially available. [e] Amorphous solid.

search tools. Some amidino and guanidino compounds[1-6] and arginine derivatives,[7] such as N^{α}-tosyl-L-arginyl-sarcosine methyl ester, have been reported to exhibit the inhibition of thrombin, but they seem to be unsatisfactory in their selectivity or potency of the inhibition of thrombin.

Thrombin cleaves only specific arginyl bonds in fibrinogen and some other proteins and does not cleave any lysyl bonds in protein.[8] Thus, thrombin is a highly specific proteolytic enzyme. On the other hand, it is well known that synthetic arginine esters, such as N^{α}-tosyl-L-arginine methyl ester (TAME), are hydrolyzed by thrombin and inhibit the clotting activity of thrombin.[9] However, TAME is hydrolyzed with a rather broad specificity also by trypsin and other trypsin-like serine proteases. Since the binding specificity of arginine derivatives would be determined by the structure of both sides of arginine, amino and carboxyl sides, a series of studies were undertaken to obtain potent and specific inhibitors to thrombin by modification of the N^{α}-substituent and methyl ester portions of TAME. As the first stage, we investigated the effect of variation of the substituent on the α-nitrogen and the ester alcohol portion of N^{α}-substituted L-arginine esters on the inhibition of thrombin and susceptibility to enzyme hydrolysis. A part of this work has been reported briefly[10] and orally presented.[11,12]

Scheme I



Chemistry. The various derivatives of L-arginine esters were synthesized according to Scheme I. L-Arginine (I) was sulfonylated with an appropriate arylsulfonyl chloride at the α-amino group in the presence of an inorganic base, such as K_2CO_3, or organic base, such as Et_3N. Then the corresponding N^{α}-(arylsulfonyl)-L-arginine (II) was converted to N^{α}-(arylsulfonyl)-L-arginine ester (III) with an appropriate ROH and thionyl chloride or p-toluenesulfonic acid. These compounds were purified by recrystallization or reprecipitation and lyophylized if necessary.

Enzyme Results and Discussion

The potency of the synthetic arginine derivatives as inhibitors of thrombin was measured in the assay system of clotting activity using commercial topical bovine

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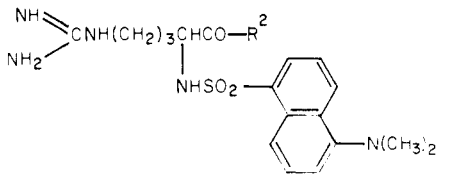
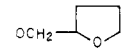
Table II. N^{α}-Dansyl-L-arginine Esters



no.	R^2	mp,[a] °C	formula[b]	I_{50},[c] M
12	OH	199-200	$C_{18}H_{25}N_5O_4S$	$>10^{-3}$
10	OCH_3	145-150	$C_{19}H_{27}N_5O_4S \cdot 2HCl \cdot H_2O$	2.0×10^{-5}
13	OC_2H_5	140-144	$C_{20}H_{29}N_5O_4S \cdot 2HCl$	8.0×10^{-6}
14	O-*n*-C_3H_7	*d*	$C_{21}H_{31}N_5O_4S \cdot 2HCl$	2.0×10^{-6}
15	O-*n*-C_4H_9	160-164	$C_{22}H_{33}N_5O_4S \cdot 2TsOH$	2.0×10^{-6}
16	O-*n*-C_5H_{11}	164-169	$C_{23}H_{35}N_5O_4S \cdot 2TsOH$	4.9×10^{-5}
17	O-*n*-C_6H_{13}	190-193	$C_{24}H_{37}N_5O_4S \cdot 2TsOH$	1.0×10^{-5}
18	$OCH(CH_3)_2$	110-120	$C_{21}H_{31}N_5O_4S \cdot 2HCl$	3.0×10^{-5}
19	$OCH_2CH(CH_3)_2$	146-151	$C_{22}H_{33}N_5O_4S \cdot 2TsOH$	1.0×10^{-5}
20	$OCH(CH_3)CH_2CH_3$	145-150	$C_{22}H_{33}N_5O_4S \cdot 2TsOH$	2.0×10^{-3}
21	$OCH_2C(C_2H_5)H(CH_2)_3CH_3$	170-174	$C_{26}H_{41}N_5O_4S \cdot 2TsOH$	5.0×10^{-5}
22	$OCH_2C_6H_5$	150-153	$C_{25}H_{31}N_5O_4S \cdot 2TsOH$	2.0×10^{-6}
23	$O(CH_2)_3Cl$	140-145	$C_{21}H_{30}ClN_5O_4S \cdot 2TsOH$	4.0×10^{-6}
24	$O(CH_2)_4Cl$	177-194	$C_{22}H_{32}ClN_5O_4S \cdot 2TsOH$	7.3×10^{-6}
25	$OCH_2CH{=}CHCH_3$	148-153	$C_{22}H_{31}N_5O_4S \cdot 2TsOH$	2.0×10^{-6}
26	$OCH_2CH_2C{\equiv}CH_3$	133-143	$C_{22}H_{29}N_5O_4S \cdot 2TsOH$	4.0×10^{-6}
27	$OCH_2CH_2OCH_3$	171.5-173	$C_{21}H_{31}N_5O_5S \cdot 2TsOH$	5.0×10^{-6}
28	O-c-C_6H_{11}	177-182	$C_{24}H_{35}N_5O_4S \cdot 2TsOH$	6.0×10^{-5}
29		144-150	$C_{23}H_{33}N_5O_5S \cdot 2TsOH$	2.0×10^{-5}
30	$OCH_2CH(NO_2)CH_2CH_3$	155-163	$C_{22}H_{32}N_6O_6S \cdot 2TsOH$	2.0×10^{-4}
31	S-*n*-C_4H_9	95-105	$C_{22}H_{33}N_5O_3S_2 \cdot 2TsOH$	2.0×10^{-5}
32	OCH_3[e]	*d*	$C_{19}H_{27}N_5O_4S \cdot 2HCl$	2.0×10^{-3}

[a-c] See corresponding footnotes in Table I. [d] Amorphous solid. [e] D-Arginine was used.

thrombin. Since α-thrombin possesses much higher fibrinogen-clotting activity than β- or γ-thrombin, the inhibition of clotting activity in this study would be regarded as the inhibition resulting from the interaction between α-thrombin and the inhibitors, i.e., arginine derivatives. I_{50} values were determined by the measurement of clotting time in the presence of varying amounts of inhibitors, and their standard errors were 15–20% when calculated for some inhibitors (ten measurements).

Substituted benzenesulfonyl compounds (Table I) were less inhibitory than TAME, except N^{α}-[(*p*-methoxybenzene)sulfonyl]-L-arginine methyl ester (**3**). Unsubstituted naphthalenesulfonyl compounds **8** and **9** were more inhibitory than TAME. The introduction of a dimethylamino group into the naphthalene ring resulted in an increase in the inhibitory effect, and N^{α}-[5-(dimethylamino)naphthalene-1-sulfonyl]-L-arginine (dansyl-L-arginine) methyl ester (**10**) was the most inhibitory to thrombin of the N^{α}-substituted L-arginine methyl esters, showing an I_{50} 50 times smaller than that for TAME. Further work was therefore focused on N^{α}-dansyl-L-arginine derivatives.

The variation of the alcohol portion of the N^{α}-dansyl-L-arginine ester caused a substantial change in inhibitory potency (Table II). The change of methyl ester to *n*-propyl ester (**14**) or *n*-butyl ester (**15**) resulted in a 10 times increase in inhibitory potency. However, the *n*-pentyl ester **16** or *n*-hexyl ester **17** was less inhibitory than the *n*-propyl or *n*-butyl ester. The inhibitory effect was totally lost by deprivation of an ester group, as in **12**. Butyl thioester **31** was also less inhibitory than *n*-butyl ester **15**. Branched chain alkyl esters **18**–**21** showed less potent inhibition than the corresponding straight chain alkyl esters. An inhibition as potent as that for *n*-butyl ester **15** was observed with esters of unsaturated straight-chain alcohols or substituted straight-chain alcohols with a chain length corresponding to four carbon atoms, as in **23** and **25**–**27**. These results suggest that the binding site of thrombin for the carboxyl side fixes a straight-chain alkyl group with a carbon number of three to four most effectively. The far less inhibition of N^{α}-dansyl-D-arginine methyl ester (**32**) suggests the absolute requirement of the L configuration of arginine for binding to thrombin.

Table III. Hydrolysis of N^{α}-Dansyl-L-arginine Esters by Thrombin and Trypsin

	rel hydrolysis rate by[a]	
no.	thrombin	trypsin
1	1.00	1.00
10	0.093	0.58
13	0.080	0.49
14	0.090	0.53
15	0.082	0.54
27	0.077	0.49
23	0.084	0.50

[a] Hydrolysis rate of TAME (1) was given as 1.00.

N^{α}-Dansyl-L-arginine esters were examined for susceptibility to enzyme hydrolysis at 1 mM concentration (Table III). All of the examined compounds were hydrolyzed by thrombin or trypsin. The rate of hydrolysis was approximately one-tenth and one-half that of TAME hydrolysis by thrombin and trypsin, respectively.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The results of elemental analyses were within ±0.4% of the theoretical values. Compounds were checked by IR on a JASCO IR-A2, and the spectral data were consistent with the assigned structure in all cases. TLC was performed on fluorescent silica gel plates (Merck) to a distance of 20 cm with a solvent system of *n*-BuOH–acetic acid–water (3:1:1), and spots were detected under a UV lamp or by exposure to I_2 vapor. In the following, experimental details are presented

for typical examples of the synthetic method (Scheme I).

N^{α}-Dansyl-L-arginine (12). To a solution of L-arginine (10.8 g, 62 mmol) and K_2CO_3 (23.7 g, 172 mmol) in H_2O (100 mL) was added dansyl chloride (25 g, 92.7 mmol) in Et_2O (100 mL) with stirring at 0–5 °C. After the solution was stirred for 2 days at room temperature, the precipitate was collected, washed with H_2O (30 mL) and Et_2O (30 mL) successively, and then recrystallized from 50% aqueous MeOH to give 12 (20.4 g, 81.0%): mp 199–200 °C.

N^{α}-Dansyl-L-arginine Methyl Ester Dihydrochloride Monohydrate (10). A suspension of 12 (1.0 g, 2.5 mmol) in MeOH (15 mL) was cooled to 0–5 °C and $SOCl_2$ (2.4 g, 25 mmol) was added dropwise with vigorous stirring. After stirring for 2 h at room temperature, the mixture was refluxed for 2 h. After evaporation of the solvent from the mixture, the residue was triturated in cooled H_2O and Et_2O. The solid obtained was recrystallized from MeOH–Et_2O to yield 10 (1.2 g, 92%): mp 147–150 °C.

N^{α}-Dansyl-L-arginine *n*-Butyl Ester Bis(*p*-toluenesulfonate) (15). A mixture of 12 (1.0 g, 2.5 mmol), *p*-TsOH·H_2O (1.0 g, 5.3 mmol), and *n*-BuOH (10 mL) was heated for 30 min at 100 °C. After the addition of benzene (100 mL), the mixture was refluxed for 3 h with removing water by azeotropic distillation. The solvent was evaporated in vacuo and the residue was triturated in petroleum ether–Et_2O, filtered, and recrystallized from acetone to give 15 (1.9 g, 95%): mp 160–164 °C.

Inhibition Studies of Clotting Activity of Thrombin. To the mixture of 0.8 mL of 0.12% fibrinogen dissolved in borate-saline buffer (pH 7.4) and 0.1 mL of various concentrations of the inhibitor to be tested was added 0.1 mL of 5 units/mL bovine thrombin (Mochida Pharmaceutical). The assay was carried out at 25 °C, and the time from the addition of thrombin to the formation of a clot was recorded.

Hydrolysis Studies by Thrombin and Trypsin. The rates of hydrolysis of test compounds were determined titrimetrically at 37 °C and pH 8.0 with a pH-stat fitted with an automatic burette (Toa Electronics). The reaction mixture contained 1 mM test compounds, 0.15 M KCl, and 50 units of thrombin or 1.8 μg of trypsin in a total volume of 7 mL.

Acknowledgment. The authors thank M. Sugano and A. Sugiyama for their technical assistance and Dr. S. Hattori, General Manager of Biosciences Laboratory, Central Research Laboratories, Mitsubishi Chemical Industries Limited, for his valuable advice and encouragement throughout the work. We are also indebted to members in Systems Engineering Laboratory, Central Research Laboratories, Mitsubishi Chemical Industries Limited, for elemental analyses.

Thrombin Inhibitors. 2. Amide Derivatives of N^{α}-Substituted L-Arginine

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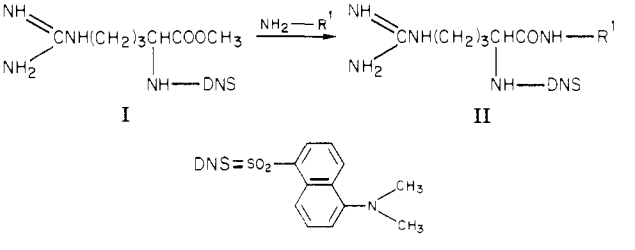
A series of N^{α}-(arylsulfonyl)-L-arginine amide derivatives with substituted or unsubstituted naphthalene and heterocyclic compounds as the N^{α}-substituent was prepared and tested as inhibitors of the clotting activity of thrombin. *N*-*n*-Butyl and *N*-*n*-butyl-*N*-methyl derivatives of N^{α}-dansyl-L-arginine amide were the most inhibitory of *N*-alkyl and *N*,*N*-dialkyl derivatives of N^{α}-dansyl-L-arginine amide. Their inhibitory effect was as potent as that of N^{α}-dansyl-L-arginine *n*-butyl ester, with an I_{50} of 2×10^{-6} M. N^{α}-Substituted naphthalenesulfonyl-L-arginine amide derivatives of 4-methyl- and 4-ethylpiperidine also showed a potent inhibition with an I_{50} of 10^{-7} to 10^{-6} M. The most potent inhibitor in this study was 1-[N^{α}-(4,6-dimethoxynaphthalene-2-sulfonyl)-L-arginyl]-4-methylpiperidine, with an I_{50} of 7.5×10^{-8} M. Arginine amide derivatives of 4-methyl- or 4-ethylpiperidine with tetralin or an oxygen-containing heterocyclic compound as a N^{α}-substituent showed an inhibition with an I_{50} less than 10^{-5} M. N-Monosubstituted derivatives of N^{α}-dansyl-L-arginine amide were not hydrolyzed at all by thrombin and were hydrolyzed very slowly by trypsin, and N,N-disubstituted derivatives were not hydrolyzed at all by both enzymes.

N^{α}-Dansyl-L-arginine *n*-propyl or *n*-butyl ester has been shown to inhibit the clotting activity of thrombin but to be hydrolyzed by thrombin and trypsin.[1] Therefore, these compounds are considered to be hydrolyzed easily in vivo and would be inappropriate as an antithrombotic agent. It is, however, noteworthy that compounds with a high affinity to thrombin were found in L-arginine derivatives. We therefore aimed to obtain thrombin-inhibitory L-arginine amide derivatives which have the advantage of protection from hydrolysis. In this paper, we synthesized various N^{α}-(arylsulfonyl)-L-arginine amide derivatives with substituted or unsubstituted naphthalene and heterocyclic compounds in N^{α}-substituents and examined the inhibitory effect on thrombin in order to investigate the relationship between a structure and an inhibitory effect on thrombin. A part of this work has been reported briefly[2] and presented orally.[3,4]

Scheme I



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