Biological Activity. The origin of the viruses and the techniques used for measuring inhibition of virus-induced cytopathogenicity and virus multiplication have been described previously.[14] Further details are provided in the footnotes to Tables III and IV and the legend to Figure 1.

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Thromboxane Synthetase Inhibitors (TXSI). Design, Synthesis, and Evaluation of a Novel Series of ω-Pyridylalkenoic Acids

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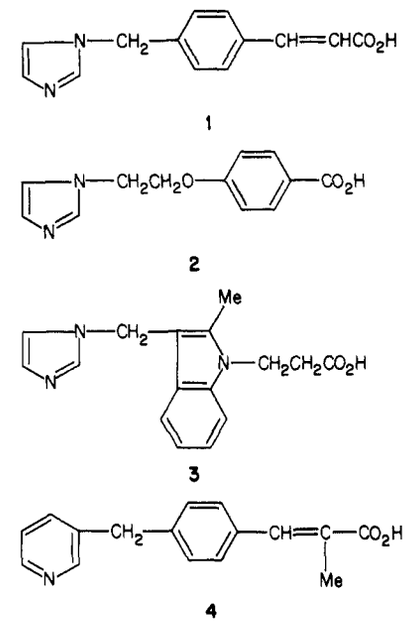
A novel series of ω-pyridylalkenoic acids has been prepared by applying the Wittig reaction. Modifications were made in the ω-aryl moiety, the alkylene chain length, the α-methylene group adjacent to the carbonyl group, and the carboxyl group of the molecule. The compounds were tested as inhibitors of thromboxane synthetase in an in vitro assay and in ex vivo experiments with the rat. Most members of this new class of thromboxane synthetase inhibitors (TXSI) showed good activity in both assay systems. (*E*)-7-Phenyl-7-(3-pyridyl)-6-heptenoic acid (**9c**; CV-4151) was one of the most potent compounds in in vitro enzyme inhibition ($IC_{50} = 2.6 \times 10^{-8}$ M) and, when orally administered, the most potent and long acting in the inhibition of blood thromboxane A_2 production in the rat. New conceptual models I–III for the enzyme–substrate (prostaglandin H_2, PGH_2) and the enzyme–TXSI interactions are proposed for understanding the molecular design and structure–activity relations.

Since the discovery of a thromboxane synthetase inhibitor (TXSI), imidazole, in 1977,[1] numerous analogues[2a–f] have been prepared in the hope of improving its pharmacological profile. In the search for potent inhibitors 1–4 (Chart I), many compounds of diverse structure, but all containing an imidazole or pyridine moiety, have been identified. The basic structural requirements for congeneric compounds inhibiting thromboxane synthetase are a 1-imidazolyl or a 3-pyridyl moiety at one end of the molecule and a carboxylic acid group at the other. Further, the distance between the carboxyl group and the nitrogen atom at the 3-position of the imidazole or pyridine moiety in potent compounds is concentrated between 8.5 and 10 Å. The distance appears to be similar to that between the carboxyl group and the endoperoxide moiety in prostaglandin H_2 (PGH_2), the substrate of thromboxane synthetase.

Recently, Ullrich and Haurand[3] reported that the cytochrome P-450 enzyme from human platelets possesses a kind of thromboxane synthetase activity and forms ligand complexes with TXSI. Kinetic studies indicate that TXSI appear to interact with the heme iron, the active site of the enzyme. The affinities are close to stoichiometric binding and correspond to the inhibitory action on biological activity. This investigation suggests that it is the 3-pyridyl nitrogen of TXSI that is oriented in close proximity of the heme iron. This finding enabled us to formulate the construction of new conceptual models I and II for the enzyme–substrate (PGH_2) and the enzyme–TXSI interactions (Figure 1). These models were constructed on the basis of reference data on cytochrome *c*[4] and cytochrome P-450 enzyme.[5] Since it is thought that enzymes that include a heme iron have a space in which the substrate molecule such as PGH_2 can be received, the so-called crevice between the substrate-binding site and the heme iron, the optimal molecular size of TXSI to reach the space through the entrance of the crevice, can be presumed to be nearly equal in size to the molecular size of PGH_2. The conceptual feature of the crevice would not be unexpected when one considers the lipophilic character of the substrate (PGH_2) that competes with a TXSI at the same active site.

Chart I



† Chemistry Laboratories.
‡ Biology Laboratories.

(1) Needleman, P.; Raz, A.; Ferrendelli, J. A.; Minkes, M. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 1716.
(2) (a) Yoshimoto, T.; Yamamoto, S.; Hayaishi, O. *Prostaglandins* **1978**, *16*, 529. (b) 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. (c) Tanouchi, T.; Kawamura, M.; Ohyama, I.; Kajiwara, I.; Iguchi, Y.; Okada, T.; Iizuka, K.; Nakazawa, M. *Ibid.* **1981**, *24*, 1149. (d) Parry, M. J.; Randall, M. J.; Hawkeswood, E.; Cross, P. E.; Dickinson, R. P. *Br. J. Pharmacol.* **1982**, *77*, 547. (e) Burke, S. E.; DiCola. G; Lefer, M. A. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 842. (f) Corey, E. J.; Pyne, S. G.; Schafer, A. I. *Tetrahedron Lett.* **1983**, *24*, 3291.
(3) Ullrich, V.; Haurand, M. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1983**, *11*, 105.
(4) Takano, T.; Dickerson, R. E. *J. Mol. Biol.* **1981**, *153*, 95.

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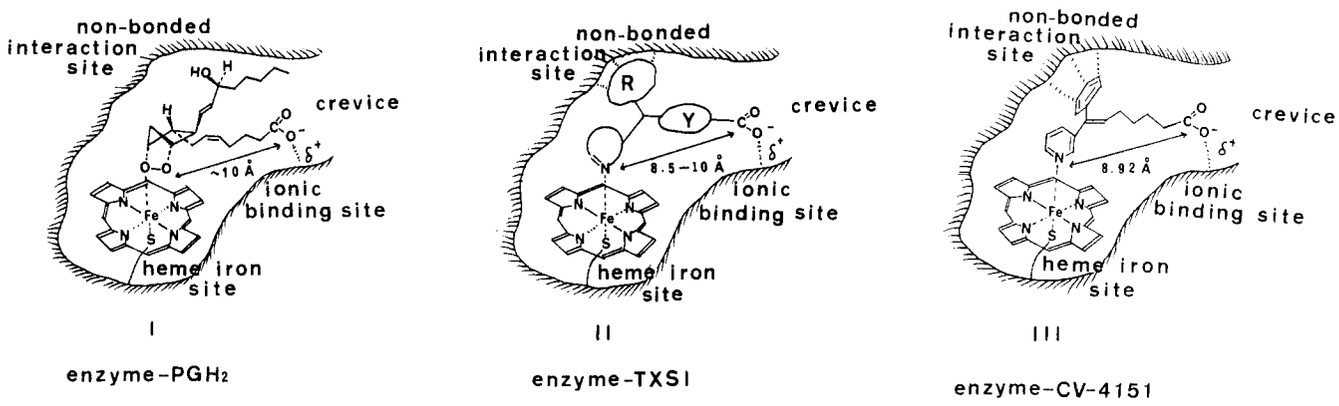
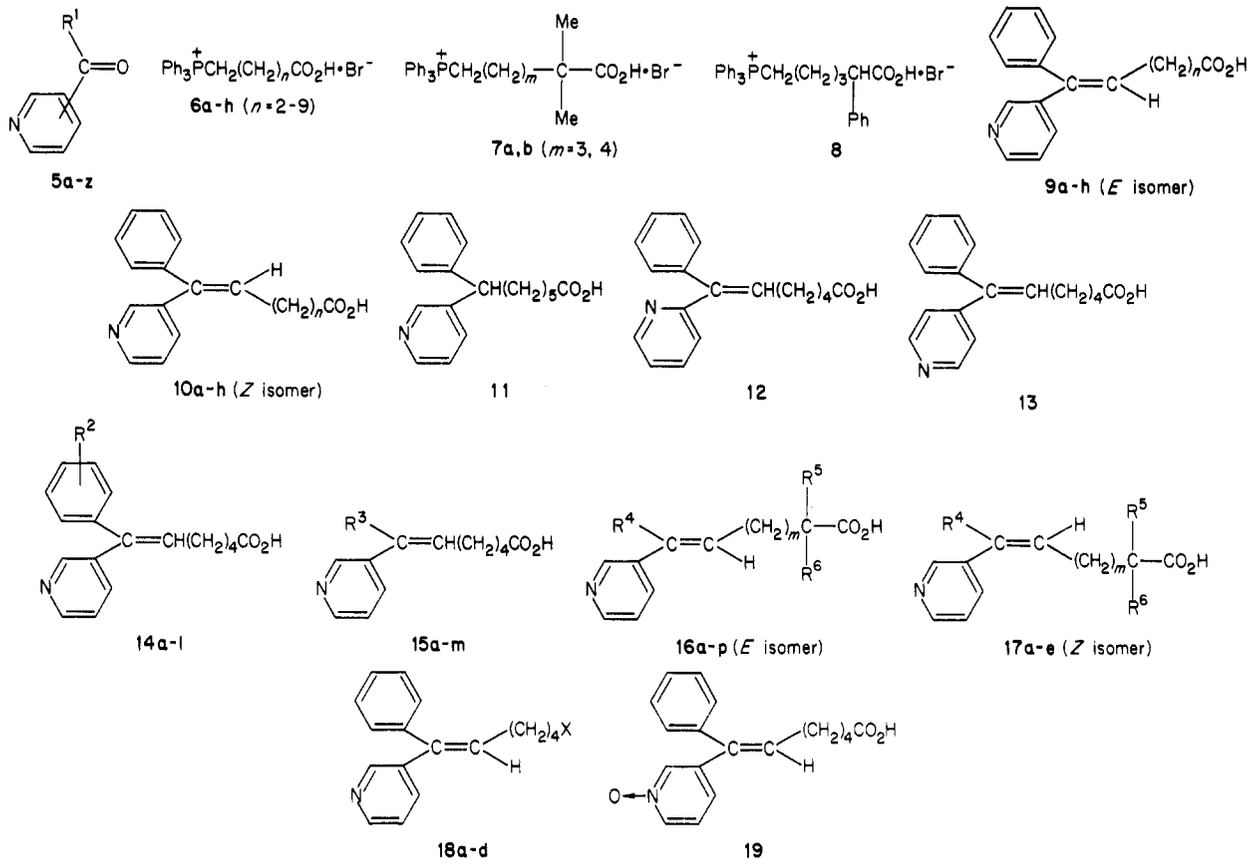


Figure 1. Illustration depicting conceptual models I–III for the enzyme–substrate (PGH_2) and the enzyme–TXSI (CV-4151) interactions.

Chart II



The conceptual models I and II should provide a useful guideline for understanding the structure–activity relation and planning the molecular design of TXSI.

In this article the synthesis, structure–activity relations, and pharmacological evaluation of a novel series of ω-pyridylalkenoic acids are described. One member of this series, (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid (**9c**; CV-4151) has been selected for further pharmacological and clinical evaluation as a TXSI.

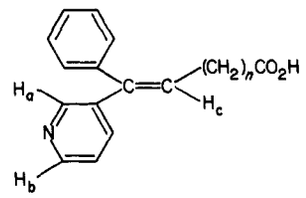
Chemistry. The synthesis of the target series of ω-(3-pyridyl)alkenoic acids (**9a–h**, **10a–h**, **12**, **13**, **14a–l**, **15a–m**, **16a–e**, and **17a–e**) was carried out by applying the reaction[6] of Wittig reagents (**6a–h**, **7a,b**, and **8**) with various 2- and 3-pyridyl ketones **5a–z**.

(5-Carboxypentyl)triphenylphosphonium bromide (**6c**; $n = 4$; Chart II) was particularly chosen as one favorable component of the Wittig reaction leading to the formation of compounds that would fulfill the structural requirements for TXSI. Condensation of various pyridyl ketones **5a–z** with phosphonium bromides (**6a–h**, **7a,b**, and **8**) in the presence of sodium amide or sodium methylsulfinylmethide in dimethyl sulfoxide mostly gave mixtures of *E* and *Z* isomers in good yields (Tables I–III and IV in part).

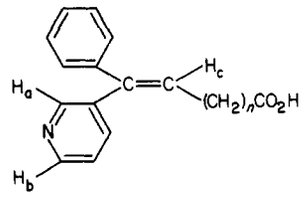
The two geometrical isomers were separated either by fractional crystallization or HPLC on a reverse-phase column. When the isomers could not be isolated in a pure state, the isomeric mixtures were esterified to ease the separation. Hydrolysis of each of esters of *E* and *Z* isomers yielded the respective isomers of *E* isomers **9a–d,f–h** and **16a–e** and *Z* isomers **10a–d,f–h** and **17a–e**. Some structures of geometrical isomers **9c**, **10c**, **10f**, **15g** (*E* isomer), and **15g** (*Z* isomer) were established by their X-ray crystallographic analyses (Figure 2) because no significant spectral evidence to distinguish the stereochemical configurations from their IR, UV, and MS spectra was available. By directly comparing the ^1H NMR spectra of

(5) Imai, Y. *J. Biochem.* **1982**, *92*, 77.
(6) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

Table I. Physical Properties and Inhibitory Activity of ω-Phenyl-ω-(3-pyridyl)alkenoic Acids **9a–h** and **10a–h** and Compounds **11**, **12**, and **13**



9a–h



10a–h

compd	*n*	formula[b]	mp, °C	yield,[a] %	characteristic chemicals shifts in ^{1}H NMR spectra, ppm H_a	H_b	H_c	inhibitory activity: IC_{50},[d] M
9a	2	$C_{16}H_{15}NO_2$	109–110	74	8.58	8.41	6.20	1.1×10^{-7}
10a	2	$C_{16}H_{15}NO_2$	oil		8.47	8.54	6.17	4.5×10^{-7}
9b	3	$C_{17}H_{17}NO_2$	82–83	87	8.56	8.42	6.12	3.0×10^{-8}
10b	3	$C_{17}H_{17}NO_2$	100–101		8.45	8.56	6.15	2.8×10^{-7}
9c	4	$C_{18}H_{19}NO_2$	114–115	86	8.53	8.44	6.12	2.6×10^{-8}
10c	4	$C_{18}H_{19}NO_2$	93–94		8.45	8.55	6.16	5.1×10^{-8}
9d	5	$C_{19}H_{21}NO_2$	oil	84	8.52	8.44	6.11	2.9×10^{-8}
10d	5	$C_{19}H_{21}NO_2$	oil		8.44	8.55	6.16	6.5×10^{-8}
(**9e** + **10e**)[c]	6	$C_{20}H_{23}NO_2$	oil	73	8.52, 8.44	8.44, 8.53	6.10, 6.16	4.1×10^{-8}
9f	7	$C_{21}H_{25}NO_2$	oil	76	8.52	8.43	6.12	3.2×10^{-8}
10f	7	$C_{21}H_{25}NO_2$	79–80		8.44	8.55	6.16	2.3×10^{-7}
9g	8	$C_{22}H_{27}NO_2$	oil	85	8.51	8.44	6.11	4.2×10^{-8}
10g	8	$C_{22}H_{27}NO_2$	90–91		8.42	8.54	6.16	3.1×10^{-7}
9h	9	$C_{23}H_{29}NO_2$	52–53	62	8.54	8.43	6.12	5.5×10^{-8}
10h	9	$C_{23}H_{29}NO_2$	94–95		8.46	8.54	6.16	5.2×10^{-7}
11		$C_{18}H_{21}NO_2$	oil	96				2.7×10^{-7}
12[c]		$C_{18}H_{19}NO_2$	oil	83				$>10^{-4}$
13[e]		$C_{18}H_{19}NO_2$	149–150[e]	32				$>10^{-4}$

[a] Yields (percent) are shown as a mixture of *E* and *Z* isomers. [b] Analyses (C, H, N) within ±0.4% of calculated values. [c] It was difficult to separate each isomer in a pure state by HPLC on a reverse-phase column. [d] IC_{50} = the molar concentration of test compound required to reduce the amount of thromboxane B_2 (the stable metabolite of thromboxane A_2) formed by incubating PGH_2 with horse platelet microsomes by 50%. [e] HPLC analysis of the product showed it to be a 1:1 mixture of *E* and *Z* isomers, one of which is crystalline, but the stereochemistry is not clear.

E isomers **9a–h** with *Z* isomers **10a–h**, it was found that two protons of H_a and H_b in the 3-pyridyl moieties for the *E* and *Z* isomers appear, respectively, at δ 8.51–8.58 (1 H, J = 2 Hz) and δ 8.41–8.46 (1 H, quartet, J = 1.5 and 5 Hz) and at δ 8.45–8.47 (1 H, J = 2 Hz) and δ 8.54–8.55 (1 H, quartet, J = 1.5 and 5 Hz). The relation of these chemical shifts for H_a and H_b was revealed to be the reverse of each other. The signals of Hc in *E* isomers **9a–h** appear in slightly higher field (δ 6.10–6.12) than those in *Z* isomers **10a–h** (δ 6.15–6.16). These results have been helpful in the structure assignments of the geometrical isomers in the related analogues.

Most reactions proceeded smoothly within a few hours, but with pyridyl ketones having sterically bulky groups and/or an active hydrogen next to the carbonyl group, the reactivities were somewhat low and yields somewhat poor. Stereochemical assignments of most products rested on their ^{1}H NMR spectra and mobility on silica gel. In general, *E* isomers **9a–h** were more polar on silica gel than were *Z* isomers **10a–h**.

No significant change in the ratio of the mixture of *E* and *Z* isomers **9a–h** and **10a–h** was observed under various reaction conditions of temperatures, solvents, and bases employed. Since *E* isomers generally exhibited more potent inhibitory action than *Z* isomers (Table I), chemical isomerization of *Z* isomer **10c** was examined. Acid-catalyzed isomerization of the *Z* isomer **10c** or a mixture of *E* and *Z* isomers **9c** and **10c** was effected in an aqueous hydrobromic acid at a refluxing temperature to give a 2:1 equilibrium mixture of the *E* and *Z* isomers.

To examine the biological roles of the trisubstituted double bond, catalytic hydrogenation of the compound **9c** was carried out in the presence of 5% palladium charcoal to give the corresponding dihydro compound **11**.

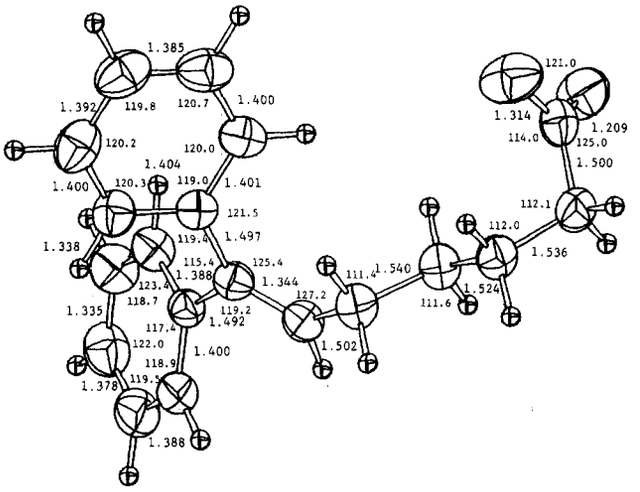


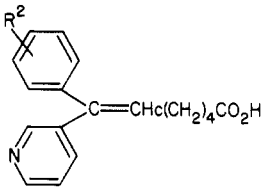
Figure 2. ORTEP presentation of (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid (**9c**; CV-4151).

The Wittig reagents **6a–h**, **7a,b**, and **8** employed above were prepared by reacting the corresponding ω-bromo carboxylic acids with triphenylphosphine, whereas pyridyl ketones **5a–z** were obtained commercially or by the reactions of lithiopyridines or aryllithium compounds with aldehydes followed by oxidation of the resulting alcohols.

A series of analogues (**16f–p**), in which the substitution on α-methylene was varied, was prepared from the reactions of the methyl ester of compound **9c** in the presence of lithium diisopropylamide with various kinds of electrophiles such as ketones, disulfides, and alkyl and aralkyl halides (Table IV).

Other modifications of compound **9c** were made in the

Table II. Physical Properties and Inhibitory Activity of 7-(Substituted-phenyl)-7-(3-pyridyl)-6-heptenoic Acids **14a–l**

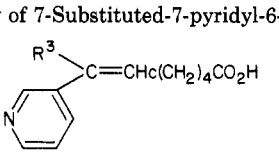


14a-l

compd[a]	R^2	formula[b]	yield, %	characteristic chemical shifts of H_c in ^1H NMR spectra, values in ppm	E/Z[e,f]	IC_{50},[d] M
14a[c]	4-Me	$C_{19}H_{21}NO_2$	73	6.09/6.13	1:1	8.5×10^{-8}
14b	4-OMe	$C_{19}H_{21}NO_3$	76	6.02/6.05	1:1	8.0×10^{-8}
14c	4-$CHMe_2$	$C_{21}H_{25}NO_2$	85	6.07/6.13	1:1	6.3×10^{-8}
14d	4-Br	$C_{18}H_{18}NO_2Br$	44	6.10/6.14	2:3	8.2×10^{-8}
14e	3-Br	$C_{18}H_{18}NO_2Br$	62	6.10/6.14	2:3	1.8×10^{-7}
14f	2-Br	$C_{18}H_{18}NO_2Br$	22	6.28[g]		1.3×10^{-7}
14g	4-F	$C_{18}H_{18}NO_2F$	45	6.09/6.12	2:3	8.3×10^{-8}
14h	3-F	$C_{18}H_{18}NO_2F$	65	6.14/6.20	2:3	5.5×10^{-8}
14i	2-F	$C_{18}H_{18}NO_2F$	33	6.07/6.28	1:9	7.0×10^{-8}
14j	3-CF_3	$C_{19}H_{18}F_3NO_2$	61	6.20/6.22	2:3	5.2×10^{-8}
14k	3-NO_2	$C_{18}H_{18}N_2O_4$	82	6.20/6.28	2:3	7.3×10^{-8}
14l[h]	H	$C_{18}H_{19}NO_2$	86	6.12/6.16	1:1	3.6×10^{-8}

[a] All compounds are a mixture of *E* and *Z* isomers and were oily substances except for **14a**. [b] Analyses (C, H, N) within ±0.4% of calculated values. [c] The *Z* isomers is a crystalline compound with mp 126–127 °C. [d] IC_{50} = the molar concentration of test compound required to reduce the amount of thromboxane B_2 (the stable metabolite of thromboxane A_2) formed by incubating PGH_2 with horse platelet microsomes by 50%. [e] The ratios were obtained from the peak height of proton H_c in isomers. [f] Isomers in which chemical shifts of H_c are higher are tentatively presented as *E* isomers and other as *Z* isomers. [g] Single product was observed. [h] **14l** represents a 1:1 mixture of **9c** and **10c**.

Table III. Physical Properties and Inhibitory Activity of 7-Substituted-7-pyridyl-6-heptenoic Acids **15a–m**



15a-m

compd	R^3	stereochem[a]	formula[b]	mp, °C	yield,[c] %	characteristic chemical shifts of H_c in ^1H NMR spectra, ppm	E/Z[e]	IC_{50},[d] M
15a	H	*E/Z*	$C_{12}H_{15}NO_2$	oil	92	5.80/6.29	2:3	2.5×10^{-7}
15b	Me	*E*	$C_{13}H_{17}NO_2$	oil	35	5.58	3:7	7.1×10^{-8}
	Me	*Z*	$C_{13}H_{17}NO_2$	82–83		6.29		$2:1 \times 10^{-7}$
15c	$(CH_2)_5Me$	*E/Z*	$C_{18}H_{27}NO_2$	oil	41	5.54/5.67	3:1	7.5×10^{-8}
15d	$(CH_2)_3Ph$	*E/Z*	$C_{21}H_{25}NO_2$	oil	23	5.55/5.69	4:1	6.5×10^{-8}
15e	1-naphthyl	*Z*	$C_{22}H_{21}NO_2$	oil	20	6.50[f]		3.4×10^{-8}
15f	2-naphthyl	*E*	$C_{22}H_{21}NO_2$	oil	51	6.21	3:2	1.9×10^{-8}
		Z	$C_{22}H_{21}NO_2$	157–158		6.30		6.0×10^{-8}
15g	2-thienyl	*E*	$C_{16}H_{17}NO_2S$	84–85	84	6.04	2:3	2.0×10^{-8}
		Z	$C_{16}H_{17}NO_2S$	93–94		6.22		5.4×10^{-8}
15h	3-thienyl	*E*	$C_{16}H_{17}NO_2S$	oil	73	6.06	2:3	3.1×10^{-8}
		Z	$C_{16}H_{17}NO_2S$	100–102		6.21		6.2×10^{-8}
15i	3-methyl-2-thienyl	*E/Z*	$C_{17}H_{19}NO_2S$	oil	64	6.04	1:4	2.9×10^{-8}
15j	2-thiazolyl	*Z*	$C_{15}H_{16}N_2O_2S$	97–98	44	6.21/6.85	1:5	9.8×10^{-7}
15k	2-benzo[*b*]thienyl	*Z*	$C_{20}H_{19}NO_2S$	145–146	63	6.33[f]		1.3×10^{-6}
15l	3-pyridyl		$C_{17}H_{18}N_2O_2$	oil	43	6.21[f]		1.0×10^{-7}
15m	3,4-(methylenedioxy)phenyl	*E*	$C_{19}H_{19}NO_4$	oil	76	6.05	2:3	4.1×10^{-8}
		Z	$C_{19}H_{19}NO_4$	90–91		6.06		5.6×10^{-8}

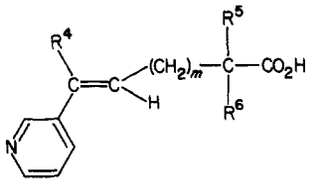
[a] Stereochemistry rested on their ^1H NMR spectra as shown in Table II. [b] Analyses (C, H, N) within ±0.4% of calculated values. [c] Yield (percent) represents a mixture of *E* and *Z* isomers. [d] IC_{50} = the molar concentration of test compound required to reduce the amount of thromboxane B_2 (the stable metabolite of thromboxane A_2) formed by incubating PGH_2 with horse platelet microsomes by 50%. [e] Ratios were obtained from the peak height of H_c in stereoisomers. [f] Single product was observed.

carboxyl portion of the molecule by esterification, amidation, and reduction with lithium aluminum hydride to give compounds **18a–d**. Oxidation of compound **9c** with *m*-chloroperbenzoic acid gave the corresponding pyridine *N*-oxide **19** (Table V).

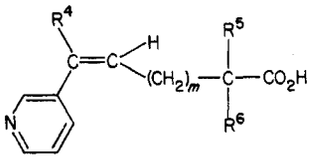
Pharmacological Results and Discussion. In vitro and ex vivo inhibitory actions of compounds on TXA_2 synthetase are summarized in Tables I–VI.

In a series of in vitro tests for the inhibition of TXA_2-synthetase, the first compound **9c** exhibited a very potent effect (Table I). To determine the compound with the highest potency and the longest duration in action in both assay systems, we synthesized a series of ω-phenyl-ω-(3-pyridyl)alkenoic acids **9a–h** and **10a–h** with two to

Table IV. Physical Properties and Inhibitory Activity of Compounds **16a–p** and **17a–e**



16a-p

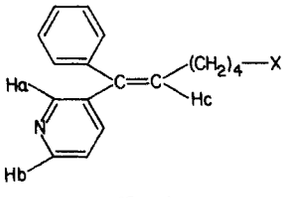


17a-e

compd	m	R^4	R^5	R^6	formula[a]	mp, °C	yield, %	IC_{50},[b] M	characteristic chemical shifts in ^1H NMR spectra, ppm H_a	H_b	H_c
16a	3	Ph	Me	Me	$C_{20}H_{23}NO_2$	oil	43	2.1×10^{-8}	8.56	8.44	6.12
17a	3	Ph	Me	Me	$C_{20}H_{23}NO_2$	137–138	42	3.0×10^{-8}	8.46	8.55	6.16
16b	4	Ph	Me	Me	$C_{21}H_{25}NO_2$	oil	54	4.5×10^{-8}	8.54	8.46	6.11
17b	4	Ph	Me	Me	$C_{21}H_{25}NO_2$	109–110	58	3.8×10^{-8}	8.46	8.55	6.14
16c	3	2-Th[c]	Me	Me	$C_{18}H_{21}NO_2S$	oil	41	1.8×10^{-8}	8.60	8.49	6.03
17c	3	2-Th	Me	Me	$C_{18}H_{21}NO_2S$	141–142	40	3.7×10^{-8}	8.49	8.60	6.22
16d	4	2-Th	Me	Me	$C_{19}H_{23}NO_2S$	oil	32	4.8×10^{-8}	8.58	8.46	6.01
17d	4	2-Th	Me	Me	$C_{19}H_{23}NO_2S$	138–139	30	4.3×10^{-8}	8.49	8.59	6.20
16e	3	2-Th	Ph	H	$C_{22}H_{21}NO_2S$	135–136	58	3.2×10^{-8}	8.56	8.44	5.99
17e	3	2-Th	Ph	H	$C_{22}H_{21}NO_2S$	174–175	57	5.0×10^{-8}	8.48	8.60	6.17
16f	3	Ph	SPh	H	$C_{24}H_{23}NO_2S$	oil	97	3.3×10^{-8}	8.56	8.43	6.12
16g	3	Ph	SMe	H	$C_{19}H_{21}NO_2S$	oil	50	3.0×10^{-8}	8.64	8.42	6.13
16h	3	Ph	S-*i*-Bu	H	$C_{22}H_{27}NO_2S$	oil	49	1.1×10^{-7}	8.54	8.46	6.13
16i	3	Ph	Bz	H	$C_{25}H_{25}NO_2$	oil	87	5.8×10^{-8}	8.56	8.43	6.11
16j	3	Ph	CH_2=$CHCH_2$	H	$C_{21}H_{23}NO_2$	oil	85	5.0×10^{-8}	8.53	8.46	6.13
16k	3	Ph	HC≡CCH_2	H	$C_{21}H_{21}NO_2$	oil	82	2.8×10^{-8}	8.60	8.43	6.13
16l	3	Ph		H	$C_{23}H_{27}NO_3$	oil	85	6.5×10^{-8}	8.57	8.43	6.13
16m	3	Ph		H	$C_{21}H_{25}NO_3$	oil	86	4.2×10^{-8}	8.63	8.41	6.13
16n	3	Ph	CH_2OMe	H	$C_{20}H_{23}NO_3$	oil	87	4.1×10^{-8}	8.57	8.46	6.13
16o	3	Ph		H	$C_{23}H_{25}NO_2$	oil	74	6.0×10^{-8}	8.53	8.43	6.12
16p	3	Ph	–(Me)C=CH_2	H	$C_{21}H_{23}NO_2$	oil	68	2.8×10^{-8}	8.56	8.43	6.13

[a] Analyses (C, H, N) within ±0.4% of calculated values. [b] IC_{50} = the molar concentration of test compound required to reduce the amount of thromboxane B_2 (the stable metabolite of thromboxane A_2) formed by incubating PGH_2 with horse platelet microsomes by 50%. [c] 2-Th means 2-thienyl group.

Table V. Physical Properties and Inhibitory Activities in in Vitro and ex Vivo Systems of Compounds **18a–d**, **9g**, and **19**



18a-d

compd	X	formula[a]	mp, °C	characteristic chemical shifts in ^1H NMR spectra, ppm H_a	H_b	H_c	IC_{50},[b] M	ex vivo test system, % inhibn[c]
18a	COOMe	$C_{19}H_{21}NO_2$	oil	8.49	8.42	6.07	1.0×10^{-7}	92
18b	COOEt	$C_{20}H_{23}NO_2$	oil	8.49	8.41	6.08	6.0×10^{-7}	90
18c	CH_2OH	$C_{18}H_{21}NO$	oil	8.48	8.40	6.09	2.2×10^{-6}	92
18d	$CONH_2$	$C_{18}H_{20}N_2O$	97–98	8.48	8.42	6.08	4.0×10^{-7}	93
9g	$(CH_2)_4COOH$	$C_{22}H_{27}NO_2$	oil	8.51	8.44	6.11	4.2×10^{-8}	92
19		$C_{18}H_{19}NO_3$	166–167	8.28	8.26	6.22	$>10^{-5}$	85

[a] Analyses (C, H, N) within ±0.4% of calculated values. [b] IC_{50} = the molar concentration of test compound required to reduce the amount of thromboxane B_2 (the stable metabolite of thromboxane A_2) formed by incubating PGH_2 with horse platelet microsomes by 50%. [c] Percent inhibition on the production of serum TXB_2 2 h after oral administration of compound (10 mg/kg) to the rat.

nine methylene groups. The highest potency appeared in compound **9c**, (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid (CV-4151), with four methylene groups. On the basis of X-ray analysis, the distances between the nitrogen atom and the carbonyl group in *E* isomer **9c** and *Z* isomer **10c** were found to be 8.92 and 4.92 Å, respectively (Figure 2). The distance in **9c** is very similar to that between the endoperoxide bonding (O–O) and the carboxyl group in PGH_2. The in vitro potency of compounds **9a–h** and **10a–h** depended on the number of methylene groups. In general, the inhibitory activity of *E* isomers **9a–h** was more potent than *Z* isomers **10a–h**, when compared with compounds with the same number of methylene groups. When the trisubstituted double bond in **9c** was hydrogenated,

Table VI. Comparison of TXA_2-Synthetase Inhibitory Activity of the High Potent Compounds in ex Vivo Test System

compd	no. of rats	production of serum TXB_2 24 h after oral administration of drug (1 mg/kg) to the rat: % inhibn[a]
9c	5	53 (90)[b]
9d	5	24
9e	5	17
9g	5	10
16a	5	14
16c	5	17
16h	5	8
16m	5	37
16r	5	18
18b	5	35

[a] The percent inhibition was calculated from the equation of $[1 - (B/A)] \times 100$, in which A is the amount of thromboxane B_2 (167 ng/mL, $n = 14$) in the rat untreated with the compound and B is the amount of thromboxane B_2 in the rat treated with the compound. [b] The number in bracket shows percent inhibition 24 h after the oral administration of 10 mg/kg.

the activity of product **11** was decreased by 10-fold from that of the original compound **9c**. These results indicate that the molecular size, stereochemistry, and presence of the trisubstituted double bond play important roles in higher potency.

When compounds with a substituent(s) on the phenyl group were compared with the original compound **9c** (Table II), the phenyl analogues were observed to be slightly weaker inhibitors of thromboxane synthetase. This suggests that phenyl groups with diverse electronic and lipophilic properties may reduce a possible interaction with a hydrophobic region of the enzyme by π–π stacking or nonbonded interaction to enhance the potency. The potency of the compounds in which R^3 is 1- or 2-naphthyl, 2- or 3-thienyl, and 3-methyl-2-thienyl groups was much the same as **9c** (Table III). This result indicates that an aromatic group of phenyl, naphthyl, or thienyl in R^3 may enhance the activity by possible interaction with a lipophilic region at the active site of the enzyme. Insertion of methylene groups between the phenyl group and the trisubstituted double bond also decreased the potency. The presence of an aromatic ring directly bound to the double bond seems to be favorable for high potency. However, compounds (**15a,b,j–l**) in which R^3 is a hydrogen, methyl, 3-pyridyl, 2-thiazolyl, or 2-benzo[*b*]thienyl group were considerably less active. Positional isomers **12** and **13** were almost completely inactive, even the same molecular feature as **9c** in size, weight, and stereochemistry (Table I). This indicates that the 3-pyridyl nitrogen atom in the molecules is the essential factor for TXSI.

As shown in Table IV, introducing substituents on the α-methylene group did not produce the significant expected biological improvements in the derivatives **16a–p** and **17a–e** when they were compared with the original compounds **9c** and **15g** (*E* isomer). However, some compounds (**16a, 16c, 16k**, and **16p**) with dimethyl, propargyl, isopropenyl groups on the α-methylene group were slightly more potent than original compounds **9c** and **15g** (*E* isomer).

On the basis of molecular modifications and biological results, one might envision a vague feature of the thromboxane synthetase in which there would be some tolerance in the region at the entrance of the crevice of the enzyme to meet with a TXSI molecule. However, some limitations might exist, possibly due to charge or steric factors in the region of the active site of the enzyme where the 3-pyridyl nitrogen interacts.

In vitro assay of the compounds **18a–d** derived by chemical modifications in the region of the carboxyl group showed them to be weaker than the original compound **9c** (Table V). The pyridine *N*-oxide **19** was completely inactive in vitro. However, in the ex vivo test system, when these compounds were administered orally to the rat, they exhibited almost the same activity as **9c** (Table V). It is of great interest that the compounds that are less active in vitro can be metabolically transformed into common active metabolites in a living system. This was proved by isolating their metabolic products from rat plasma by HPLC and determining the structure of the plasma metabolite by mass spectrometry, which revealed that the main metabolite was **9c**. These results indicated that the reduction of the methylene groups by β-oxidation, reduction of pyridine *N*-oxide, hydrolysis of esters and amides, and oxidation of the terminal hydroxymethyl group to generate active metabolites easily occurred in the rat.

Table VI gives the ex vivo assay results when the highly potent compounds in the present study were administered orally to the rat. It was found that compounds **9c** was most potent and acted for the longest time.

Compound **9c** did not show any effects on other enzymes[7] involved in arachidonic acid metabolism, such as fatty acid cyclooxygenase and prostaglandin I_2 synthetase, and 15- and 5-lipoxygenase from soybean and rat basophilic leukemia (RBL-1) cells, respectively. Thus, the potent compounds that we have synthesized specifically and strongly inhibit thromboxane synthetase.

Considerations of the Enzyme–Drug Interaction. The structure–activity relations between the synthesized compounds is consistent with our conceptual model II. The compounds with high potency and the already known TXSI have almost the same size and volume as PGH_2, and the distance between the nitrogen atom and the terminal carboxyl group is concentrated in the range of about 8.5–10 Å, which is nearly equal to that between the endoperoxide bonding and the carboxyl group in PGH_2. In its molecule size and molecular features, the most potent compound **9c** (CV-4151) appears to be one of the most suitable molecules for the conceptual model II. Therefore, model II could be rewritten as model III in Figure 1. It seems reasonable to postulate that, at least for conceptual model II, three binding sites, which may have great relevance to the molecular volume and size, may exist in the enzyme. Such postulated sites might undergo interactions with the aromatic ring, carboxyl group, and pyridine moiety in the drug molecules by π–π stacking or by nonbonded interaction to enhance the potency, by ionic binding, and by coordinated interaction with the heme iron at the active site of the enzyme. The structure–activity relations and molecular design for TXSI might be understood in terms of the enzyme–drug interaction by using the conceptual models I–III.

Experimental Section

Melting points were obtained with a Yanaco micro-melting apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. Where elemental analyses are given, results obtained were within ±0.4% of the theoretical values. Solutions in organic solvents were dried with anhydrous $MgSO_4$. Column chromatography was carried out on silica gel (E. Merck, particle size 0.70–230 mesh). High-performance liquid chromatography

(7) Nishikawa, K.; Terashita, Z.; Imamoto, T.; Imura, Y.; Tanabe, M.; Kawazoe, K.; Hirata, M.: a biological study has been presented at the 9th International Congress of Pharmacology in London, England, July 1984. The results will be published elsewhere.

(HPLC) was carried out on a Hitachi 638-30 liquid chromatograph. Nucleosil 5 C_{18} (Macherey-Nagel, Germany) was used for analytical HPLC. Single crystallographic analyses were performed by M. Takamoto and Y. Wada.

Pyridyl Ketones 5a–z. 2-, 3-, and 4-pyridylphenyl ketones were commercially available (Wako pure Chemical Industries, Osaka). 4-Methylphenyl 3-pyridyl ketone (mp 77–78 °C) and 3-nitrophenyl 3-pyridyl ketone (mp 75–76 °C) were prepared according to the method of Högberg et al.[8] 4-Methoxyphenyl 3-pyridyl ketone (mp 98–99 °C), 4-isopropylphenyl 3-pyridyl ketone (oil), 4-bromophenyl 3-pyridyl ketone (mp 125–126 °C), 3-bromophenyl 3-pyridyl ketone (57–58 °C), 2-bromophenyl 3-pyridyl ketone (oil), 4-fluorophenyl 3-pyridyl ketone (mp 92–93 °C), 3-fluorophenyl 3-pyridyl ketone (mp 45–46 °C), 2-fluorophenyl 3-pyridyl ketone (oil), 1-naphthyl 3-pyridyl ketone (oil), 2-naphthyl 3-pyridyl ketone (mp 71–72 °C), 2-thienyl 3-pyridyl ketone (mp 93–94 °C), 3-thienyl 3-pyridyl ketone (mp 74–75 °C), bis(3-pyridyl) ketone (mp 115–116 °C), 3,4-(methylenedioxy)-phenyl 3-pyridyl ketone (mp 112–113 °C), 3-methyl-2-thienyl 3-pyridyl ketone (oil), 2-thiazolyl 3-pyridyl ketone (mp 72–73 °C), *n*-hexyl 3-pyridyl ketone (oil), 3-phenylpropyl 3-pyridyl ketone (oil), 2-benzo[*b*]thienyl 3-pyridyl ketone (mp 94–95 °C) were prepared from pyridylmethanols described below according to the method of Huang and Swern.[9] The following 3-pyridylmethanols were prepared by the coupling reaction of 3-lithiopyridine with aldehydes according to the method of Pearce et al:[10] (4-methoxyphenyl)(3-pyridyl)methanol (mp 106–107 °C), (4-isopropylphenyl)(3-pyridyl)methanol (mp 107–108 °C), (4-bromophenyl)(3-pyridyl)methanol (mp 125–126 °C), (3-bromophenyl)(3-pyridyl)methanol(mp 95–95 °C), (2-bromophenyl)(3-pyridyl)methanol (mp 125–126 °C), (4-fluorophenyl)(3-pyridyl)methanol (oil), (3-fluorophenyl)(3-pyridyl)methanol (mp 86–87 °C), (2-fluorophenyl)(3-pyridyl)methanol (mp 73–74 °C), [3-(trifluoromethyl)phenyl](3-pyridyl)methanol (oil), (1-naphthyl)(3-pyridyl)methanol (mp 123–124 °C), (2-naphthyl)-(3-pyridyl)methanol (mp 135–136 °C), (2-thienyl)(3-pyridyl)-methanol (mp 59–60°C), (3-thienyl)(3-pyridyl)methanol (oil), (3-methyl-2-thienyl)(3-pyridyl)methanol (oil), [3,4-(methylenedioxy)phenyl](3-pyridyl)methanol (mp 105–106 °C), bis(3-pyridyl)methanol (oil), and (3-pyridyl)(2-thiazolyl)methanol (oil).

Preparation of Phosphonium Bromides 6a–h, 7a,b, and 8 for Wittig Reagents. A solution of ω-bromo carboxylic acid (0.1 mol) and triphenylphosphine (0.1 mol) in MeCN (100 mL) was heated at refluxing temperature for 18 h and then the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure to give the following phosphonium bromides: (3-carboxypropyl)triphenylphosphonium bromide (**6a**; mp 246–248 °C), (4-carboxybutyl)triphenylphosphonium bromide (**6b**; mp 209–210 °C), (5-carboxypentyl)triphenylphosphonium bromide (**6c**; mp 204–205 °C), (6-carboxyhexyl)triphenylphosphonium bromide (**6d**; mp 185–187 °C), (7-carboxyheptyl)triphenylphosphonium bromide (**6e**; mp 122–124 °C), (8-carboxyoctyl)triphenylphosphonium bromide (**6f**; mp 90–95 °C), (9-carboxynonyl)triphenylphosphonium bromide (**6g**; oil), (10-carboxydecyl)triphenylphosphonium bromide (**6h**; oil), (5-carboxy-5-methylhexyl)triphenylphosphonium bromide (**7a**; mp 160–165 °C), (6-carboxy-6-methylheptyl)triphenylphosphonium bromide (**7b**; oil), and (5-carboxy-5-phenylpentyl)triphenylphosphonium bromide (**8**; mp 210–215 °C).

ω-Pyridylalkenoic Acids 9a–h, 10a–h, 12, 13, 14a–l, 15a–m, 16a–e, and 17a–e. General Procedure. A stirred suspension of NaH (12 mmol, 60% mineral oil dispersion, washed with hexane to remove the oil and dried before use) in Me_2SO (10 mL) was heated at 85 °C for 40 min under Ar; the solution was then cooled. To the solution was added a phosphonium bromide (5.5 mmol) described above portionwise at such a rate as to keep a temperature of 25–30 °C. After the addition was completed, the mixture was stirred for 10 min at ambient temperature. To the mixture was added a solution of a pyridyl ketone (5.0 mmol) described above in Me_2SO (5 mL) for 10 min and then the mixture was stirred under the same conditions until the color of the phospholane had disappeared. When the reaction was completed, water (50 mL) and toluene (50 mL) were added, and then the mixture was shaken vigorously. The organic layer was partitioned and the aqueous layer was acidified to pH 5.5 with 2 M HCl. The resulting product was extracted with EtOAc. The extract was washed with water, dried, and concentrated. The residue was chromatographed on silica gel with an IPE–EtOAc solvent system as eluent to give a mixture of *E* and *Z* isomers of ω-pyridylalkenoic acids.

Some isomeric mixtures were separated into respective *E* and *Z* isomers by fractional recystallization. When respective isomers could not be isolated in a pure state, the isomeric mixture was esterified to ease the separation. Esterification of isomeric mixtures (1.0 g) was carried out in an ethanolic solution (20 mL) by adding thionyl chloride (2 mL) at room temperature. The ethyl ester of *E* and *Z* isomers were chromatographed on a reverse-phase column using a water–MeCN–acetic acid solvent system as eluent to afford the ethyl esters of the respective isomers. The respective ethyl esters were hydrolyzed in 1 M NaOH aqueous ethanolic solution at room temperature for 1 h, followed by acidification with 2 M HCl to pH 4.5. Working up in the usual manner gave the respective isomers. The physical properties and biological results of **9a–h, 10a–h, 12, 13, 14a–l, 15a–m, 16a–e,** and **17a–e** are shown in Tables I–IV and VI.

Acid-Catalyzed Isomerization of 10c. A solution of (*Z*)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid (**10c**; 3.0 g) in 25% hydrobromic acid (20 mL) was heated at refluxing temperature for 18 h. After the reaction was cooled and then adjusted with ammonia to pH 4.5, the product was extracted twice with EtOAc (50 mL). The combined organic layer was washed with water, dried, and evaporated under reduced pressure. HPLC analysis of the product showed it to be a 2:1 mixture of *E* and *Z* isomers **9c and 10c**. The crystalline product was recrystallized from EtOAc to give *E* isomer **9c** (1.4 g, purity >98%).

7-Phenyl-7-(3-pyridyl)heptanoic Acid (11). A solution of (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid (**9c**; 0.7 g, 2.5 mmol) in methanol (20 mL) was hydrogenated over 5% Pd–C (0.7 g) under atmospheric pressure until 1 molar equiv of hydrogen had been absorbed. After the reaction was completed, the catalyst was removed by filtration and the filtrate was concentrated in reduced pressure. The residue was chromatographed on silica gel with a IPE–EtOAc (1:1) solvent system as eluent to give the dihydro compound **11** (0.6 g, 86%) as an oil. The physical properties and biological results are listed in Table I.

Methyl (*E*)-7-Phenyl-7-(3-pyridyl)-6-heptenoate (18a). To a solution of **9c** (28 g, 0.1 mol) in MeOH (200 mL) was added thionyl chloride (10 mL) at ambient temperature. After it was stirred for 18 h at room temperature, the solution was concentrated under reduced pressure. To the residue was added a saturated $NaHCO_3$ solution (200 mL), and the product was then extracted twice with EtOAc. The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with IPE–EtOAc (1:1) as eluent to give the methyl ester **18a** (30 g, 97%). The physical properties and biological results are listed in Table V.

Ethyl (*E*)-7-phenyl-7-(3-pyridyl)-6-heptenoate (**18b**) was prepared from **9c** similarly to the above method with use of ethanol instead of methanol. Physical properties and biological results are given in Table V.

Preparation of Compounds 16f–p. General Procedure. *n*-Butyllithium (1.6 M solution in hexane, 5 mL, 8 mmol) was added to a solution of diisopropylamine (0.8 g, 8 mmol) in THF (10 mL) at −70 °C under Ar during 10 min, followed by the addition of a solution of **18a** (1.2 g, 4 mmol) in THF (4 mL) under the same conditions. The solution was stirred for 15 min and then an electrophile (disulfides, ketones, propargyl bromide, allyl bromide) (4.5 mmol) in HMPA (2 mL) was added. After the mixture was stirred for 15 min at −60 °C, 2 M HCl (5 mL) was added and the solution was allowed to warm to room temperature. The reaction mixture was made alkaline with $NaHCO_3$ and the product was extracted with EtOAc. The extract was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with IPE–EtOAc as eluent to give the methyl ester, which was hydrolyzed and worked up in the usual way to give the free acid **16f–p**. Physical properties and biological results

(8) Högberg, T.; Ulff, B.; Renyi, A. L.; Ross, S. B. *J. Med. Chem.* **1981**, *24*, 1499.
(9) Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 4537.
(10) Pearce, P. J.; Richards, D. H.; Scilly, N. F. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1655.

are shown in Tables IV and VI.

(*E*)-7-Phenyl-7-(3-pyridyl)-6-hepten-1-ol (18c). A solution of **18b** (15 g, 48 mmol) in THF (100 mL) was added to a suspension of lithium aluminum hydride (5 g) in THF (100 mL) at 0 °C. After the solution was stirred for 30 min, a saturated solution of Rochelle salt (15 mL) was added to the reaction mixture to precipitate the inorganic material. The organic layer was isolated, and the precipitates were washed with THF (100 mL). The THF layers were combined, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc as eluent to give the alcohol **18d** (12.1 g, 94%) as an oil. The physical properties and biological results are given in Table V.

(*E*)-7-Phenyl-7-(3-pyridyl)-6-heptenamide (18d). A solution of **9c** (1.0 g) in oxalyl chloride (5 mL) was heated at 60 °C for 1 h. The solution was concentrated under reduced pressure to dryness. The residue was treated with 5% methanolic ammonia (20 mL) with cooling at 0 °C. After it was stirred for 30 min, the solution was evaporated and the residue was crystallized from EtOAc to give the amide **18d** (870 mg). The physical properties and biological results are shown in Table V.

(*E*)-7-Phenyl-7-(1-oxido-3-pyridyl)-6-heptenoic Acid (19). To a solution of **9c** (1.5 g, 5.3 mmol) in $CHCl_3$ (50 mL) was added *m*-chloroperbenzoic acid (1.3 g, 70% purity, 5.3 mmol) portionwise. After the reaction was completed, the solvent was removed under reduced pressure. The residue was recrystallized from EtOAc to give the *N*-oxide **19** (1.5 g) as crystals. The physical properties and biological results are shown in Table V.

Pharmacological Assay for Thromboxane A_2 Synthetase Inhibition. In Vitro Experiments. Horse platelet microsomes (HPM)[11] were prepared as the enzyme source of thromboxane synthetase according to the method of Needleman et al.[12] Inhibitory action of compounds on the enzyme activity was examined by using radioimmunoassay for thromboxane B_2 (the stable metabolite of thromboxane A_2) produced by incubating PGH_2 with horse platelet microsomes. Duplicate samples of PGH_2 (30 ng/20 μL) in 50 mM Tris buffer (pH 7.50) were preincubated at room temperature for 5 min with or without compounds synthesized here (final concentrations of the compounds were from 10^{-5} to 10^{-8} M in 0.01% dimethyl sulfoxide), and then thromboxane synthetase (HPM) (23 μg of protein/50 μL of the Tris buffer) was added and incubation was continued for 5 min at 4 °C. The reactions were stopped by the addition of 1 mL of the Tris buffer and stored at −78 °C until determination of TXB_2 by radioimmunoassay. Five microliters of the reaction mixture was used to determine the amount of TXB_2. A rabbit antiserum to TXB_2 was diluted 1:1000 with buffer I (0.1 M phosphate buffer at pH 7.50 containing 0.1% gelatin, 0.9% NaCl, and 0.01% NaN_3). The authentic TXB_2 (10–1000 pg) for the standard curve was dissolved in 50 μL of buffer I. [^{3}H]TXB_2 in buffer (10000 cpm/100 μL) was added to the reaction mixture or authentic TXB_2, after which the 50 μL of diluted rabbit antiserum was added. The tubes were shaken for 15 s and incubated for 1 h at 25 °C then kept for 16–20 h at 4 °C. To separate the antiserum-bound and free TXB_2, dextran-coated charcoal (0.1 mL of buffer I containing 2.5 mg of charcoal and 0.25 mg of dextran) was added to each tube and mixed for 15 s. The tubes were left standing on ice for 10 min followed by centrifugation for 5 min at 3000 rpm at 4 °C. The radioactivity of the supernatant (180 μL) was measured in 4 mL of ACS II scintillator with a scintillation counter (LKB-1216, Rackbeta). The counts of antiserum blank tubes, containing no antiserum, were subtracted from the counts of all other tubes as nonspecific binding. The standard curve was plotted as a function of logit vs. the amount of authentic TXB_2 and the binding in each sample was compared to the standard curve. The IC_{50} value of each compound was obtained from the concentration–inhibition curves. The IC_{50} values are averages of duplicate samples.

Ex Vivo Experiments. Compounds at a dose of 1 or 10 mg/kg were given orally to 7–8-week-old male Sprague–Dawley rats. Control rats were given the vehicle (2 mL/kg of water containing small amounts of gum arabic) alone. Twenty-four hours later, blood (1 mL) was withdrawn from the abdominal aorta under anesthesia with sodium pentobarbital (50 mg/kg, intraperitoneally) and incubated for 90 min at 25 °C. Serum was then separated (15000 rpm, 2 min) for the radioimmunoassay of thromboxane B_2 produced during incubation.

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Registry No. **6a**, 17857-14-6; **6b**, 17814-85-6; **6c**, 50889-29-7; **6d**, 50889-30-0; **6e**, 52956-93-1; **6f**, 88462-46-8; **6g**, 93943-65-8; **6h**, 7530-96-3; **7a**, 93943-66-9; **7b**, 93943-67-0; **8**, 93943-68-1; **9a**, 93943-69-2; **9b**, 89667-38-9; **9c**, 89667-40-3; **9d**, 89667-42-5; **(9e + 10e)**, 93943-71-6; **9f**, 89667-46-9; **9g**, 93943-72-7; **9h**, 93943-74-9; **10a**, 93943-70-5; **10b**, 89667-37-8; **10c**, 89667-39-0; **10d**, 89667-41-4; **10f**, 89667-45-8; **10g**, 93943-73-8; **10h**, 93943-75-0; **11**, 93943-76-1; **12**, 93943-77-2; **13**, 89667-89-0; **14a**, 93943-78-3; **14b**, 93943-79-4; **14c**, 93943-80-7; **14d**, 93943-81-8; **14e**, 93943-82-9; **14f**, 89667-60-7; **14g**, 93943-83-0; **14h**, 93943-84-1; **14i**, 89667-67-4; **14j**, 93943-85-2; **14k**, 93943-86-3; **14l**, 93943-87-4; **15a**, 93943-88-5; **(*E*)-15b**, 93943-89-6; **(*Z*)-15b**, 93943-90-9; **15c**, 93943-91-0; **15d**, 93943-92-1; **15e**, 93943-93-2; **(*E*)-15f**, 89667-50-5; **(*Z*)-15f**, 89667-49-2; **(*E*)-15g**, 89667-57-2; **(*Z*)-15g**, 89667-58-3; **(*E*)-15h**, 89667-77-6; **(*Z*)-15h**, 89667-76-5; **15i**, 93943-94-3; **15j**, 93943-95-4; **15k**, 93965-97-0; **15l**, 89667-61-8; **(*E*)-15m**, 89901-49-5; **(*Z*)-15m**, 89667-54-9; **16a**, 92571-71-6; **16b**, 92571-69-2; **16c**, 92571-73-8; **16d**, 93943-96-5; **16e**, 92571-76-1; **16f**, 92571-82-9; **16g**, 92571-81-8; **16h**, 93943-98-7; **16i**, 92572-29-7; **16j**, 92572-30-0; **16k**, 92571-78-3; **16l**, 92571-32-9; **16m**, 92571-86-3; **16n**, 92571-79-4; **16o**, 92587-17-2; **16p**, 92571-30-7; **17a**, 92571-72-7; **17b**, 92571-70-5; **17c**, 92571-74-9; **17d**, 93943-99-8; **17e**, 93943-97-6; **18a**, 89668-28-0; **18b**, 93944-00-4; **18c**, 93944-01-5; **18d**, 93965-98-1; **19**, 93944-02-6; thromboxane A_2 synthetase, 60832-04-4; 2-pyridyl phenyl ketone, 91-02-1; 3-pyridyl phenyl ketone, 5424-19-1; 4-pyridyl phenyl ketone, 14548-46-0; 4-methylphenyl 3-pyridyl ketone, 34950-04-4; 3-nitrophenyl 3-pyridyl ketone, 79568-05-1; 4-methoxyphenyl 3-pyridyl ketone, 23826-71-3; 4-isopropylphenyl 3-pyridyl ketone, 61780-08-3; 4-bromophenyl 3-pyridyl ketone, 14548-45-9; 3-bromophenyl 3-pyridyl ketone, 79362-44-0; 2-bromophenyl 3-pyridyl ketone, 77744-06-0; 4-fluorophenyl 3-pyridyl ketone, 52779-56-3; 3-fluorophenyl 3-pyridyl ketone, 79568-07-3; 2-fluorophenyl 3-pyridyl ketone, 89667-32-3; 1-naphthyl 3-pyridyl ketone, 89667-29-8; 2-naphthyl 3-pyridyl ketone, 89242-98-8; 2-thienyl 3-pyridyl ketone, 21327-72-0; 3-thienyl 3-pyridyl ketone, 21314-78-3; bis(3-pyridyl) ketone, 35779-35-2; 3,4-(methylenedioxy)phenyl 3-pyridyl ketone, 89667-28-7; 3-methyl-2-thienyl 3-pyridyl ketone, 93943-63-6; 2-thiazolyl 3-pyridyl ketone, 90418-59-0; *n*-hexyl 3-pyridyl ketone, 6294-61-7; 3-phenylpropyl 3-pyridyl ketone, 93943-64-7; 2-benzo[*b*]thienyl 3-pyridyl ketone, 89667-33-4; (4-methoxyphenyl)(3-pyridyl)methanol, 89667-06-1; (4-isopropylphenyl)(3-pyridyl)methanol, 89667-07-2; (4-bromophenyl)(3-pyridyl)-methanol, 63779-12-4; (3-bromophenyl)(3-pyridyl)methanol, 89667-08-3; (2-bromophenyl)(3-pyridyl)methanol, 89667-09-4; (4-fluorophenyl)(3-pyridyl)methanol, 89901-51-9; (3-fluorophenyl)(3-pyridyl)methanol, 89667-19-6; (2-fluorophenyl)(3-pyridyl)methanol, 89667-18-5; [3-(trifluoromethyl)phenyl](3-pyridyl)methanol, 89667-20-9; (1-naphthyl)(3-pyridyl)methanol, 89667-14-1; (2-naphthyl)(3-pyridyl)methanol, 89667-13-0; (2-thienyl)(3-pyridyl)methanol, 21314-77-2; (3-methyl-2-thienyl)(3-pyridyl)methanol, 93944-03-7; [3,4-(methylenedioxy)phenyl](3-pyridyl)methanol, 89667-12-9; bis(3-pyridyl)methanol, 89667-15-2; (3-pyridyl)(2-thiazolyl)methanol, 1011-28-5; (3-thienyl)(3-pyridyl)methanol, 21314-79-4.

Supplementary Material Available: Tables listing crystal data and atomic coordinates of the bonded atoms of CV-4151 (2 pages). Ordering information is given on any current masthead page.

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