carbonate. The aqueous solution was extracted with chloroform/2-propanol (2/1, 2 × 200 mL). The organic phases were washed with sodium thiosulfate (10%, 30 mL), dried (Na_2SO_4), filtered, and evaporated to give the **8** as an oil in 80% yield (110 mg): ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1 H), 6.82 (s, 1 H), 4.4–4.3 (m, 1 H), 4.2–3.9 (m, 2 H), 3.62 (s, 3 H), 3.7–3.5 (m, 1 H), 3.1–2.9 (m, 2 H), 2.78 (m, 1 H), 1.20 (t, 3 H).

The free base **8** was crystallized as the hemifumarate salt by adding a solution of fumaric acid (55 mg, 0.48 mmol) to a solution of **8** (100 mg, 0.48 mmol) in 2-propanol. The salt crystallized upon addition of ether: yield, 109 mg, 70%; mp 129–131 °C; ^{1}H NMR (D_2O) δ 8.70 (s, 1 H), 7.32 (s, 1 H), 6.60 (s, 2 H), 4.6–4.3 (m, 2 H), 4.18 (m, 1 H), 3.86 (s, 3 H), 3.6–3.4 (m, 1 H), 3.3–3.1 (m, 3 H), 1.20 (t, 3 H); $[\alpha]^{22}_D$ 40.3° (*c* 1.0, H_2O). Anal. ($C_{14}H_{19}N_3O_6$) C, H. N.

(*S*)-3-Ethyl-4-[(4′-imidazolyl)methyl]-2-oxazolidinone (9) Fumarate. Compound **6** (1.00 g, 3.50 mmol) was dissolved in liquid ammonia (50 mL) at −70 °C, and sodium pieces were added to a permanent blue color. The reaction mixture was stirred at −70 °C for 2 min, and ammonium chloride was added to quench excess sodium. The ammonia was allowed to evaporate spontaneously at room temperature. The residue was dissolved in water (20 mL) and extracted with chloroform/2-propanol (2/1, 2 × 70 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated. Crystallization from toluene gave **9** (483 mg, 71% yield) as yellow crystals: mp 92–93 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 1 H), 6.90 (s, 1 H), 4.4–4.1 (m, 3 H), 3.7–3.5 (m, 1 H), 3.3–3.0 (m, 2 H), 2.9–2.7 (m, 1 H), 1.20 (t, 3 H). Anal. ($C_9H_{13}N_3O_2$) C, H, N.

A sample of **9** (70 mg, 0.36 mmol) was crystallized as the fumarate salt by adding a solution of fumaric acid (42 mg, 0.36 mmol) in 2-propanol to a solution of **9** in 2-propanol. The **9** fumarate crystallized upon addition of ether (78 mg, 70% yield): mp 157–160 °C; ^{1}H NM (D_2O) δ 8.65 (s, 1 H), 7.34 (s, 1 H), 6.68 (s, 2 H), 4.4–4.2 (m, 2 H), 4.18 (m, 1 H), 3.5–3.4 (m, 1 H), 3.3–3.1 (m, 3 H), 1.20 (t, 3 H); $[\alpha]^{22}_D$ 23.3° (*c* 0.46, H_2O). Anal. ($C_{13}H_{17}N_3O_6$) C, H, N.

(*S*)-3-Ethyl-4-[(1′-methyl-4′-imidazolyl)methyl]-2-oxazolidinone (10) Fumarate and (*S*)-3-Ethyl-4-[(1′-methyl-5′-imidazolyl)methyl]-2-oxazolidinone (8) Fumarate. A solution of **9** (382 mg, 1.96 mmol) in THF (40 mL) was added to a suspension of potassium hydride (2.1 mmol) in THF (10 mL). The suspension was stirred for 15 min at room temperature and methyl iodide (141 μL, 2.1 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, filtered, and evaporated. The residue (365 mg, 98%) contained **8** and **10** in a 1/2 mixture. Separation by preparative TLC gave pure **10** (145 mg, 35% yield) as the upper spot and pure **8** (60 mg, 15% yield) as the lower spot; both compounds were obtained as oils. **10**: ^{1}H NMR ($CDCl_3$) δ 7.39 (s, 1 H), 6.72 (s, 1 H), 4.4–4.1 (m, 3 H), 3.67 (s, 3 H), 3.71–3.5 (m, 1 H), 3.3–3.1 (m, 1 H), 3.00 (dd, 1 H), 2.70 (dd, 1 H), 1.20 (t, 3 H). The ^{1}H NMR spectra of compound **8** was identical with the product from debenzylation of compound **7**.

Crystallization of **10** as the fumarate salt from 2-propanol gave either the fumarate salt, mp 100–104 °C [Anal. ($C_{14}H_{19}N_3O_6$)] or the hemifumarate salt: mp 133–135 °C; $[\alpha]^{22}_D$ 38.3° (*c* 0.75, H_2O); ^{1}H NMR (D_2O) δ 8.59 (s, 1 H), 7.31 (s, 1 H), 6.53 (s, 1 H), 4.5–4.3 (m, 2 H), 4.15 (m, 1 H), 3.86 (s, 3 H), 3.6–3.4 (m, 1 H), 3.3–3.1 (m, 3 H), 1.20 (t, 3 H). Anal. ($C_{12}H_{17}N_3O_4$) C, H, N.

Cross-Ring Coupling Constants. The cross-ring coupling constants of compounds **6**, **8**, and **10** were measured on a Bruker AM500 spectrometer operating at 500.13 MHz. The experiments were done in $CDCl_3$ at room temperature, using the imidazole 2-H resonance. We employed the resolution enhancement techniques of single zero filling and a squared sine bell apodization in addition to homonuclear decoupling of the *N*-methylene group of **6** or the *N*-methyl group of **8** and **10**.

Guinea Pig Bioassay. We used the bioassay method described by the Edinburgh staff.[13] Briefly, a distal portion of guinea pig ileum was cut and a segment (1–1.5 cm) was tied at both ends. One end was connected to a force displacement transducer and the other end to a muscle holder in a 5-mL organ bath. The tissue was suspended with 1 g tension in Tyrode solution (composition as follows in mM: NaCl 137, KCl 2.7, $CaCl_2$ 1.8, $MgCl_2$ 1.0, $NaHCO_3$ 11.9, Na_2HPO_4 0.4, glucose 5.6; pH 7.4) which was aerated with 95% O_2 and 5% CO_2 and maintained at 37 °C. After the tissue was allowed to equilibrate for 45–60 min, single doses of agonists were administered into the bath and isotonic contractions were recorded on a Grass polygraph.

Acknowledgment. We thank John F. O'Connell for assistance in determining the cross-ring coupling constants. Per Sauerberg was a Danish Research Council/Fulbright Scholar.

Registry No. 1, 16832-24-9; **2**·2 *p*-$CH_3C_6H_4SO_3H$, 116438-47-2; **3**, 119998-67-3; **4**, 119998-68-4; **5**, 119998-69-5; **6**, 119998-70-8; **7**, 119998-71-9; **8**, 119998-72-0; **8**·fumarate, 119998-78-6; **9**, 119998-73-1; **9**·fumarate, 119998-74-2; **10**, 119998-75-3; **10**·fumarate, 119998-76-4; **10**·$^1/_2$fumarate, 119998-77-5; L-histidine, 71-00-1.

Thromboxane A_2 Synthetase Inhibitors. 2. Syntheses and Activities of Tetrahydronaphthalene and Indan Derivatives

Munefumi Kanao,* Yoshifumi Watanabe, Youichi Kimura, Junji Saegusa, Kenjiro Yamamoto, Hideyuki Kanno, Naoaki Kanaya, Hideo Kubo, Shin-ichiro Ashida, and Fumiyoshi Ishikawa

Research Institute, Daiichi Seiyaku Co., Ltd., 13 Kita-kasai 1-16, Edogawa-ku, Tokyo 134, Japan.
Received September 12, 1988

A series of 1-imidazolylalkyl-substituted or 5-thiazolylalkyl-substituted tetrahydronaphthalenecarboxylic acid and indancarboxylic acid derivatives were prepared and tested for the inhibitory activities of thromboxane A_2 (TXA_2) production in vitro and ex vivo. Most of the compounds showed potent TXA_2 synthetase inhibitory activities in vitro and had long duration of inhibition of TXA_2 production in rats when orally or intravenously administrated. The imidazole analogues had slightly less potency in vitro than the thiazole analogues, but the activities of the imidazole analogues in ex vivo models were equal or superior to the activities of the thiazole analogues. 6-(1-Imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid hydrochloride hemihydrate (**47a**, DP-1904) was chosen for clinical studies.

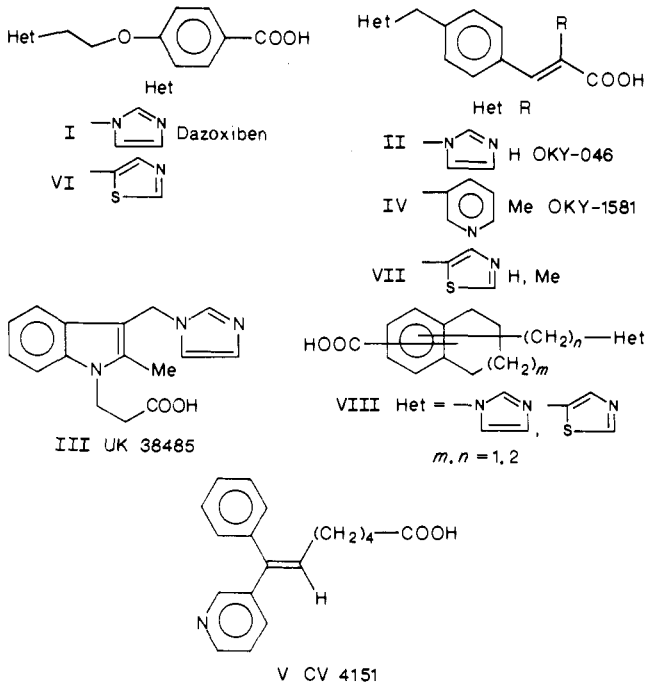
Thromboxane A_2 (TXA_2) and prostacyclin (PGI_2) are natural bioactive compounds and are produced from prostaglandin G_2 (PGG_2) and/or prostaglandin H_2 (PGH_2) by TXA_2 synthetase and PGI_2 synthetase, respectively. TXA_2 has potent vasoconstricting and platelet-aggregating activities.[1]

Selective TXA_2 synthetase inhibitors that do not inhibit PGI_2 synthetase and cyclooxygenase were noted as ther-

(1) (a) Moncada, S.; Vane, J. R. *Pharmacol. Rev.* **1979**, *30*, 293. (b) Needleman, P.; Wyche, A.; Raz, A. *J. Clin. Invest.* **1979**, *63*, 345.

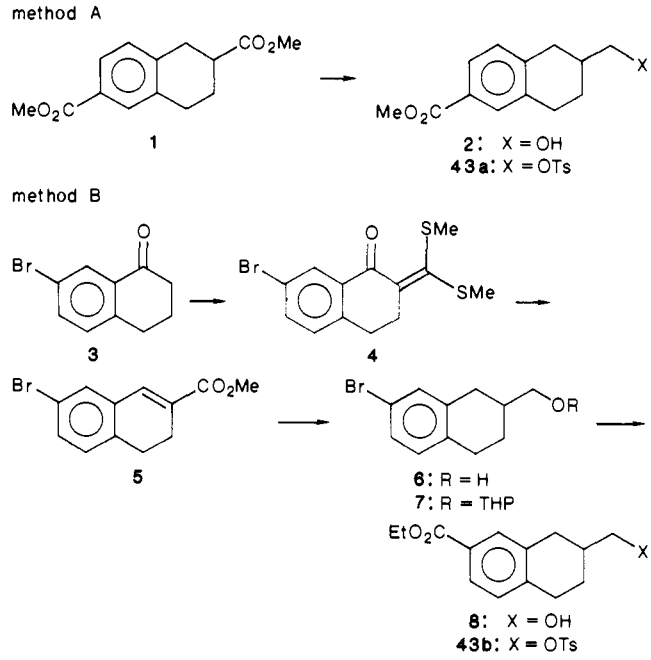
0022-2623/89/1832-1326$01.50/0

Chart I

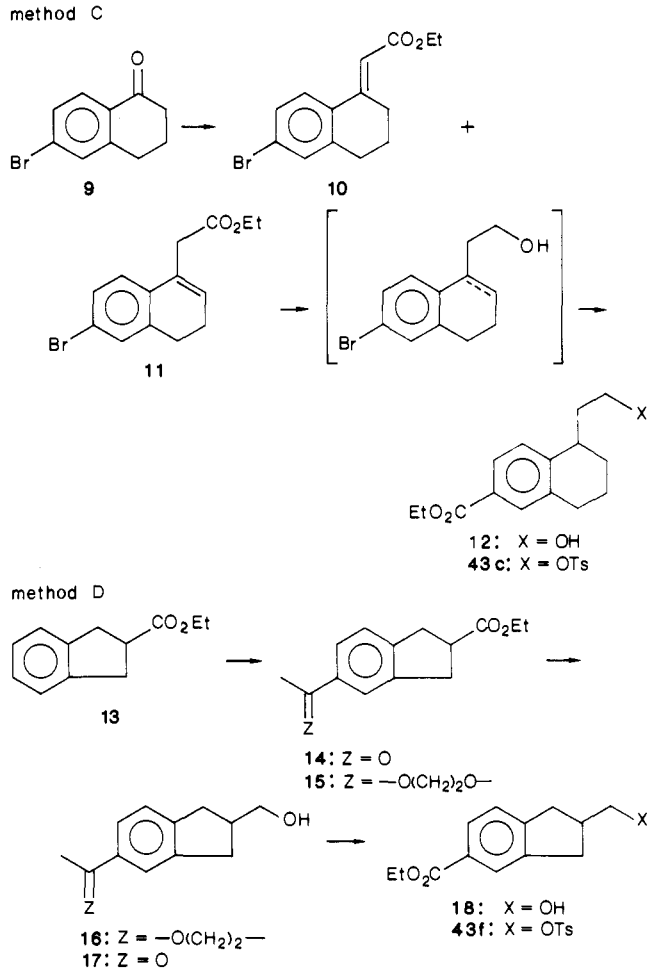


apeutic agents for ischemic heart disease, thromboembolic disorders, and cerebral circulatory disorders.[2] It has been theorized that the complete and long-lasting suppression of TXA_2 is necessary in the ischemic heart disease because of the highly potent biological activities of TXA_2. Thus potent and long-lasting agents will be of value in the treatment of ischemic heart disease. Many potent compounds have been reported: 4-[2-(1-imidazolyl)ethoxy]-benzoic acid (I, UK-37248-01, dazoxiben;[3] see Chart I), 3-[4-(1-imidazolylmethyl)phenyl]-2-propenoic acid (II, OKY-046),[4] 3-[3-(imidazolylmethyl)-2-methylindol-1-yl]-propionic acid (III, UK-38485),[5] 2-methyl-3-[4-(3-pyridylmethyl)phenyl]-2-propenoic acid (IV, OKY-1581),[6] and (*E*)-m-phenyl-7-(3-pyridyl)-6-heptenoic acid (V, CV-4151).[7] These compounds have a basic heterocyclic ring, such as 1-substituted imidazole or 3-substituted pyridine, and a carboxyl group at the end of the substituent. We have previously reported that 5-substituted thiazole derivatives (VI, VII) also possess the inhibitory activity of TXA_2 production, which was equal to that of imidazole or pyridine derivatives.[8] Some studies[4,7] of structure–activity relationships have shown that the distance between N-1 of the imidazole ring and the carboxyl group is important and optimal in the range of 8.5–10 Å. We presumed that introduction of a relatively rigid structure such as naphthalene or indan into the molecule would keep the above distance essentially constant and also affect the molecular affinity to the target enzyme. On the basis of this assumption, we designed the structure represented as VIII, which contains imidazole or thiazole as the hetero-

Scheme I

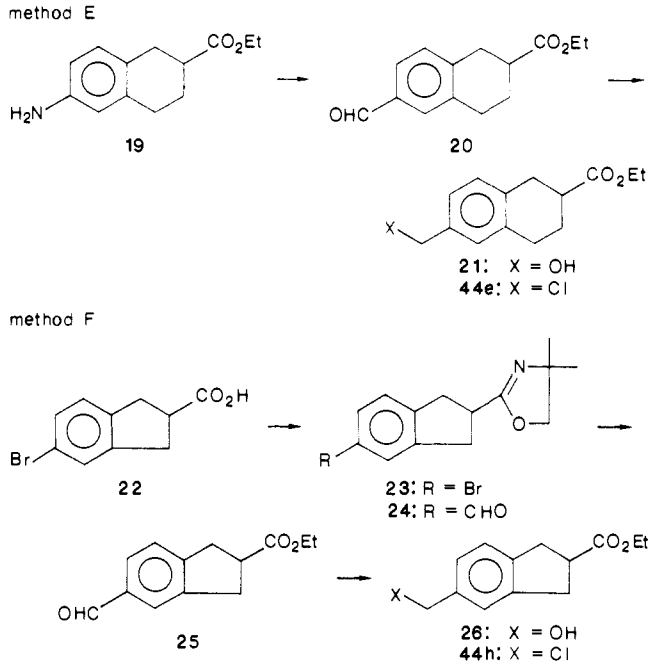


Scheme II

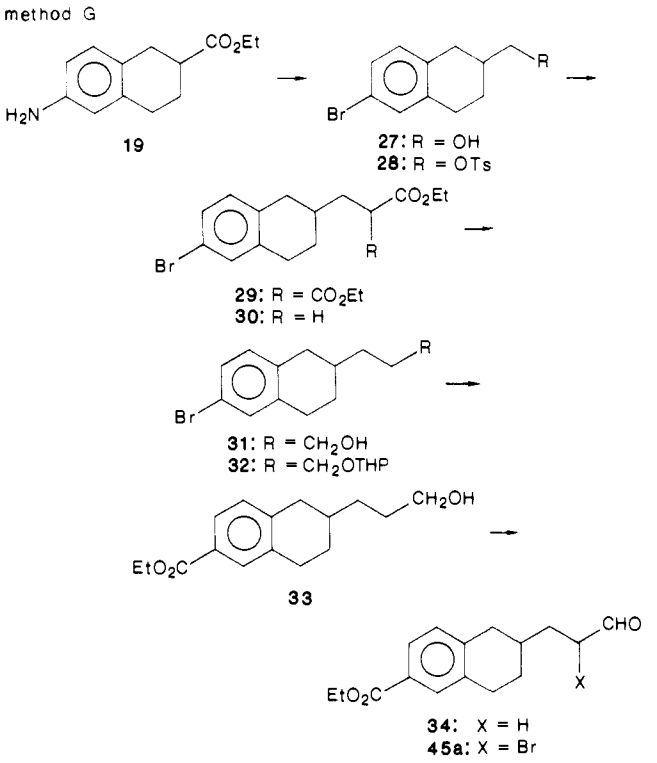


(2) (a) Lefer, A. M.; Messenger, M.; Okamatsu, S. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1982**, *321*, 130. (b) Sefreyn, G.; Deckmyn, H.; Vermylen, J. *Thrombosis Res.* **1982**, *26*, 389.
(3) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1985**, *28*, 1427.
(4) Iizuka, K.; Akahane, K.; Momose, D.; Nakazawa, M.; Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M. *J. Med. Chem.* **1981**, *24*, 1139.
(5) Cross, P. E.; Dickinson, R. P.; Parry, M. J.; Randall, M. J. *J. Med. Chem.* **1986**, *29*, 342.
(6) Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Taniguchi, K.; Miyamoto, T.; Hayashi, M.; Iizuka, K.; Momose, D.; Nakazawa, M. *J. Med. Chem.* **1981**, *24*, 1149.
(7) Kato, K.; Ohkawa, S.; Terao, S.; Terashita, Z.; Nishizawa, K. *J. Med. Chem.* **1985**, *28*, 287.
(8) Kanao, M.; Kimura, Y.; Kanno, H.; Watanabe, Y.; Kubo, H.; Ashida, S. *Chem. Pharm. Bull.* **1988**, *36*, 2968.

Scheme III



Scheme IV



cycle and the carboxylic acid attached to the carbocyclic ring. Synthesis and biological evaluation of this series of compounds are described in the present paper.

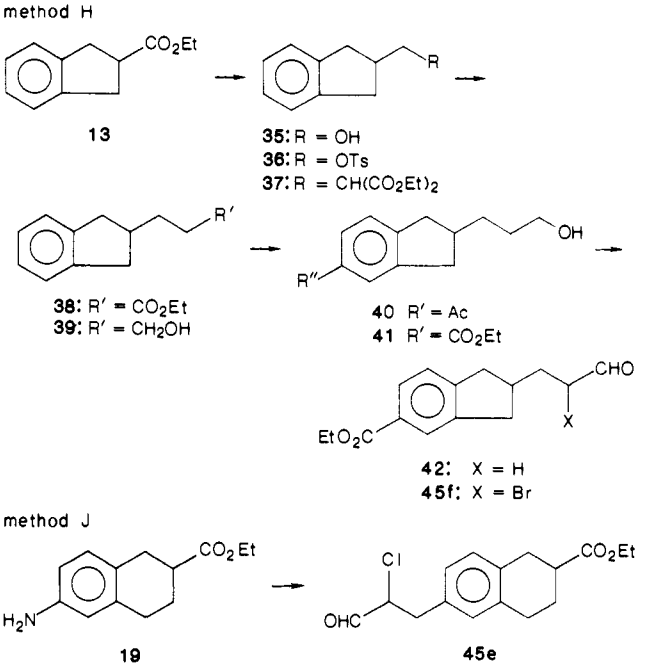
Chemistry

Syntheses of the desired tetrahydronaphthalene and indan derivatives were carried out by the synthetic routes shown in Schemes I–VII.

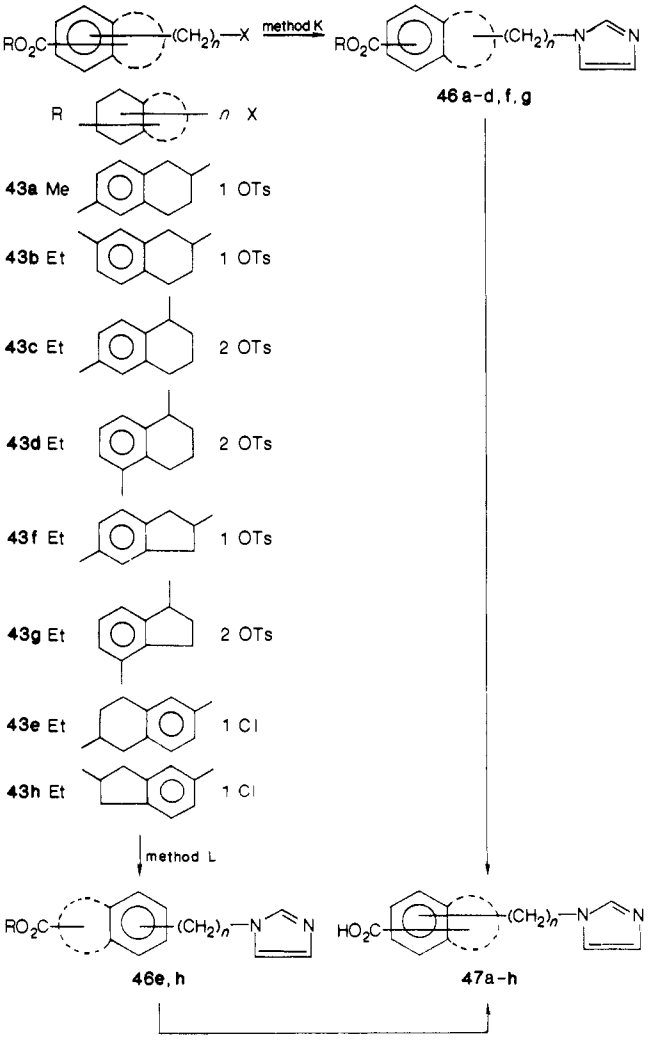
The tosylates **43** and the chlorides **44**, the intermediates for prepartion of the desired imidazole derivatives **47**, were synthesized by methods A–F as follows.

Methyl 6-[(tosyloxy)methyl]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (**43a**), as an intermediate for preparation of the 6-(1-imidazolylmethyl) analogue (**47a**),

Scheme V

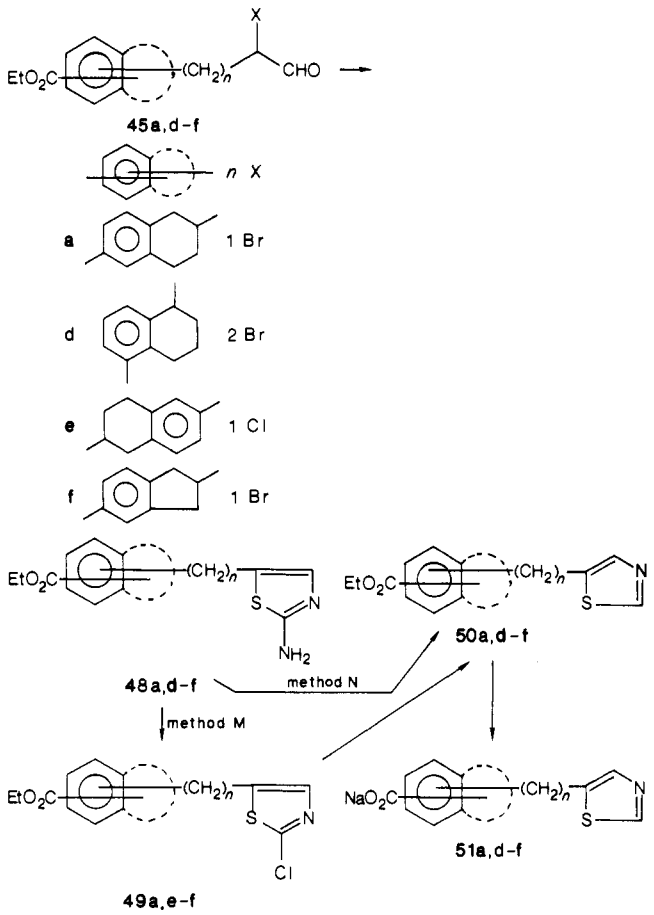


Scheme VI



was prepared from the diester **1**. Reduction of **1** with a mixture of sodium borohydride and trifluoroacetic acid gave the alcohol **2**, tosylation of which afforded **43a** (method A).

Scheme VII



7-Bromo-1-tetralone (**3**) was converted to the ester **5** by a similar method to that described by Myrboh.[9] The ester **5** was reduced and then treated with dihydropyran to give **7**. Grignard reaction of **7** with CO_2 followed by esterification gave **8**, which was tosylated to give compound **43b** (method B).

Wittig–Horner reaction of 6-bromo-1-tetralone (**9**) gave a mixture of **10** and **11**. The mixture was reduced with lithium aluminum hydride, and then the crude alcohols were treated with dihydropyran to give THP ethers. The Grignard reagent of the THP ethers was treated with CO_2 to give a mixture of acids which were esterified. The esters obtained here were hydrogenated to give **12**, which was converted to the tosylate **43c** (method C). Compounds **43d** and **43g** were also synthesized by this method, respectively.

Compound **43f**, an intermediate of the preparation for **47f**, was synthesized from ethyl indan-2-carboxylate (**13**) by method D shown in Scheme II. The ketone **14** prepared from **13** by acetylation was converted to the ketal **15**. The preparation of the desired **43f** and **15** was carried out by reduction with LAH, hydrolysis, oxidation with iodide and pyridine, and tosylation, successively.

The chloro derivative **44e** was synthesized from **19**. Compound **9** was converted to the aldehyde **20**, which was reduced with sodium borohydride, followed by chlorination to give compound **44e** (method E).

Preparation of ethyl 5-(hydroxymethyl)indan-2-carboxylate (**44h**) was carried out by the method as follows. 5-Bromoindan-2-carboxylic acid (**22**), prepared from 4-bromo-1,2-xylene according to the method described by Newman,[10] was treated with 2-amino-2-methyl-1-propanol to give oxazoline **23**. The Grignard reagent of **23** was treated with *N,N*-dimethylformamide, and crude **24** was esterificated to give **25**. Compound **25** was reduced and then chlorinated to give the desired **44h** (method F).

Syntheses of the halogenoaldehydes (**45a** and **-d–f**), the intermediates for preparation of thiazole derivatives, were carried out by methods G–J described below. 6-Bromo-2-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (**27**), prepared from **19**, was tosylated, and then the tosylate **28** was treated with sodium diethyl malonate to give the diester **29**. Compound **29** was converted to **30** by hydrolysis, decarboxylation, and esterification. Compound **30** was converted to the alcohol **33** according to a method described for the preparation of **8** from **6**. Oxidation of **33** with pyridinium chlorochromate gave the aldehyde **34**, which was converted to the bromoaldehyde **45a** by bromination with bromine in dioxane-CH_2Cl_2 (method G).

Ethyl 2-(2-bromo-2-formylethyl)indan-2-carboxylate (**45f**) was prepared from ethyl indan-2-carboxylate (**13**) by the route shown in Scheme V. Compound **13** was reduced by the method described by Soai[11] to give indan-2-methanol (**35**). 3-(Indan-1-yl)-1-propanol (**39**) was obtained from compound **35** by a method described for the preparation of **31** from **27**. Introduction of an ethoxycarbonyl group to **39** was carried out by Friedel–Crafts reaction, followed by oxidation and esterification. The compound **41** thus obtained was converted to the bromoaldehyde **45f** by the method described in the preparation of **45a** (method H).

Ethyl 6-(2-chloro-2-formylethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**45e**), an intermediate for preparation of the desired thiazole analogue **51e**, was prepared from the amine **19** (method J).

The desired imidazole derivatives were prepared from the tosylates **43** or the halides **44** by method K or L shown in Scheme VI. Condensation of the tosylates (**43a**, **-d**, **-f**, and **-g**) with imidazole in the presence of sodium hydride gave the esters (**46a**, **-d**, **-f**, and **-g**), which were converted to the desired compounds (**47a**, **-d**, **-f**, and **-g**) by hydrolysis (method K).

Treatment of the chloromethyl analogues (**44e** and **-h**), prepared by method E and F, with 1-acetylimidazole and then hydrolysis gave the desired compounds (**47e** and **-h**), respectively (method L).

The desired thiazole derivatives **51** were synthesized from the haloaldehydes **45** according to methods M and N shown in Scheme VII.

The haloaldehydes **45**, prepared by method G, H, or J, were treated with thiourea to give 2-aminothiazole derivatives **48**. Compounds (**48a**, **-d**, and **-f**) were converted to the desired compounds (**51a**, **-d**, and **-f**) by Sandmeyer reaction, followed by reduction and hydrolysis (method M).

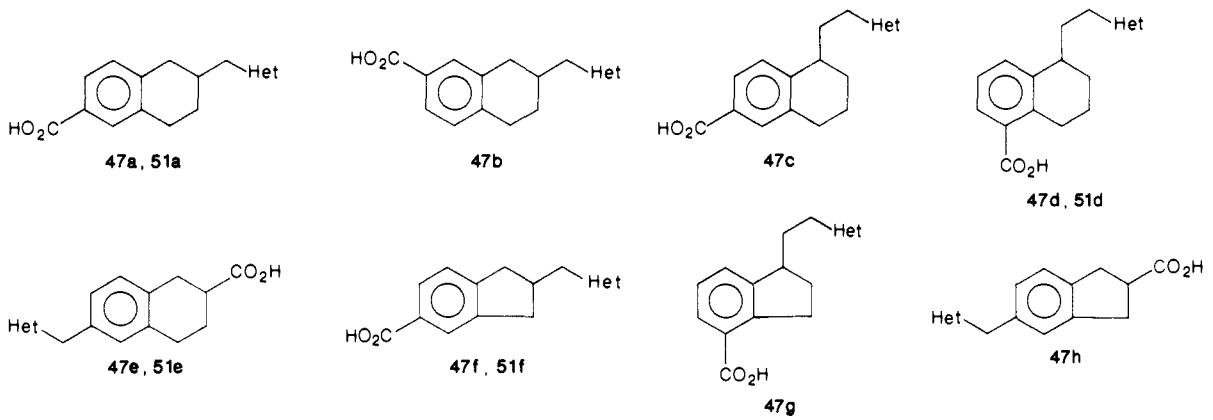
The compound **51e** was prepared from the 2-aminothiazole analogue **48e** by direct deamination according to a method similar to that described by Doyle[12] (method N).

Biological Evaluation and Discussion

The activities against TXA_2 production of the compounds obtained here are shown in Table I. In this paper, the activities were determined by measuring the IC_{50} values for the inhibition of TXA_2 production in rat platelet-rich plasma (PRP) according to the method described in the previous paper.[8] Usually, the potency of a TXA_2 synthetase inhibitor is expressed as its inhibitory activity against the TXA_2 synthetase obtained from a partially

(9) Myrboh, B.; Ila, H.; Junjappa, H. *J. Org. Chem.* **1983**, *48*, 5329.
(10) Newman, R. S.; Seshardi, S. J. *J. Org. Chem.* **1962**, *27*, 76.
(11) Soai, K. *Synth. Commun.* **1982**, *12*, 463.
(12) Doyle, M. P.; Siegfried, B.; Dellaria, F., Jr. *J. Org. Chem.* **1977**, *42*, 2426.

Table I. Benzocycloalkanes and Their Inhibitory Activities of TXA_2 Production



no.	Het	method	mp, °C	formula[a]	in vitro[b] IC_{50}, μM[c]	ex vivo (rats, po) TXB_2 (% inhibn)[d] dose, mg/kg	1[e]	3[e]	6[e]	enhancement,[f] x-fold PGI_2	PGE_2	ex vivo (rats, 0.1 mg/kg iv) TXB_2 (% inhibn)[g] 15[h]	45[h]	75[h]
47	Im[j]	K	270–275	$C_{15}H_{16}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$	1.1	1.0	98	93	88	2.91	5.90	95	93	88
						0.1	85	76[n]						
47b	Im	K	269–271	$C_{15}H_{16}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$	5.6	1.0	57	NT[p]	NT	1.99	4.27	NT	NT	NT
47c	Im	K	242–244	$C_{16}H_{18}N_2O_2 \cdot HCl$	14	1.0	93	59	28	3.38	10.05	84	53	46
47d	Im	K	219–220	$C_{16}H_{18}N_2O_2 \cdot HCl$	5.4	1.0	93	93	76	3.02	5.88	79	74	64
47e	Im	L	223	$C_{15}H_{16}N_2O_2 \cdot HCl$	1.4	1.0	88	69	49	2.22	4.79	NT	NT	NT
47f	Im	K	258–262	$C_{14}H_{14}N_2O_2 \cdot HCl$	6.6	1.0	95	90	74	3.57	6.93	73	60	51
47g	Im	K	172–174	$C_{15}H_{16}N_2O_2 \cdot HCl \cdot {}^1/_2H_2O$	0.86	1.0	97	NT	NT	NT	NT	NT	NT	NT
47h	Im	L	186–189	$C_{14}H_{14}N_2O_2 \cdot HCl$	7.2	1.0	87	75	61	3.14	7.27	58	46	32
51a	Th[k]	M	>280	$C_{15}H_{14}NNaO_2S$	0.14	1.0	93	88	78	2.55	5.26	90	87	75
51d	Th	M	104–115	$C_{15}N_{14}NNaO_2S$	0.37	1.0	97	93	86	2.68	5.63	88	79	67
51e	Th	N	256–262	$C_{15}H_{14}NNaO_2S$	1.9	1.0	69	NT	NT	2.65	5.91	NT	NT	NT
51f	Th	M	146–152	$C_{14}H_{12}NNaO_2S$	0.40	1.0	94	87	52	3.52	9.55	77	62	26
I[l] (dazoxiben)					11.0	1.0	50	21	8	1.90	3.91	25	6	NT
II[l] (OKY-046)					4.5	1.0	91	42	11	2.50	4.80	89	72	46
III[l] (UK-38485)					12.0	1.0	92	71	40	2.26	5.36	11	46	29
IV[l] (OKY-1581)					0.15	1.0	71	64	44	2.55	3.87	NT	NT	NT
V[l] (CV-4151)					0.25	1.0	96	80[n]	NT	NT	NT	NT	NT	NT
						0.1	75	40[n]						
VI[m]					3.8	1.0	88	83	54	3.14	NT	NT	NT	NT
VII, R = H[m]					1.5	1.0	39	NT	NT	NT	NT	NT	NT	NT
VII, R = Me[m]					0.22	1.0	44	NT	NT	NT	NT	NT	NT	NT

[a] All compounds gave C, H, and N analyzes within ±0.4% of the theoretical values. [b] In vitro test in rat PRP. [c] Concentrations required for 50% inhibition of TXB_2 production. [d] Inhibition (% inhibition) of TXA_2 production in whole blood of rats following single oral dose. [e] Hours post dose. [f] Enhancement of 6-keto-$PGF_{1\alpha}$ (a stable metabolite of PGI_2) or PGE_2 levels in serum of incubated whole blood at 1 h after an oral dose of 1 mg/kg of the test compounds. [g] Inhibition (% inhibition) of TXB_2 production in rat whole blood after intravenous injection of the test compounds (0.1 mg/kg). [h] Minutes post dose. [j] 1-Imidadolyl. [k] 5-Thiazolyl. [l] These compounds were prepared in our institute for experimental use. The structures are shown in Chart I. [m] See ref 8. The structure is shown in Chart I. [n] These values were for inhibition of TXA_2 production 4 h after a single oral dose. [p] Not tested.

purified enzyme fraction such as platelet microsomes. However, we think that the value of the inhibitory activity obtained by use of PRP reflects the combined effects of the compound on TXA_2 synthetase, permeability through the plasma membrane of platelets, and interactions with other substances in blood plasma and the cytoplasm of platelets. The assay system using PRP is hence, in our opinion, more suitable for selection of in vivo active compounds than that using the purified synthetase fraction, while the latter gives more precise information on the relationship between structure and direct inhibitory activity against the enzyme.

In some kinds of cells, tissues, and organs, some selective TXA_2 synthetase inhibitors have been found to increase the production of particular prostaglandins (PGs) such as PGE_2, $PGF_{2\alpha}$, PGD_2, and PGI_2 along with the inhibition of TXA_2 production. Cyclooxygenase inhibitors inhibit not only the production of TXA_2, but also those of the PGs synthesized through the reaction catalyzed by cyclooxygenase. The suppression of the production of certain PGs, especially PGI_2, and PGD_2, is undesirable for the treatment of ischemic heart disease, because the former has a potent vasodilating activity and both have potent antiaggregative activities against platelets. Usually, it has been known that the selective inhibition of TXA_2 synthetase results in the marked increase in PGI_2 and PGE_2 production. The ex vivo inhibitory activities of TXA_2 production were also measured after oral administration to rats. The levels of TXB_2, 6-keto-$PGF_{1\alpha}$, and PGE_2 were measured, and we calculated the inhibitory potency of TXA_2 production and the increase of 6-keto-$PGF_{1\alpha}$ and PGE_2 after oral administration, respectively. The results are shown in Table I. Most of the compounds exhibited potent inhibitory activities against TXB_2 production and the potent enhancement of 6-keto-$PGF_{1\alpha}$ and PGE_2 productions. These results show that the inhibitory activities of the compounds against the TXA_2 production are due to the selective inhibition of TXA_2 synthetase.

Compounds **47a**, **51a**, and **51d** had a potent and long-lasting inhibition of TXA_2 production. These inhibitions of TXA_2 production at 1 h after single oral administration of 1 mg/kg of body weight to rats were 98%, 93%, and 97%, and those at 6 h were 88%, 78%, and 86%, respectively. Some of the compounds that show potent inhibition

of TXA_2 production by oral administration were also tested for their ability to inhibit TXA_2 production after administration by intravenous injection, and the results are shown in Table I. Compound **47a** exhibited the most potent and long-lasting activities. It was found that the potency of the inhibitory activity was considerably affected by the kind of heterocyclic ring and the position of substituents on tetrahydronaphthalene or indan. The inhibitory activities of thiazole analogues in vitro were more potent than those of imidazole analogues. However, the activities of the thiazole analogues at 1 h after oral administration to rats were almost equal to those of the imidazole analogues, and the durations of activities of the thiazole analogues after oral or intravenous administration in rats were inferior to those of the imidazole analogues.

The activities of 5-[2-(1-imidazolyl)ethyl]- or 5-[2-(5-thiazolyl)ethyl]-5,6,7,8-tetrahydronaphthalane-1-carboxylic acid were slightly less than 2,6-substituted isomers (e.g., **47d < 47a**; **51d < 51a**), and the activities of 2,7-substituted isomer **47b** were less than those of 2,6-isomer **47a**. The activities of the compounds having an aromatic carboxyl group were superior to those of the compounds having an aliphatic carboxyl group (for example, **47a > 47e**; **47f > 47h**; **51a > 51e**). From these results, the most favorable positions of the substituents on 1,2,3,4-tetrahydronaphthalene ring seemed to be 2 and 6.

Replacement of tetrahydronaphthalene to indane did not affect the potency, but the activities of 1,4-substituted indan derivative **47g** were superior to those of 1,5-substituted tetrahydronaphthalene analogue **47d**.

In summary, the activities were influence by the position of the substituents, the kind of the heterocycle, and the kind of the benzocycloalkane in addition to the distance between the heterocycle and the carboxyl group.

Among the compounds reported here, 6-(1-imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid hydrochloride hemihydrate (**47a**, DP-1904) was the most favorable compound found in biological evaluation (the potency of TXA_2 synthesis inhibition, the duration of the potency, and the primary safety studies). Clinical evaluations and further biological studies of DP-1904 (**47a**) including the safety studies are in progress.

Experimental Section

Melting points are uncorrected. Analyses for C, H, and N were within ±0.4% of theoretical values, and ^1H NMR spectra were recorded with Hitachi R40 and JEOL JNM-FX90Q spectrometers (Me_4Si as an internal standard). For column chromatography, silica gel (Merck, Kieselgel 60, 0.05–0.2 mm) was used.

Method A. (a) Methyl 6-(Hydroxymethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (2). Trifluoroacetic acid (1.84 g, 16.1 mmol) was added dropwise to a suspension of $NaBH_4$ (0.71 g, 18.8 mmol) in dimethoxyethane (20 mL) with ice cooling, and the mixture was stirred at room temperature for 0.5 h. Dimethyl 1,2,3,4-tetrahydronaphthalene-2,6-dicarboxylate (**1**)[13] (0.4 g, 1.6 mmol) was added to the mixture. After stirring under reflux for 24 h, the mixture was treated with 10% HCl and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give **2** (0.32 g, 90%) as an oil: ^1H NMR ($CDCl_3$) δ 1.20–3.12 (8 H, m), 3.63 (2 H, d), 3.89 (3 H, s), 7.14 (1 H, d), 7.60–7.84 (2 H, m).

(b) Methyl 6-[(Tosyloxy)methyl]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (43a). Tosyl chloride (25.1 g, 0.13 mol) was added to a solution of **2** (14.5 g, 66 mmol) in pyridine (130 mL). After being stirred at room temperature for 18 h, the mixture was poured into ice water to give **43a** (14.9 g, 60%) as a colorless powder: ^1H NMR ($CDCl_3$) δ 1.11–3.20 (7 H, m), 2.45 (3 H, s), 3.88 (3 H, s), 4.00 (2 H, s), 7.08 (1 H, d), 7.36 (2 H, d), 7.65–7.96 (4 H, m). This crude **43a** was used for the next reaction without further purification.

Method B. (a) Methyl 7-Bromo-3,4-dihydronaphthalene-2-carboxylate (5). Compound **5** was prepared from **3** via **4** according to the method described by Myrboh[9] to give **5** as a colorless oil: yield 58%; ^1H NMR ($CDCl_3$) δ 2.4–3.0 (4 H, m), 3.82 (3 H, s), 6.96–7.50 (4 H, m).

(b) 7-Bromo-1,2,3,4-tetrahydronaphthalene-2-methanol (6). A solution of **5** (11.9 g, 43 mmol) in THF (30 mL) was added to a suspension of $LiAlH_4$ (2.4 g, 64 mmol) in THF (30 mL), and the mixture was stirred at room temperature for 14 h. The mixture was worked up as usual to give **6** (5.8 g, 56%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20–2.20 (3 H, m), 2.24–3.00 (4 H, m), 3.62 (2 H, d), 6.88–7932 (3 H, m).

(c) 7-Bromo-2-[(tetrahydropyranyloxy)methyl]-1,2,3,4-tetrahydronaphthalene (7). A mixture of **6** (8.8 g, 36.5 mmol), dihydropyran (3.4 g, 40 mmol), and concentrated HCl (10 drops) was stirred at room temperature for 15 h. The mixture was worked up as usual to give **7** (11.5 g, quantitatively) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.20–2.20 (9 H, m), 2.30–3.00 (4 H, m), 3.20–4.04 (4 H, m), 4.60 (1 H, s), 6.88–7.40 (3 H, m).

(d) Ethyl 7-(Hydroxymethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (8). A solution of **7** (11.5 g, 35 mmol) and EtBr (7.7 g, 71 mmol) in THF (15 mL) was added to a mixture of Mg (2.6 g, 0.11 mol) in THF (40 mL) at 60–70 °C under N_2 atmosphere. After being stirred under reflux for 2 h, the mixture was poured onto dry ice. The mixture was treated with 50% HCl (50 mL) and concentrated in vacuo. The residue was extracted with EtOAc. The extract was washed with water, dried, and concentrated in vacuo. The residue was refluxed with EtOH (200 mL) and sulfuric acid (25 mL) for 16 h, and the mixture was concentrated in vacuo. The residue was extracted with $CHCl_3$, washed with water, dried, and concentrated in vacuo to give **8** (5.5 g, 66%) as an oil: ^1H NMR ($CDCl_3$) δ 1.38 (3 H, t), 1.80–2.70 (3 H, m), 2.76–2.96 (4 H, m), 3.63 (2 H, d), 4.35 (2 H, q), 7.12 (1 H, d), 7.68–7.88 (2 H, m).

(e) Ethyl 7-[(Tosyloxy)methyl]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (43b). This compound was prepared by the method described for the preparation of **43a** from **2** as a colorless oil: yield 95%; ^1H NMR ($CDCl_3$) δ 1.38 (3 H, t), 1.80–2.40 (3 H, m), 2.45 (3 H, m), 2.30–3.04 (4 H, m), 4.00 (2 H, d), 4.35 (2 H, q), 7.00–7.92 (7 H, m).

Method C. (a) Wittig–Horner Reaction of 6-Bromo-3,4-dihydro-1(2*H*)-naphthalenone (9). Triethyl phosphonoacetate (3.2 g, 66 mmol) was added to a mixture of 50% NaH (3.2 g, 66 mmol) in THF (90 mL) and stirred for 0.5 h. 6-Bromo-3,4-dihydro-1(2*H*)-naphthalenone (**9**)[14] (14.8 g, 66 mmol) was added to this mixture, and the mixture was stirred at room temperature for 48 h. After stirring at 40–50 °C for an additional 20 h, the mixture was worked up as usual to give an oil (15.5 g) which was a mixture of ethyl (6-bromo-1,2,3,4-tetrahydronaphthalen-1-ylidene)acetate (**10**) and ethyl 6-bromo-3,4-dihydronaphthalene-1-acetate (**11**). The mixture was used for the next reaction without separation.

(b) Preparation of 12 from the Mixture of 10 and 11. The mixture (15.5 g) of **10** and **11** was reduced with $LiAlH_4$ (3.0 g, 80 mmol) in THF (200 mL) by the procedure described for preparation of **6** to give an oil (11.7 g) which was a mixture of 6-bromo-1-(2-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene and 6-bromo-1-(2-hydroxyethyl)-3,4-dihydronaphthalene. This mixture was worked up according to the method described for the synthesis of **8** from **6** to give an oil (2.0 g). This oil was hydrogenated in the presence of 10% Pd/C as catalyst under H_2 atmosphere to give **12** (1.4 g): ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t), 1.6–3.2 (9 H, m), 3.63 (2 H, t), 4.3 (2 H, q), 7.16 (1 H, d), 7.68–7.7 (2 H, m).

(c) Ethyl 5-[2-(Tosyloxy)ethyl]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (43c). This compound was prepared from **12** (2.0 g) by the method described for the synthesis of **43b**; a colorless oil (2.95 g, 91%) was obtained: ^1H NMR ($CDCl_3$) δ

(13) Fujimoto, H.; Urasaki, T. *Japan Patent Kokai* 76105045, 1976; *Chem. Abstr.* **1977**, *86*, 55203z.

(14) Itoh, K.; Miyake, A.; Tada, N.; Hirata, M. *Chem. Pharm. Bull.* **1984**, *32*, 130.

1.37 (3 H, t), 2.45 (3 H, s), 2.91–3.15 (1 H, m), 4.11 (2 H, t), 4.31 (2 H, q), 6.9–7.8 (7 H, m).

By this method, compounds **43d** and **43g** were prepared.

Ethyl 5-[2-(tosyloxy)ethyl]-5,6,7,8-tetrahydronaphthalene-1-carboxylate (43d), a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.36 (3 H, t), 1.60–2.20 (6 H, m), 2.45 (3 H, s), 2.60–3.25 (3 H, m), 4.13 (2 H, t), 4.32 (2 H, q), 7.0–7.9 (7 H, m).

Ethyl 1-[2-(tosyloxy)ethyl]indan-4-carboxylate (43g), a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.36 (3 H, t, 2.45 (3 H, s), 4.13 (2 H, t), 4.30 (2 H, q), 7.0–7.9 (7 H, m).

Method D. (a) Ethyl 5-Acetylindan-2-carboxylate (14). Acetyl chloride (5.2 g, 0.03 mol) was added to a mixture of ethyl indan-2-carboxylate (**13**)[15] (5.7 g, 0.03 mol) and $AlCl_3$ (9.3 g, 0.07 mmol) in dichloroethane (50 mL). After being stirred at room temperature for 2 h, the mixture was poured into a mixture of ice and concentrated HCl, and the mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give **14** (6.2 g, 89%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (3 H, t), 2.58 (3 H, s), 3.1–3.4 (5 H, m), 4.19 (2 H, q), 7.28 (1 H, d), 7.77 (1 H, d), 7.81 (1 H, s).

(b) Ethyl 5-Acetylindan-2-carboxylate Ethyl Acetal (15). A mixture of 14 (6.2 g, 27 mmol), ethylene glycol (1.9 g, 0.03 mol), and TsOH (0.1 g) in benzene (100 mL) was refluxed for 16 h. The mixture was washed with 5% K_2CO_3, dried, and concentrated to give 15 (6.2 g, 83.8%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (3 H, t), 1.64 (3 H, s), 3.1–3.35 (5 H, m), 3.68–3.92 (2 H, m), 3.94–4.04 (2 H, m), 4.18 (2 H, q), 7.1–7.4 (3 H, m).

(c) 5-Acetylindan-2-methanol Ethylene Acetal (16). Compound **15** (6.2 g, 22 mmol) was reduced with $LiAlH_4$ (0.9 g, 24 mmol) according to the procedure described for preparation of **6** to give **16** (4.0 g, 76.1%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.64 (3 H, s), 2.57–3.50 (5 H, m), 3.66 (2 H, d), 3.7–3.92 (2 H, m), 3.94–4.18 (2 H, m), 7.1–7.4 (3 H, m).

(d) Ethyl 2-(Hydroxymethyl)indan-5-carboxylate (18). A mixture of **16** (4.0 g, 17 mmol) in concentrated HCl (30 mL) and MeOH (30 mL) was refluxed for 3 h. The mixture was concentrated. and the residue was extracted with $CHCl_3$. The extract was concentrated to give a crude 5-acetyl-2-(hydroxymethyl)indan (**17**) as an oil. A mixture of this oil and I_2 (2.5 g) in pyridine (5 mL) was refluxed for 1 h. The mixture was added into a solution of NaOH (1 g) in 50% EtOH (60 mL). After being stirred under reflux for 2 h, the mixture was concentrated in vacuo. The residue was made acid with concentrated HCl and extracted with EtOAc. The extract was washed, dried, and concentrated. Esterification of the residue with concentrated H_2SO_4 (2 mL) and EtOH (30 mL) by the usual method gave **18** (1.2 g, 54.5%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.38 (3 H, t), 2.5–3.3 (5 H, m), 3.65 (2 H, d), 4.35 (2 H, q), 7.23 (1 H, d), 7.83 (1 H, d), 7.87 (1 H, s).

(e) Ethyl 2-[(Tosyloxy)methyl]indan-5-carboxylate (43f). This compound was prepared from **18** according to the procedure described for the synthesis of **43b** as a colorless oil in quantitative yield. This oil was used for the next reaction without further purification.

Method E. (a) Ethyl 6-Formyl-1,2,3,4-tetrahydronaphthalene-2-carboxylate (20). A solution of $NaNO_2$ (4.46 g) in H_2O (7 mL) was added to a mixture of ethyl 6-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**19**)[16] (15.2 g, 51 mmol) in concentrated HCl (12 mL) and H_2O (10 mL) below 0 °C. After stirring for 0.5 h, NaOC (7 g) was added to the mixture to give a diazonium solution. A mixture of Na_2SO_3 (0.2 g), $CuSO_4{\cdot}5H_2O$ (1.28 g), and NaOAc (33.4 g) in H_2O (36 mL) was added to a mixture of paraformaldehyde (2.32 g) and hydroxylamine hydrochloride (5.33 g) in H_2O (35 mL), and the mixture was added dropwise to the diazonium solution at 10 °C. After being stirred for 1 h, the mixture was treated with concentrated HCl (50 mL) and refluxed for 2 h. The mixture was extracted with EtOAc. The extract was washed, dried, and concentrated. The residue was added to a 40% $NaHSO_3$ aqueous solution and stirred at 60–80 °C for 3 h. Sulfuric acid (15 mL) was added to this mixture and stirred under reflux for 0.5 h, and then the mixture was extracted with EtOAc. The extract was washed, dried, and concentrated. Esterification of the residue with concentrated H_2SO_4 (4.4 g) in EtOH (150 mL) by the usual method gave **20** (4.8 g, 33%) as an oil, which was used for the next reaction without further purification.

(b) Ethyl 6-(Hydroxymethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (21). A mixture of **20** (5.0 g, 21.5 mmol) and $NaBH_4$ (0.4 g, 10.6 mmol) in EtOH (100 mL) was stirred at room temperature for 0.5 h. The mixture was treated with 2 N HCl and concentrated in vacuo. The residue was extracted with $CHCl_3$, and the extract was washed, dried, and concentrated in vacuo to give **21** (5.03 g, 100%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (3 H, t), 1.76 (1 H, s), 1.6–2.4 (2 H, m), 2.5–3.1 (5 H, m), 4.18 (2 H, q), 4.61 (2 H, s), 7.09 (3 H, s).

(c) Ethyl 6-(Chloromethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (44e). A mixture of **21** (5.03 g) in $SOCl_2$ (40 mL) was refluxed for 1.5 h and concentrated in vacuo to give **44e** as an oil. This oil was used for the next reaction without further purification.

Method F. (a) 2-(5-Bromoindan-2-yl)-4,4-dimethyloxazoline (23). A mixture of 5-bromoindan-2-carboxylic acid (**22**)[17] (3.9 g, 16.4 mmol) and 2-amino-2-methyl-1-propanol (2.0 g, 22.4 mmol) in xylene (100 mL) was refluxed for 24 h. After the mixture was concentrated, the residue was extracted with $CHCl_3$. The extract was dried and concentrated to give **23** (3.0 g, 63%) as an oil: ^{1}H NMR ($CHCl_3$) δ 1.27 (6 H, s), 3.0–3.4 (5 H, m), 3.94 (2 H, s), 7.05 (1 H, d), 7.05 (1 H, d), 7.32 (1 H, s).

(b) 2-(4,4-Dimethyloxazolin-2-yl)indan-5-carbaldehyde (24). A solution of **23** (3.0 g, 0.01 mol) and EtBr (2.2 g, 0.02 mol) in THF (30 mL) was added to a mixture of Mg (0.7 g, 0.03 mol) in THF (10 mL) under N_2 atmosphere under reflux, and the mixture was refluxed for 1 h. A solution of DMF (3.0 g) in THF (10 mL) was added to this cooled mixture and then refluxed for 1 h. The mixture was poured into a saturated solutio of NH_4Cl (100 mL), and then the mixture was worked up as usual to give **24** (1.0 g, 41.2%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (6 H, s), 3.31 (5 H, m), 3.95 (2 H, s), 7.35 (1 H, d), 7.68 (1 H, d), 7.73 (1 H, s), 9.96 (1 H, s).

(c) Ethyl 5-Formylindan-2-carboxylate (25). A solution of **24** (1.0 g, 4.1 mmol) and sulfuric acid (2 mL) in EtOH (50 mL) was refluxed for 4 h. After removal of the solvent, the residue was extracted with $CHCl_3$. The extract was dried and concentrated to give **25** (0.5 g, 56%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (3 H, t), 3.3 (5 H, m), 4.19 (2 H, q), 7.35 (1 H, d), 7.69 (1 H, d), 7.73 (1 H, s), 9.96 (1 H, s).

(d) Ethyl 5-(Chloromethyl)indan-2-carboxylate (44h). This compound was prepared from **25** (0.5 g, 2.3 mmol) by the method described in the preparation of **44e** from **20** to give an oil (0.4 g) of **44h**. This oil was used for the next reaction without further purification.

Method G. (a) 6-Bromo-1,2,3,4-tetrahydronaphthalene-2-methanol (27). A solution of $NaNO_2$ (1.73 g, 25 mmol) in H_2O (5 mL) was added to a mixture of **19** (7.5 g, 25 mmol) in 48% HBr (4 mL) and H_2O (50 mL) at 0–5 °C and stirred for 0.5 h. The mixture was added dropwise to a mixture of CuBr (9.1 g) in 48% HBr (50 mL) and H_2O (50 mL). After being stirred at 60 °C for 0.5 h, the mixture was treated with H_2O and extracted with $CHCl_3$. The extract was washed, dried, and concentrated to give an oil of ethyl 6-bromo-1,2,3,4-tetrahydronaphthalene-2-carboxylate. Reduction of this oil with $LiAlH_4$ (1.23 g) according to the method described for the preparation of **6** gave **27** (2.97, 49%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.66 (1 H, s), 3.61 (2 H, d), 6.93 (1 H, d), 9.02–9.30 (2 H, m).

(b) (6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl Tosylate (28). This compound was prepared from **27** according to the procedure described in the synthesis of **43a**; a colorless powder was obtained: yield 92%; ^{1}H NMR ($CDCl_3$) δ 2.44 (3 H, s), 3.96 (2 H, d), 6.82 (1 H, d), 7.07–7.23 (2 H, m), 7.30 and 7.75 (each 2 H, d). This compound was used for the next reaction without further purification.

(c) Diethyl 2-[2-(6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)ethyl]malonate (29). Compound **28** (36 g, 0.091 mol) was

(15) Schaf, T. K.; Johnson, M. R.; Constantine, J. W.; Bindra, J. S.; Hess, H. J.; Elger, W. *J. Med. Chem.* **1983**, *26*, 328.

(16) Sergievskaya, S. I.; Volynskii, N. P. *Zhur. Obshch. Khim.* **1952**, *22*, 1446.

(17) Seka, R.; Bach, G.; Kellermann, W. *Monatsh. Chem.* **1943**, *74*, 223.

added to the solution of diethyl malonate (20.4 g, 0.128 mol) in NaOEt solution prepared from Na (2.1 g) and EtOH (100 mL). The mixture was refluxed for 24 h and concentrated in vacuo. The residue was extracted with $CHCl_3$, washed, dried, and concentrated to give **29** as an oil. This oil was used for the next reaction without further purification.

(**d**) Ethyl **3-(6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)propionate (30)**. A solution of the crude **29** and NaOH (10 g) in H_2O (100 mL) was refluxed for 4 h, and the mixture was made acid with 50% H_2SO_4 to give a colorless powder. After this powder was heated at 180 °C for 20 min, the residue was dissolved in a mixture of H_2SO_4 (5 mL) and EtOH (250 mL). The mixture was refluxed for 4 h and concentrated in vacuo. The residue was extracted with $CHCl_3$, dried, and concentrated in vacuo to give **30** (17.4 g, 60% from **28**) as an oil.

(**e**) **3-(6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)-1-propanol (31)**. Compound **30** (17.3 g, 0.056 mol) was reduced with $LiAlH_4$ according to the procedure described in the preparation of **6** to give **31** (14.2 g, 95%) as a colorless powder: mp 60–64 °C; ^1H NMR ($CDCl_3$) δ 2.6–2.90 (4 H, m), 3.63 (2 H, t), 6.85 (1 H, d), 7.04–7.25 (2 H, m).

(**f**) **6-Bromo-2-[3-(tetrahydropyranyloxy)propyl]-1,2,3,4-tetrahydronaphthalene (32)**. Compound **31** (14.2 g, 52.8 mmol) was treated with dihydropyran by the method described for preparation of **7** to give **32** (18.5 g, 99%) as an oil.

(**g**) Ethyl **6-(3-Hydroxypropyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (33)**. Compound **32** (18.5 g, 52.4 mmol) was treated by the procedure described for the preparation of **8** to give **33** as an oil (11.6 g, 84%): ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t), 3.67 (2 H, d), 4.34 (2 H, q), 7.10 (1 H, d), 7.66–7.80 (2 H, m).

(h) Ethyl **6-(2-Formylethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (34)**. A solution of **33** (11.6 g, 44.2 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a mixture of pyridinium chlorochromate (14.3 g), and the mixture was stirred for 1.5 h. The organic layer was washed with water, dried, and concentrated. The residue was purified by silica gel chromatography to give **34** (10.5 g, 91%) as an oil: ^1H NMR ($CDCl_3$) δ 1.36 (3 H, t), 4.32 (2 H, q), 7.05 (1 H, d), 7.60–7.80 (2 H, m), 9.75 (1 H, s).

(i) Ethyl **6-(2-Bromo-2-formylethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (45a)**. A mixture of Br_2 (2 mL) and dioxane (6 mL) in CH_2Cl_2 (25 mL) was added to a solution of **34** (10.5 g, 40 mmol) in CH_2Cl_2 (20 mL) below −5 °C under N_2 atmosphere. After stirring at −5 °C for 1 h, the mixture was treated with a solution of Na_2CO_3 (3.1 g) in H_2O (13 mL). The organic layer was washed, dried, and concentrated in vacuo to give **45a** (13 g) as an oil. This compound was used for the next reaction without further purification.

Ethyl 5-(3-bromo-3-formylpropyl)-5,6,7,8-tetrahydronaphthalene-1-carboxylate (**45d**) was prepared by this method, giving a colorless oil in quantitative yield: ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t), 1.4–2.2 (8 H, m), 2.78 (2 H, m), 3.0 (1 H, m), 3.5 (1 H, m), 4.34 (2 H, q), 7.0–7.4 (2 H, m), 7.60 (1 H, dd), 9.44 (1 H, t, CHO).

Method H. (**a**) **Indan-2-methanol (35)**. MeOH (428 mL) was added to a mixture of **13** (188 g, 0.99 mol) and $NaBH_4$ (94 g, 2.5 mol) in *t*-BuOH (1.5 L) under reflux. After 2.5 h, the mixture was treated with H_2O (0.5 L) and concentrated in vacuo. The residue was extracted with $CHCl_3$. The extract was washed, dried, and concentrated to give **35** (145 g, quantitatively) as an oil: ^1H NMR ($CDCl_3$) δ 2.55–3.25 (5 H, m), 3.67 (2 H, d), 7.18 (4 H, s).

(**b**) **3-(Indan-2-yl)-1-propanol (39)**. Compound **39** was prepared from **35** via **36–38** according to the method described for the preparation of **31** from **27** to give a colorless oil; overall yield was 58% from **35**.

(**c**) **3-(5-Acetylindan-2-yl)-1-propanol (40)**. Compound **40** was prepared from **39** by the method described for the synthesis of **14** as an oil. This oil was used for the next reaction without further purification.

(**d**) Ethyl **2-(3-Hydroxypropyl)indan-5-carboxylate (41)**. A sodium hypobromite solution prepared from Br_2 (118 mL) and NaOH (243 g) in H_2O (2 L) was added to a solution of **40** in dioxan (1.5 L). The mixture was stirred at 10 °C for 1 h. After being stirred at room temperature for further 3 h, the mixture was made acidic with concentrated HCl. The precipitate was filtered. This precipitate was esterified with concentrated H_2SO_4 (30 mL) and EtOH (800 mL) by the usual manner to give **41** (112 g, 51.3% from **40**): ^1H NMR ($CDCl_3$) δ 1.37 (3 H, t), 3.50–3.70 (2 H, m), 4.34 (2 H, q), 7.18 (1 H, d), 7.50–7.90 (2 H, m).

(**e**) Ethyl **2-(2-Formylethyl)indan-5-carboxylate (42)**. Compound **42** was prepared from **41** by a method described for the preparation of **34**, giving an oil: yield 94%; ^1H NMR ($CDCl_3$) δ 1.46 (3 H, t), 1.89 (2 H, t), 2.2–3.4 (7 H, m), 4.35 (2 H, q), 7.21–7.84 (3 H, m), 9.81 (1 H, t).

(**f**) Ethyl **2-(2-Bromo-2-formylethyl)indan-5-carboxylate (45f)**. Compound **45f** was prepared by the method described for the preparation of **45**; yield was quantitative. This compound was used for the next reaction without further purification.

Method J. Ethyl **6-(2-Chloro-2-formylethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (45e)**. A solution of $NaNO_2$ (3.3 g, 48 mmol) in H_2O (7 mL) was added to a solution of **19** (11 g, 43 mmol) and concentrated HCl (4 mL) in acetone (40 mL) at 0–5 °C. After 20 min, acrolein (25 mL) and CuCl (0.2 g) was added to the mixture. After being stirred at 35–40 °C for 3 h, the mixture was concentrated. The residue was extracted with C_6H_6. The extract was washed, dried, and concentrated to give **45e** as an oil, which was used for the next reaction without further purification.

Method K. (**a**) Methyl **6-(1-Imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (46a)**. Imidazole (2.1 g, 43.8 mmol) was added to an ice-cooled suspension of 50% NaH (2.1 g, 43.8 mmol) in DMF (50 mL). Then, **43a** (14.9 g, 39.7 mmol) was added to this mixture. After being stirred at room temperature for 17 h, the mixture was concentrated. The residue was extracted with $CHCl_3$, washed, dried, and concentrated to give **46a** (9.95 g, 93%) as an oil: ^1H NMR ($CDCl_3$) δ 1.1–3.1 (7 H, m), 3.89 (3 H, s), 3.95 (2 H, d), 6.95–7.90 (6 H, m).

(**b**) **6-(1-Imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic Acid Hydrochloride Hemihydrate (47a)**. A mixture of **46a** (9.9 g, 36.6 mmol) was NaOH (2.4 g) in H_2O (30 mL) was refluxed for 4 h. The mixture was neutralized with concentrated HCl to give a free base of **47a** (6.6 g) as a colorless powder: mp 224–227 °C; ^1H NMR (Me_2SO-d_6) δ 1.10–3.00 (7 H, m), 4.00 (2 H, d), 6.93 (1 H, s), 7.12 (1 H, d), 7.18 (1 H, s), 7.80–7.55 (3 H, m).

The free base of **47a** obtained above was treated with HCl–EtOH to give **47a** (7.3 g, 68%) as a colorless prism; mp 243–251 °C (EtOH–Et_2O). Anal. ($C_{15}H_{16}N_2O_2 \cdot {}^1/_2H_2O$) C, H, N.

Compounds **47b–d**, **-f**, and **-g** were prepared by this method, and the results are listed in Table I.

Method L. (**a**) Ethyl **6-(1-Imidazolylmethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate Hydrochloride (46e)**. A mixture of **44e** (5.1 g, 21.5 mmol), NaI (3.22 g, 21.5 mmol), and 1-acetylimidazole (3.94 g, 35.8 mmol) in MeCN (100 mL) was refluxed for 1.5 h. After the mixture was concentrated, the residue was treated with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed, dried, and concentrated. The residue was purified by silica gel chromatography to give a free base of **46e** as an oil. This oil was treated with HCl–EtOH to give **46e** (4.8 g, 70%) as a colorless powder; mp 170–172 °C. Anal. ($C_{15}H_{16}N_2O_2 \cdot HCl$) C, H, N.

(**b**) **6-(1-Imidazolylmethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid Hydrochloride (47e)**. A mixture of **46e** (4.2 g, 1.4 mmol) and concentrated HCl (15 mL) in MeOH (30 mL) was refluxed for 20 h. The mixture was concentrated in vacuo to give **47e** (2.52 g, 61%) as a colorless prism: mp 193–223 °C; ^1H NMR (D_2O) δ 5.3 (2 H, s), 7.13 (4 H, s), 7.41 and 7.43 (each 1 H, s), 8.73 (1 H, s, C_2-H). Anal. ($C_{15}H_{16}N_2O_2 \cdot HCl$) C, H, N.

Compound **47h** was prepared by this method, and the result is listed in Table I.

Method M. (**a**) Ethyl **6-[(2-Aminothiazol-5-yl)methyl]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (48a)**. A mixture of **45a** (13 g) and thiourea (3.0 g) in EtOH (180 mL) was refluxed for 10 h. The mixture was concentrated, and the residue was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and concentrated in vacuo. The residue was purified by silica gel chromatography to give **48a** (5.73 g, 45%) as a colorless powder; mp 150–153 °C. Anal. ($C_{17}H_{20}N_2O_2S$) C, H, N.

(**b**) Ethyl **6-[(2-Chloro-5-thiazolyl)methyl]-5,6,7,8-tetrahydronaphthalene-2-carboxylate (49a)**. A solution of **48a** (55

g, 0.174 mol) in MeCN (200 mL) was added to a mixture of *t*-BuONO (26.4 g, 0.256 mol) and $CuCl_2$ (28 g, 0.208 mol) in MeCN (530 mL) at 60 °C. After being stirred for 10 min, the mixture was treated with 15% HCl (300 mL) and extracted with $CHCl_3$. The extract was washed, dried, and concentrated to give **49a** (56 g, 96%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.37 (3 H, t), 2.80 (2 H, d), 4.32 (2 H, q), 7.02 (1 H, d), 7.20 (1 H, s), 7.60–7.80 (2 H, m).

(c) Ethyl 6-(5-Thiazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (50a). Zinc powder (25.5 g) was added to a solution of **49a** (56 g) in HOAc (890 mL) under reflux. After being stirred under reflux for 4 h, the mixture was concentrated in vacuo. The residue was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed, dried, and concentrated. The residue was purified by silica gel chromatography to give **50a** (41.7 g, 80%) as an oil.

(d) Sodium 6-(5-Thiazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate (51a). A mixture of **50a** (3.92 g, 13 mmol) and 10% NaOH (10 mL) in MeOH (30 mL) was refluxed for 1 h. The solution was concentrated in vacuo. The residue was dissolved in H_2O. The solution was made to pH 6 with 10% NaOH. The precipitate was filtered and suspended in H_2O. The mixture was made to pH 10 with 10% NaOH, and the mixture was concentrated in vacuo to give **51a** (1.92 g, 50%) as a colorless powder: mp >280 °C (EtOH–Et_2O); ^{1}H NMR (D_2O) δ 6.99 (1 H, d), 8.4–8.7 (3 H, m), 8.73 (1 H, s). Anal. ($C_{15}H_{14}NNaO_2S$) C, H, N.

Compound **51d** was prepared by this method, and the result is listed in Table I.

Method N. (a) Ethyl 6-[(2-Amino-5-thiazolyl)methyl]-1,2,3,4-tetrahydronaphthalene-2-carboxylate (48e). This compound was prepared from **45e** by the method described for the preparation of **48a**, giving a colorless powder; yield 44%. This crude **48e** was used for the next reaction without further purification.

(b) Ethyl 6-(5-Thiazolylmethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (50e). Compound **48e** (1.0 g, 3.16 mmol) was added to a solution of *t*-BuONO (0.49 g) in DMF (5 mL) at 50 °C, and the mixture was stirred at 60 °C for 1 h. The mixture was dissolved in EtOAc. The organic layer was washed, dried, and concentrated. The residue was purified by silica gel chromatography to give **50e** (0.72 g, 76%) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t), 1.6–2.4 (2 H, m), 2.5–3.1 (5 H, m), 3.86 (2 H, s), 4.15 (2 H, q), 6.74 (1 H, s), 6.8–7.1 (3 H, m).

(c) Sodium 6-(5-Thiazolylmethyl)-1,2,3,4-tetrahydronaphthalene-2-carboxylate (51e). Compound **51e** was prepared from **50a** (0.72 g, 2.4 mmol) according to the method described for the synthesis of **51a**, giving a colorless powder: yield 21%; mp >280 °C. Anal. ($C_{15}H_{14}NNaO_2S$) C, H, N.

Biological Assay for Inhibition of TXA_2 Synthesis. (a) In Vitro Assay of the Inhibition of TXA_2 Production in PRP. The test compound was mixed with citrated PRP (4×10^7 platelets) from rats, the mixture was preincubated for 1 min at room temperature with gentle shaking, and sodium arachidonate (final concentration 0.5 mmol) was added to initiate the reaction. The reaction mixture (total volume 0.1 mL) was incubated for 5 min at room temperature with vigorous shaking, and indomethacin (final concentration 0.1 mmol) was added to stop the reaction. Then the mixture was centrifuged (1000*g*, 5 min), and the supernatant was subjected to the measurement of TXB_2 by the radioimmunoassay method.

(b) Ex Vivo Assay at Oral Administration. The test compound was suspended in water and given orally to rats at a dose of 1 mg/kg. Control rats were given vehicle. One, three, and six hours after administration, whole blood was taken from the the external jugular vein under anesthesia. These samples were left on ice for 15 min and clotted at 37 °C for 1 h. Serum was separated by centrifugation (1000*g* for 10 min). The levels of TXB_2, 6-keto-$PGF_{1\alpha}$, and PGE_2 in the serum were measured by the radioimmunoassay method.

(c) Ex Vivo Assay at Intravenous Administration. The test compound was dissolved in a physiological saline solution and given intravenously to rats at a dose of 0.1 g/kg. Control rats were given vehicle. After 15 , 45, and 75 min, whole blood was taken from the external jugular vein under anesthesia and treated according to the procedure described above. The level of TXB_2 in the serum was measured by the radioimmunoassay method.

Registry No. 1, 23985-75-3; **2**, 105652-51-5; **3**, 32281-97-3; 4, 97903-13-4; **5**, 97903-15-6; **6**, 119924-40-2; **7**, 119924-41-3; **8**, 105652-56-0; **9**, 66361-67-9; **9d**, 68449-30-9; **9g**, 15115-60-3; **10**, 97902-99-3; **10d**, 119924-52-6; **10g**, 105957-09-3; 11, 97903-00-9; **11d**, 119924-53-7; **11g**, 119924-54-8; **12**, 97903-06-5; **13**, 81290-34-8; **14**, 119924-42-4; **15**, 119924-43-5; **16**, 119924-44-6; **17**, 119924-45-7; **18**, 119924-46-8; **19**, 97902-63-1; **20**, 97902-85-7; **21**, 97902-86-8; **22**, 97901-15-0; **23**, 97901-16-1; **24**, 97901-17-2; **25**, 97919-03-4; **26**, 97901-18-3; **27**, 97902-67-5; **28**, 97902-72-2; **29**, 97902-73-3; **30**, 97902-75-5; **31**, 119924-47-9; **32**, 119924-48-0; **33**, 97902-76-6; **33d**, 105652-53-7; **34**, 97902-77-7; **35**, 5445-45-4; **36**, 97903-17-8; **37**, 119924-49-1; **38**, 97903-18-9; **39**, 97903-19-0; **40**, 119924-50-4; **41**, 97901-11-6; **42**, 119924-51-5; **43a**, 119924-64-0; **43b**, 97903-16-7; **43c**, 97903-07-6; **43d**, 97903-08-7; **43f**, 97901-14-9; **43g**, 119945-90-3; **44e**·HCl, 97902-87-9; **44h**·HCl, 97901-19-4; **45a**, 97902-78-8; **45d**, 119924-65-1; **45d** (X = H), 119924-63-9; **45e**, 119924-66-2; **45f**, 119945-91-4; **46a**, 119924-67-3; **46b**, 97901-45-6; **46c**, 97901-39-8; **46d**, 97901-41-2; **46e**·HCl, 97901-33-2; **46f**, 97901-49-0; **46g**, 119924-68-4; **46h**·HCl, 119924-69-5; **47a**, 97901-21-8; **47a**·HCl, 97901-22-9; **47b**, 106289-19-4; **47b**·HCl, 97901-46-7; **47c**, 119924-73-1; **47c**·HCl, 97901-40-1; **47d**, 97901-55-8; **47d**·HCl, 97901-42-3; **47e**, 119924-74-2; **47e**·HCl, 97901-34-3; **47f**, 97901-57-0; **47f**·HCl, 97901-50-3; **47g**, 119924-75-3; **47g**·HCl, 119924-76-4; **47h**, 106371-31-7; **47h**·HCl, 97901-52-5; **48a**, 97902-79-9; **48d**, 97919-12-5; **48e**, 97902-82-4; **48f**, 97902-12-7; **49a**, 119924-70-8; **49d**, 119924-71-9; **49f**, 119924-72-0; **50a**, 97901-24-1; **50d**, 97901-28-5; **50e**, 97901-30-9; **50f**, 97901-47-8; **51a**, 97901-26-3; **51d**, 97901-29-6; **51e**, 97901-31-0; **51f**, 97901-48-9; TXA_2, 57576-52-0; $(EtO)_2P(O)CH_2CO_2Et$, 867-13-0; $HOCH_2C(CH_3)_2NH_2$, 124-68-5; $CH_2(CO_2Et)_2$, 105-53-3; $CH_2{=}CHCHO$, 107-02-8; 6-bromo-3,4-dihydro-1-naphthaleneethanol, 97903-02-1; 6-bromo-1,2,3,4-tetrahydro-1-naphthaleneethanol, 97903-01-0; 5-bromo-1,2,3,4-tetrahydro-1-naphthaleneethanol, 97902-80-2; 5-bromo-3,4-dihydro-1-naphthaleneethanol, 119924-55-9; 4-bromo-1-indanethanol, 105957-10-6; 7-bromo-1*H*-indene-3-ethanol, 119924-56-0; 7-bromo-1,2-dihydro-4-[2-[(tetrahydropyranyl)oxy]ethyl]-naphthalene, 97903-04-3; 6-bromo-1,2,3,4-tetrahydro-1-[2-[(tetrahydropyranyl)oxy]ethyl]naphthalene, 97903-03-2; 5-bromo-1,2,3,4-tetrahydro-1-[2-[(tetrahydropyranyl)oxy]ethyl]naphthalene, 119924-57-1; 8-bromo-1,2-dihydro-4-[2-[(tetrahydropyranyl)-oxy]ethyl]naphthalene, 119924-58-2; 4-bromo-1-[2-[(tetrahydropyranyl)oxy]ethyl]indan, 119924-59-3; 7-bromo-3-[2-[(tetrahydropyranyl)oxy]ethyl]-1*H*-indene, 119924-60-6; ethyl 7,8-dihydro-5-(2-hydroxyethyl)-2-naphthalenecarboxylate, 97903-05-4; ethyl 7,8-dihydro-5-(2-hydroxyethyl)-2-naphthalenecarboxylate, 119924-61-7; ethyl 3-(2-hydroxyethyl)-1*H*-indene-7-carboxylate, 119924-62-8; ethyl 5-(2-hydroxyethyl)-5,6,7,8-tetrahydro-1-naphthalenecarboxylate, 105652-55-9; ethyl 1-(2-hydroxyethyl)-indan-4-carboxylate, 105957-08-2; ethyl 6-bromo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate, 97902-66-4; 1-acetylimidazole, 2466-76-4.