CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 26, No. 3 March 1978

Regular Articles

[Chem. Pharm. Bull. 26(3) 685—702 (1978)]

UDC 547.536.2.04.09 : 615.276.011.5.076.9

Synthesis of α-Substituted Alkanoic Acids and Inhibition of Platelet Aggregation

Shoji Yoshimura,[1a] Susumu Takahashi, Akira Kawamata, Kiyomi Kikugawa, Hideo Suehiro, and Akiji Aoki

Research Laboratories, Kohjin Company, Ltd.[1b]

(Received February 7, 1977)

A series of 4-substituted phenyl-(A, B) and 5-substituted 2-thienyl-(C) acetic acid derivatives were synthesized. Inhibitory activity of collagen-induced rabbit platelet aggregation of 29 compounds including A, B, C and the intermediate compounds of them was studied. Compounds (A-18, B-21 and -27) were inhibitory against platelet aggregation and the most potent compound (B-21) was more effective than aspirin.

Keywords——alkanoic acids; phenyl acetic acid; vinylphenylacetic acid; thienylacetic acid; vinylphenylpropionic acid; platelet aggregation; inhibition of platelet aggregation; collagen

Ibufenac, Ibuprofen, phenylacetic acid and phenylpropionic acid derivatives are nonsteroidal antiinflammatory drugs,[2] most of which have been known as inhibitors of platelet aggregation and been expected to be antithrombotic agents. Thus, phenylacetic acid,[3] phenylpropionic acid,[3] Flubioprofen,[4] Naproxen,[5] Ibuprofen[6] and their derivatives[7] are known to be inhibitors of collagen-induced platelet aggregation.

This communication deals with the synthesis of a variety of α-substituted alkanoic acid, analogs of the above mentioned nonsteroidal antiinflammatory drugs, and the investigations on their inhibitory effects of platelet aggregation. A few derivatives of 4-styrylphenylacetic acid[8,9] have been synthesized and tested as anticholesterimic and antirheumatic agents.[10]

1) *a*) Correspondence should be addressed to *160–28 Shimo-fujisawa, Iruma-City, Saitama*; *b*) Location: *11277-Higashihama, Saiki-City, Oita.*
2) S.S. Adams, E.E. Cliffe, B. Lessel, and J.S. Nicholson, *Nature*, **200**, 271 (1963); S.S. Adams and E.E. Cliffe, *J. Pharmacol.*, **17**, 173 (1965); S.S. Adams, K.F. McCullough, and J.S. Nicholson, *Arch. int. Pharmacodyn.*, **178**, 115 (1969).
3) R.G. Herrman, W.S. Marshall, V.G. Crowe, J.E. Fronk, D.L. Marlett, and W.B. Lacefield, *Proc. Soc. Exptl. Biol. Med.*, **139**, 548 (1972).
4) E.E. Nishizawa, D.J. Wynalda, D.E. Suydam, and B.A. Molony, *Thromb. Res.*, 3, 577 (1973); A.K. Sim, A.P. McCraw, and M.F. Sim, *ibid.*, **7**, 655 (1975).
5) J. Nadell, J. Bruno, J. Varady, and E.J. Segre, *J. Clin. Pharmacol.*, **14**, 176 (1974).
6) D.J. Wynalda and C.D. Brooks, *Fed. Proc.*, **34**, 873 (1975); E.E. Nishizawa, *ibid.*, **34**, 874 (1975).
7) Belgian Patent 796910 (Japan Kokai, 49-120211); Japan Kokai, 50-77350; Japan Kokai, 49-61144; Japan Kokai, 49-6941; F. DeClerk, J. Vermylen, and R. Reneman, *Arch. int. Pharmacodyn. Ther.*, **216**, 263 (1975); *idem, ibid.*, **217**, 68 (1975).
8) G. Cavallini and E. Massarani, *Il. Farmaco-Ed. Sci.*, **11**, 167 (1956).
9) G.A.R. Kon., *J. Chem. Soc.*, **1948**, 224.
10) G. Cavallini, E. Massarani, D. Nardi, and R. D'Ambrosio, *J. Am. Chem. Soc.*, **79**, 3514 (1957); S. Garattini, C. Morpurgo, B. Murelli, K. Palotti, and N. Passerini, *Arch. int. Pharmacodyn.*, **109**, 400 (1957).

This time a wide variety of 4-substituted phenyl- and 5-substituted 2-thienylacetic acids was synthesized and examined for the inhibitory activity of collagen-induced aggregation. Among the 29 compounds synthesized, α-4-styrylphenylpropionic acid (A-18), α-4-(2-thienyl)-vinylphenylpropionic acid (B-21) and 4-(2-thienyl)vinylphenylacetic acid (B-27) were inhibitory. B-21 was the most potent compound.

Synthesis

The compounds synthesized in this paper were classified into three groups: A; 4-substituted phenylacetic acid derivatives having *p*-styryl radicals, B; 4-substituted phenylacetic acid derivatives having 2-thienylvinyl or 2-furylvinyl radicals, and C; 5-substituted 2-thienylacetic acid derivatives (Chart 1).

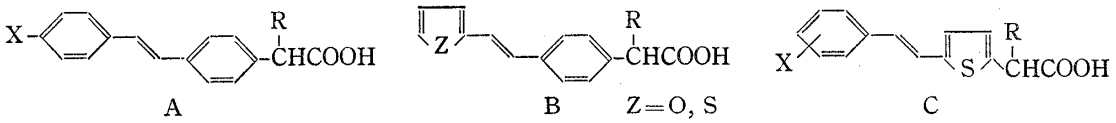


Chart 1

A and B Groups——The reaction schema on the synthesis of A and B groups are shown in Chart 2.

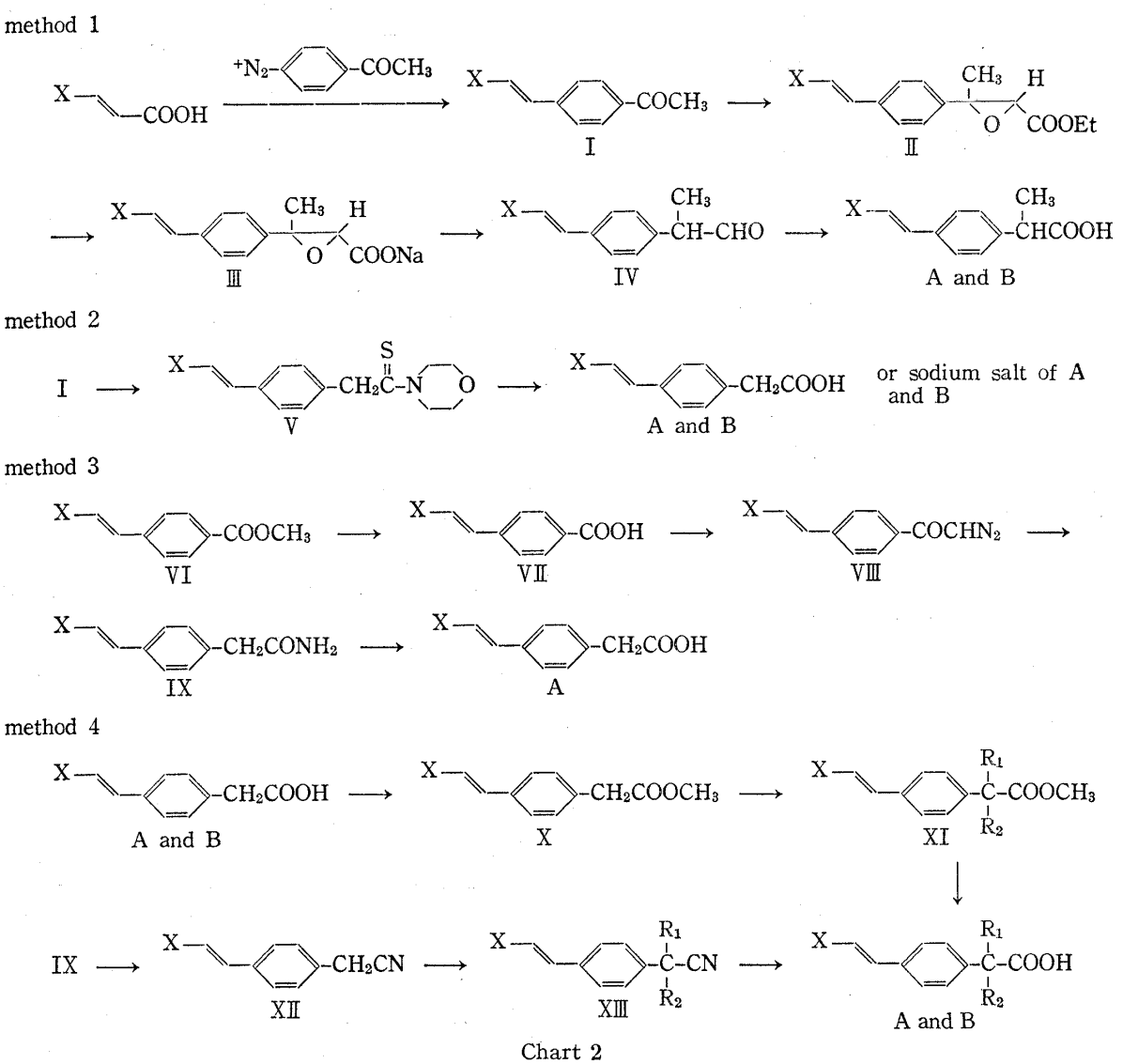
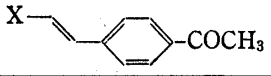


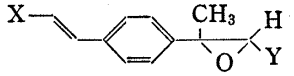
Chart 2

Table I. 4-Vinylphenyl Methyl Ketones (I)



No.	X	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
I-2	*p*-Nitrophenyl	20.44	Needles (chloroform)	194—197	$C_{16}H_{13}NO_3$	71.90 (71.34)	4.90 (4.94)	5.24 (5.34)
I-3	*p*-Acetoamino-phenyl	30.69	Crystalline powder (acetone–benzene)	238—239	$C_{18}H_{17}NO_2$	77.39 (77.36)	6.13 (6.09)	5.01 (5.00)
I-4	2-Furyl	44.66	Needles (ether–*n*-hexane)	103—105	$C_{14}H_{12}O_2$	79.22 (79.16)	5.70 (5.54)	
I-5	2-Thienyl	31.87	Crystalline powder (benzene)	130—131	$C_{14}H_{12}OS$	73.65 (73.41)	5.30 (5.22)	

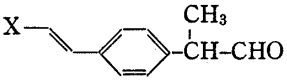
Table II. β-Methyl-β-4-vinylphenyl-glycidates (II and III)



No.	X	Y	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	IR ν_{max}^{KBr} cm^{-1} (COO)
II-6	Phenyl	COOEt	77.9	Granules (ethanol)	65— 67	1740
II-7	*p*-Nitrophenyl	COOEt	73.0	Crystalline powder (methanol)	79— 82	1740
II-8	2-Furyl	COOEt	90.0	Oil	—	1740[a]
II-9	2-Thienyl	COOEt	75.5	Crystalline powder (*n*-hexane)	105—108	1740
III-10	Phenyl	COONa	96.9	Powder	183—190[b] (dec.)	1600
III-11	*p*-Nitrophenyl	COONa	76.3	Powder	192[b] (dec.)	1600
III-12	2-Furyl	COONa	93.0	Powder	218[b] (dec.)	1600
III-13	2-Thienyl	COONa	85.17	Powder	228[b] (dec.)	1600

a) IR-spectrum was measured as oil.
b) Melting points without recrystallization.

Table III. α-4-Vinylphenylpropionaldehydes (IV)



No.	X	Yield (%)	mp (°C)	IR ν_{max}^{KBr} cm^{-1} (CHO)	NMR ($CDCl_3$) δ:
IV-14	Phenyl	85.5	105—107	1720	1.46 (3H, d, J=8 Hz, $-CH_3$) 3.60 (1H, q-d, J=8, 2 Hz, -CH) 9.70 (1H, d, J=2 Hz, CHO)
IV-15	*p*-Nitrophenyl	71.0	108—112[a]	1700	1.47 (3H, d, J=8 Hz, $-CH_3$) 3.73 (1H, q-d, J=8, 2 Hz, -CH) 8.97 (1H, d, J=2 Hz, CHO)
IV-16	2-Furyl	36.4	98—101[a]	1710	1.46 (3H, d, J=8 Hz, $-CH_3$) 3.60 (1H, q-d, J=8, 2 Hz, -CH) 9.63 (1H, d, J=2 Hz, CHO)
IV-17	2-Thienyl	85.9	89— 94[a]	1710	1.43 (3H, d, J=8 Hz, $-CH_3$) 3.63 (1H, q-d, J=8, 2 Hz, -CH) 9.66 (1H, d, J=2 Hz, CHO)

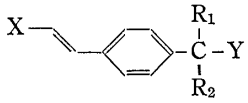
a) Melting points without recrystallization.

Method 1——4-Vinylphenyl methyl ketones (I-2, 3, 4, and 5) (Table I), prepared from acrylic acids[11] and *p*-aminoacetophenone analogously to the preparation of 4-styrylphenyl methyl ketone (I-1),[9] were converted into β-methyl-β-4-vinylphenyl glycidic esters (II-6—9) through the Darzen reaction by use of ethyl chloroacetate in the presence of potassium *t*-butoxide. The compounds(II) were hydrolyzed into sodium glycidates (III-10—13) (Table II). Decarboxylation of III with dilute hydrochloric acid gave α-4-vinylphenylpropionaldehydes(IV-14—17) (Table III) which were subsequently converted into the aimed α-4-vinylphenylpropionic acids(A-18—21) on treatment with silver oxide (Table V).

Method 2——Sodium 4-*p*-aminostyrylphenylacetate(A-26) and 4-(2-thienyl)vinylphenylacetic acid (B-27) (Table V) were prepared by hydrolysis of 4-*p*-acetoaminostyrylphenylacetthiomorpholide (V-23) and 4-(2-thienyl)vinylphenylacet-thiomorpholide(V-24), respectively, in a similar preparation of 4-styrylphenylacetic acid (A-25) from 4-styrylphenylacet-thiomorpholide (V-22).[9]

Method 3——Methyl 4-(*p*-chloro- and bromo-styryl)benzoates (VI-28 and 29)[12] were hydrolyzed to yield 4-(*p*-chloro- and bromo-styryl)benzoic acid (VII-30 and 31). In analog with the transformation of 4-styrylbenzoic acid into 4-styrylphenylacetic acid (A-25),[9] compounds (VII) were converted into acyl chlorides and subsequently treated with diazomethane

Table IV. Compounds (X, XI, XII and XIII)



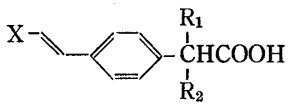
No.	X	R_1	R_2	Y	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
X-38	*p*-Chlorophenyl	H	H	COOMe	91.0	Needles (*n*-hexane–benzene)	104—106	$C_{17}H_{15}ClO_2$	71.20 (70.96)	5.27 (5.37)	
X-39	*p*-Bromophenyl	H	H	COOMe	90.0	Needles (*n*-hexane–benzene)	111—113	$C_{17}H_{15}BrO_2$	61.65 (61·86)	4.56 (4.53)	
X-40	2-Thienyl	H	H	COOMe	87.0	Granules (*n*-hexane)	84—86	$C_{15}H_{14}O_2S$	69.74 (69.92)	5.46 (5.51)	
XI-41	*p*-Chlorophenyl	CH_3	H	COOMe	90.0	Needles (*n*-hexane)	84—86	$C_{18}H_{17}ClO_2$	71.88 (72.09)	5.70 (5.54)	
XI-42	*p*-Bromophenyl	CH_3	H	COOMe	82.6	Needles (*n*-hexane)	82—84	$C_{18}H_{17}BrO_2$	62.62 (62.91)	4.96 (4.76)	
XI-43	2-Thienyl	CH_3	H	COOMe	24.4	Needles (*n*-hexane)	61—62	$C_{16}H_{16}O_2S$	70.56 (70.50)	5.92 (5.93)	
XI-45	*p*-Chlorophenyl[a]	C_2H_5	H	COOMe and COOEt	72.0	Needles (*n*-hexane)	—	—	—	—	
XII	*p*-Bromophenyl	H	H	CN	53.0	Leaves (benzene)	158—160	$C_{16}H_{12}BrN$	64.45 (64.72)	4.06 (4.01)	4.70 (4.63)
XIII-50	*p*-Bromophenyl	CH_3	H	CN	59.7	Leaves (*n*-hexane)	128—129	$C_{17}H_{14}BrN$	65.40 (65.61)	4.52 (4.47)	4.49 (4.44)
XIII-51	*p*-Bromophenyl	CH_3	CH_3	CN	—	Leaves (*n*-hexane)	113—115	$C_{18}H_{16}BrN$	66.27 (66.32)	4.94 (5.04)	4.29 (4.20)

a) Compound XI-45 was isolated as a mixture of ethylester and methylester.

11) W.B. Wright, *J. Heterocyclic Chem.*, **879** (1972); R.T. Wiely and N.R. Smith, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963. p. 731; W. Freund, *J. Chem. Soc.*, **1952**, 3068; *idem*, *ibid.*, **1953**, 288.

12) R.C. Fuson and H.G. Cooke, *J. Am. Chem. Soc.*, **62**, 1180 (1940).

TABLE V. α-4-Vinylphenylacetic Acids (A and B)



No.	$-\overset{R_1}{\underset{R_2}{C}}-COOH$	X	Method[a]	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	Inhibition of collagen-induced platelet aggregation[b] Solvent	R_{ASP}
A-18	$CH(CH_3)COOH$	Phenyl	1	31.0	Needles (ether–*n*-hexane)	181—183	$C_{17}H_{16}O_2$	80.92 (80.59)	6.39 (6.61)		N	0.7
A-19	$CH(CH_3)COOH$	*p*-Nitrophenyl	1	22.6	Crystalline powder (chloroform)	179—181	$C_{17}H_{15}NO_4$	68.68 (68.37)	5.09 (5.04)	4.71 (4.67)	D	0.2
B-20	$CH(CH_3)COOH$	2-Furyl	1	10.0	Granules (benzene–*n*-hexane)	139—140	$C_{15}H_{14}O_3$	74.30 (73.96)	5.82 (5.86)		N	0.2
B-21	$CH(CH_3)COOH$	2-Thienyl	1, (4)	44.8	Needles (ether–*n*-hexane)	182—183	$C_{15}H_{14}O_2S$	69.74 (69.30)	5.46 (5.46)		N	1.6
A-25	CH_2COOH[c]	Phenyl	2	—	Needles (acetic acid)	186—187	$C_{16}H_{14}O_2$	—	—		N	0.2
A-26	CH_2COONa	*p*-Aminophenyl	2	25.0	Granules (ethanol)	315—316	$C_{16}H_{14}NNaO_2$	69.81 (69.50)	5.13 (5.34)	5.09 (5.13)	D	0.2
A-27	CH_2COOH	2-Thienyl	2	35.0	Granules (ether–*n*-hexane)	177—178	$C_{14}H_{12}O_2S$	68.83 (68.41)	4.95 (4.91)		N	1.0
A-36	CH_2COOH	*p*-Chlorophenyl	3	82.7	Leaves (benzene)	202—204	$C_{16}H_{13}ClO_2$	70.46 (70.36)	4.80 (4.86)		D	0.1
A-37	CH_2COOH	*p*-Bromophenyl	3	12.0	Leaves (benzene)	223—225	$C_{16}H_{13}BrO_2$	60.59 (60.76)	4.13 (4.08)		D	0.0
A-46	$CH(CH_3)COOH$	*p*-Chlorophenyl	4	78.7	Crystalline powder (benzene)	212—214	$C_{17}H_{15}ClO_2$	71.21 (71.32)	5.27 (5.35)		N	0.1
A-47	$CH(CH_3)COOH$	*p*-Bromophenyl	4	75.4	Crystalline powder (benzene)	209—211	$C_{17}H_{15}BrO_2$	61.65 (61.80)	4.56 (4.50)		N	0.0
A-48	$CH(C_2H_5)COOH$	*p*-Chlorophenyl	4	37.2	Granules (benzene)	161—163	$C_{18}H_{17}ClO_2$	71.88 (72.10)	5.70 (5.68)		N	0.1

a) Methods. 1—4 were described in the text. b) See Experimental section. c) Reference 9).

to afford 4-substituted-4′-diazoacetylstilbenes (VIII-32 and 33). Compounds (VIII) gave 4-styrylphenylacetamides (IX-34 and 35) on the Wolff rearrangement in the presence of aqueous ammonia and silver oxide. The aimed phenylacetic acids (A-36 and 37) (Table V) were obtained by hydrolysis of IX with a mixture of concentrated hydrochloric acid and acetic acid.

Method 4——Alkylation and subsequent hydrolysis of the methyl ester(X) of the acetic acid derivatives (A and B) and the acetonitrile derivative (XII) gave the propionic acid and butyric acid derivatives (A and B).

Phenylacetic acid derivatives (A-36 and 37) were treated with diazomethane to yield methyl esters (X-38 and 39)(Table IV), followed by treatment with methyl iodide in dimethylformamide in the presence of 1.2 equivalent amounts of sodium hydride to yield methyl α-4-vinylphenylpropionate (XI-41 and 42). α-Methylation of X-40 prepared from B-27 was unsuccessful under the same condition. Treatment of X-40 in the presence of 4.6 molar excess of sodium hydride gave a mixture of monomethylated compound (XI-43) and dimethylated compound (XI-44) in a 3:1 ratio, which were separated by column chromatography and successive thin layer chromatography. The methyl ester (X-38) was treated with ethyl iodide in the presence of 1.2 molar excess of sodium hydride to afford a mixture of methyl and ethyl esters of α-4-vinylphenylbutyric acid (XI-45) in a ratio of 1:1.3. The α-alkylated acetic acid esters (XI-41, 42, 43, and 45) were hydrolyzed with hydrochloric acid-acetic acid mixture or caustic alkali to yield propionic acid derivatives (A-46, 47, B-21) and a butyric acid derivative (A-48).

The acetonitrile derivative (XII) prepared by dehydration of the acetamide derivative (IX-35) was treated with methyl iodide and sodium hydride to yield a mixture of monomethylated compound (XIII-50) and dimethylated compound (XIII-51) which were separated by preparative thin layer chromatography. Compound (XIII-50) was converted into the aimed carboxylic acid (A-47)(Table V).

C Group——The reaction schema on the synthesis of C group are shown in Chart 3 and 4. Treatment of 2-thienylacetonitrile(XIV)[13] with phenylacetyl chloride gave 5-phenylacetyl-2-thienylacetonitriles (XV-52—59)(Table VI) which were subsequently reduced by sodium

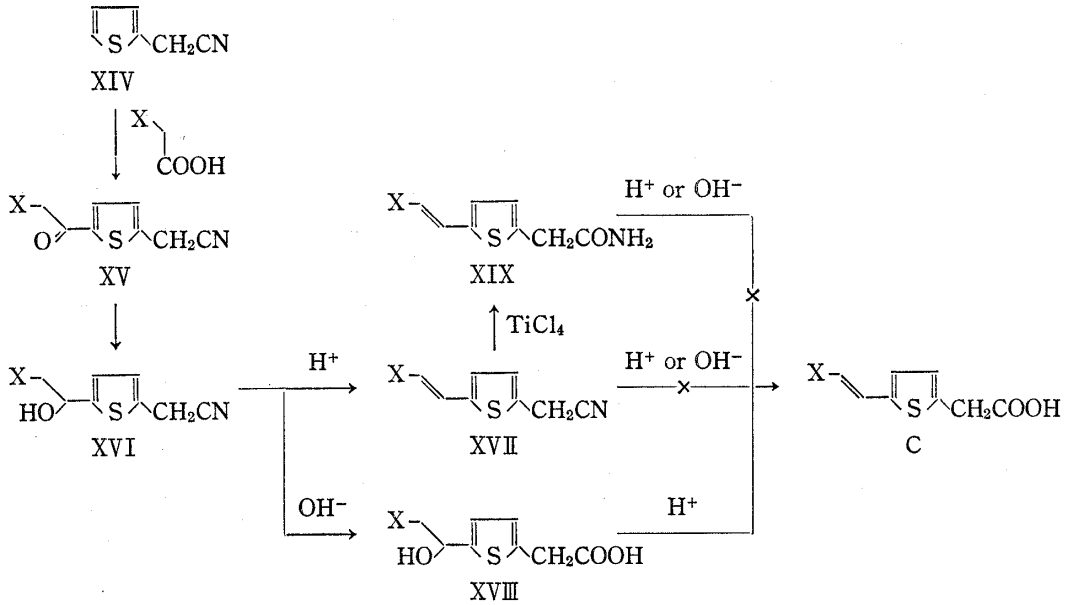
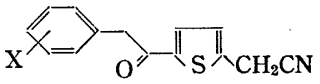


Chart 3

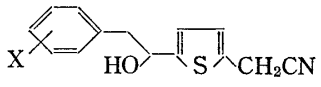
13) F.F. Blike and F. Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946).

TABLE VI. 5-Phenylacetyl-2-thienylacetonitriles (XV)



No.	X	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (CN, CO)	NMR ($CDCl_3$) δ:
XV-52	H	78.0	Granules (ether–ethyl acetate)	68	$C_{14}H_{11}NOS$	69.68 (69.64)	4.60 (4.63)	5.81 (5.82)	2230 1660	3.93 (2H, s, CH_2CN), 4.16 (2H, s, CH_2CO)
XV-53	*p*-F	81.0	Needles (methanol)	92— 93	$C_{14}H_{10}FNOS$	64.85 (64.62)	3.89 (3.90)	5.40 (5.44)	2240 1650	3.91 (2H, s, CH_2CN), 4.13 (2H, s, CH_2CO)
XV-54	*p*-Cl	82.0	Needles (methanol)	134	$C_{14}H_{10}ClNOS$	60.98 (60.93)	3.66 (3.61)	5.08 (5.68)	2240 1660	3.26 (2H, s, CH_2CN), 4.26 (2H, s, CH_2CO)
XV-55	*m*-Cl	83.0	Needles (methanol)	104—105	$C_{14}H_{10}ClNOS$	60.98 (60.73)	3.66 (3.71)	5.08 (5.20)	2240 1650	3.90 (2H, s, CH_2CN), 4.13 (2H, s, CH_2CO)
XV-56	*p*-Br	79.0	Leaves (methanol)	137—138	$C_{14}H_{10}BrNOS$	52.51 (52.63)	3.15 (3.14)	4.37 (4.53)	2240 1650	3.93 (2H, s, CH_2CN), 4.11 (2H, s, CH_2CO)
XV-57	*p*-OCH_3	73.0	Leaves (methanol–*n*-hexane)	84	$C_{15}H_{13}NO_2S$	66.40 (66.17)	4.83 (4.69)	5.16 (5.23)	2240 1660	3.90 (2H, s, CH_2CN), 4.06 (2H, s, CH_2CO)
XV-58	*p*-iso-C_4H_9	80.0	Granules (methanol)	99—101	$C_{18}H_{19}NOS$	72.69 (72.31)	6.44 (6.39)	4.71 (4.60)	2240 1650	3.90 (2H, s, CH_2CN), 4.13 (2H, s, CH_2CO)
XV-59	*p*-NO_2	75.0	Granules (benzene)	119	$C_{14}H_{10}N_2O_3S$	58.73 (59.05)	3.52 (3.56)	9.79 (9.60)	2240 1660	3.96 (2H, s, CH_2CN), 4.30 (2H, s, CH_2CO)

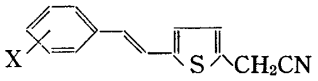
TABLE VII. 5-(2-Phenyl-1-hydroxyethyl)-2-thienylacetonitriles (XVI)



No.	X	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (OH)	NMR ($CDCl_3$) δ:
XVI-60	H	72.0	Oil	—	$C_{14}H_{13}NOS$	—	—	—	3400[a]	3.06 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH–), 5.03 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>–)
XVI-61	*p*-F	94.8	Leaves (*n*-hexane)	69—70	$C_{14}H_{12}FNOS$	64.35 (64.29)	4.63 (4.68)	5.36 (5.42)	3460[b]	3.09 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH–), 5.02 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>),
XVI-62	*p*-Cl	77.9	Leaves (*n*-hexane)	77—78	$C_{14}H_{12}ClNOS$	60.54 (60.46)	4.35 (4.31)	5.04 (5.11)	3450[b]	3.04 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH–), 5.02 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>–)
XVI-63	*m*-Cl	78.0	Oil	—	$C_{14}H_{12}ClNOS$	—	—	—	3400[a]	3.06 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH–), 5.03 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>–)
XVI-64	*p*-Br	94.2	Needles (*n*-hexane)	93.0—93.5	$C_{14}H_{12}BrNOS$	52.19 (52.08)	3.75 (3.75)	4.35 (4.38)	3440[b]	2.98 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH–), 4.96 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>–)
XVI-65	*p*-OCH_3	85.0	Needles (*n*-hexane–benzene)	93.0	$C_{15}H_{15}NO_2S$	65.91 (66.39)	5.53 (5.59)	5.12 (5.17)	3450[b]	3.00 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH–), 5.00 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>–)
XVI-66	*p*-iso-C_4H_9	90.0	Crystalline powder (*n*-hexane–benzene)	78.0	$C_{18}H_{21}NOS$	72.20 (71.80)	7.07 (7.07)	4.68 (4.40)	3450[b]	3.06 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH–), 5.06 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>–)
XVI-67	*p*-NO_2	77.0	Needles (benzene)	115.5	$C_{14}H_{12}N_2O_3S$	58.32 (58.70)	4.20 (4.22)	9.72 (9.57)	3450[b]	3.13 (2H, d, J=6 Hz, C<u>H</u>$_2$–CH),[c] 5.10 (1H, t, J=6 Hz, CH$_2$–C<u>H</u>–)

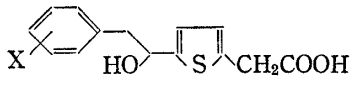
a) IR-spectrum was measured as oil.
b) IR-spectrum was measured as KBr disk.
c) Solvent was DMSO-d_6 instead of $CDCl_3$.

TABLE VIII. 5-Styryl-2-thienylacetonitriles (XVII)



No.	X	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1} (CN)	NMR ($CDCl_3$) δ:
XVII-68	H	51.5	Needles (*n*-hexane–benzene)	110—111	$C_{14}H_{11}NS$	74.63 (74.69)	4.92 (4.98)	6.22 (6.00)	2220	3.86 (2H, s, CH_2CN)
XVII-69	*p*-F	66.5	Needles (benzene–*n*-hexane)	101	$C_{14}H_{10}FNS$	69.11 (69.00)	4.14 (4.27)	5.76 (5.76)	2240	3.83 (2H, s, CH_2CN)
XVII-70	*p*-Cl	66.0	Leaves (*n*-hexane–benzene)	123	$C_{14}H_{10}ClNS$	64.73 (64.53)	3.88 (3.85)	5.39 (5.58)	2230	3.90 (2H, s, CH_2CN)
XVII-71	*m*-Cl	68.0	Crystalline powder (*n*-hexane–benzene)	83	$C_{14}H_{10}ClNS$	64.73 (64.07)	3.88 (3.77)	5.39 (5.31)	2230	3.83 (2H, s, CH_2CN)
XVII-72	*p*-Br	68.0	Needles (*n*-hexane–benzene)	143	$C_{14}H_{10}BrNS$	55.27 (55.34)	3.31 (3.34)	4.60 (4.86)	2240	3.83 (2H, s, CH_2CN)
XVII-73	*p*-OCH_3	67.0	Granules (*n*-hexane–benzene)	145	$C_{15}H_{13}NOS$	70.56 (70.62)	5.13 (5.10)	5.49 (5.39)	2220	3.83 (2H, s, CH_2CN)
XVII-74	*p*-iso-C_4H_9	71.0	Needles (*n*-hexane)	95	$C_{18}H_{19}NS$	76.82 (76.63)	6.81 (6.72)	4.98 (4.81)	2220	3.90 (2H, s, CH_2CN)
XVII-75	*p*-NO_2	53.0	Needles (*n*-hexane–benzene)	123	$C_{14}H_{10}N_2O_2S$	62.21 (62.31)	3.73 (3.83)	10.36 (10.37)	2220	3.96 (2H, s, CH_2CN)

Table IX. 5-(2-Phenyl-1-hydroxyethyl)-2-thienylacetic Acids (XVIII)

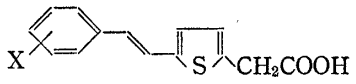


No.	X	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula
XVIII-77	H	62.0	Granules (benzene)	107.5	$C_{14}H_{14}O_3S$
XVIII-78	*p*-F	73.7	Needles (benzene)	126—127	$C_{14}H_{13}FO_3S$
XVIII-79	*p*-Cl	64.0	Needles (benzene)	129—131	$C_{14}H_{13}ClO_3S$
XVIII-80	*m*-Cl	66.0	Granules (benzene)	108	$C_{14}H_{13}ClO_3S$
XVIII-81	*p*-Br	67.4	Needles (benzene)	128—129	$C_{14}H_{13}BrO_3S$
XVIII-82	*p*-OCH_3	71.0	Leaves (benzene)	96.5	$C_{15}H_{16}O_4S$
XVIII-83	*p*-iso-C_4H_9	69.0	Needles (benzene)	123	$C_{18}H_{22}O_3S$

No.	Analysis (%) Calcd. C	Calcd. H	Found C	Found H	IR ν_{max}^{KBr} cm^{-1}	NMR δ:	Inhibition of collagen-induced platelet aggregation[a] Solvent	R_{ASP}
XVIII-77	64.10	5.38	64.30	5.43	1680	3.80 (2H, s, C$\underline{H}_2$COOH)[b]	N	0.0
XVIII-78	59.90	4.67	60.34	4.66	1670	3.74 (2H, s, C$\underline{H}_2$COOH)[c]	N	0.0
XVIII-79	56.66	4.42	56.53	4.35	1670	3.72 (2H, s, C$\underline{H}_2$COOH)[c]	N	0.0
XVIII-80	56.66	4.42	57.02	4.40	1680	3.83 (2H, s, C$\underline{H}_2$COOH)[b]	N	0.0
XVIII-81	49.28	3.84	49.34	3.74	1675	3.74 (2H, s, C$\underline{H}_2$COOH)[c]	N	0.0
XVIII-82	61.63	5.52	62.15	5.48	1680	3.80 (2H, s, C$\underline{H}_2$COOH)[b]	D	0.0
XVIII-83	67.89	6.96	68.39	6.90	1680	3.83 (2H, s, C$\underline{H}_2$COOH)[b]	D	0.3

a) See Experimental section.
b) NMR solvent was $CDCl_3$.
c) NMR solvent was DMSO-d_6.

Table X. 5-Styryl-2-thienylacetic Acids (C)



No.	X	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula
C-84	H	31.0	Leaves (chloroform)	144—145	$C_{14}H_{12}O_2S$
C-85	*p*-F	39.9	Leaves (benzene)	173—175	$C_{14}H_{11}FO_2S$
C-86	*p*-Cl	49.1	Leaves (benzene)	181—183	$C_{14}H_{11}ClO_2S$
C-87	*m*-Cl	51.0	Leaves (benzene–dichloromethane)	164	$C_{14}H_{11}ClO_2S$
C-88	*p*-Br	40.8	Leaves (benzene)	184	$C_{14}H_{11}BrO_2S$
C-89	*p*-OCH_3	48.0	Leaves (benzene)	178	$C_{15}H_{14}O_3S$
C-90	*p*-iso-C_4H_9	47.0	Leaves (*n*-hexane–dichloromethane)	163	$C_{18}H_{20}O_2S$

No.	Analysis (%) Calcd. C	Calcd. H	Found C	Found H	IR ν_{max}^{KBr} cm^{-1} (COOH)	NMR (DMSO-d_6) δ:	Inhibition of collagen-induced platelet aggregation[a] Solvent	R_{ASP}
C-84	68.83	4.95	68.89	4.81	1690	3.83 (2H, s, CH_2COOH)	N	0.0
C-85	64.11	4.23	64.12	4.21	1685	3.84 (2H, s, CH_2COOH)	N	0.0
C-86	60.32	3.98	60.25	3.96	1690	3.84 (2H, s, CH_2COOH)	N	0.0
C-87	60.32	3.98	60.23	3.94	1680	3.83 (2H, s, CH_2COOH)	N	0.0
C-88	52.03	3.43	51.74	3.37	1690	3.83 (2H, s, CH_2COOH)	N	0.0
C-89	65.67	5.14	65.45	5.12	1680	3.73 (2H, s, CH_2COOH)	D	0.0
C-90	71.96	6.71	72.02	6.63	1680	3.80 (2H, s, CH_2COOH)	D	0.0

a) See Experimental section.

brohydride into 5-(2-phenyl-1-hydroxyethyl)-2-thienylacetonitriles (XVI-60—67)(Table VII). Dehydrated products (XVII-68—75)(Table VIII) were obtained by treatment of compounds (XVI) with 20—40% sulfuric acid. Treatment of XVI with potassium hydroxide gave 2-thienylacetic acid derivatives (XVIII-77—83)(Table IX) except XVI-67 which was decomposed under the conditions. The acid or alkali treatment of XVII yielded only a tar without formation of C. Reaction of XVII-75 with titanium tetrachloride[14] in aqueous acetic acid afforded the compound(XIX), which was unable to be converted into C by the acid or alkali treatment. Dehydration of XVIII with 50% sulfuric or 50% phosphoric acid by heating readily led to 5-styryl-2-thienylacetic acids (C-84—90)(Table X).

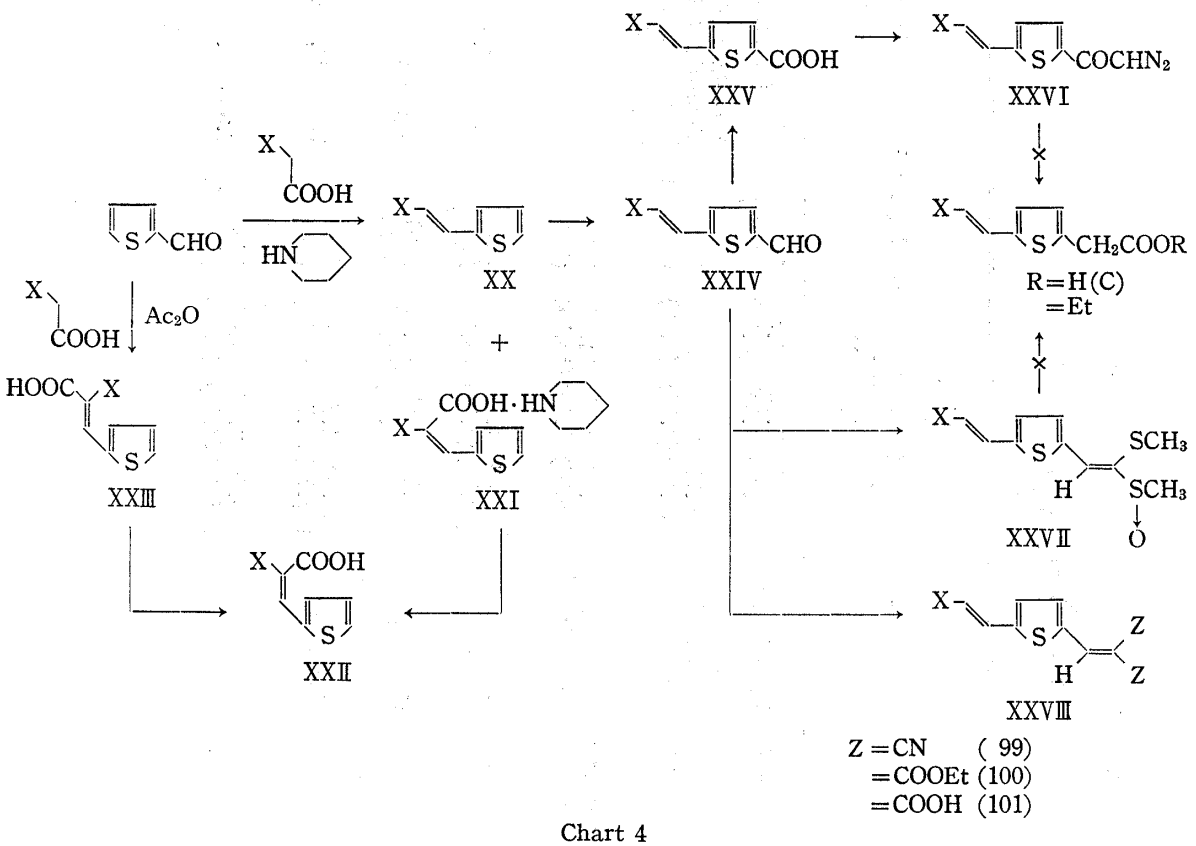
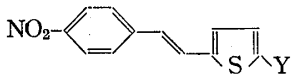


Chart 4

Treatment of 2-formylthiophene with *p*-nitrophenylacetic acid gave *trans*-*p*-nitrostyryl thiophene (XX) along with *cis*-α-*p*-nitrophenyl-β-2-thienylacrylic acid piperidinium salt (XXI). The compound (XX) was identical with the same compound prepared in different routes.[15] Compound (XXI) was treated with dilute hydrochloric acid to yield *cis*-α-*p*-nitrophenyl-β-2-thienylacrylic acid(XXII). It was then isomerized with iodine[15] to *trans*-acrylic acid derivative (XXIII)[16] which was identical with the compound derived from the reaction of 2-formylthiophene and *p*-nitrophenylacetic acid in acetic anhydride. 5-*p*-Nitrostyryl-2-formylthiophene (XXIV) prepared from XX was converted into *trans*-5-*p*-nitrostyryl-2-thienylcarboxylic acid (XXV). The Wolff rearrangement of *trans*-5-*p*-nitrostyryl-2-diazoacetylthiophene (XXVI) derived from XXV was unsuccessful. The condensed product (XXVII) of the aldehyde (XXIV) with methyl methylthiomethyl sulfoxide[17] could not be converted into the ester derivative of C under acidic conditions.[17] The aldehyde (XXIV) was treated with malono-

14) T. Mukaiyama and K. Kamio, *Chem. Lett.*, **1973**, 357.
15) A. Arcoria, S. Fisichella, G. Scarlata, and M. Torre, *J. Heterocyclic Chem.*, **1973**, 643.
16) H.E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, **81**, 2086 (1959).
17) K. Ogura and G. Tsuchihashi, *Tetrahedron Lett.*, **1972**, 1383.

TABLE XI. 5-*p*-Nitrostyryl-2-substituted Thiophenes



No.	Y	Yield (%)	Appearance (Recrystn. solvent)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}	NMR δ:	Inhibition of collagen-induced platelet aggregation[a] Solvent	R_{ASP}
XXIV	-CHO	89.2	Needles (ethanol)	169—170	$C_{13}H_9NO_3S$	60.22 (60.39)	3.50 (3.54)	5.40 (5.55)	1650 (CHO)	9.93 (1H, s, CHO)[b]	—	—
XXV	-COOH	70.0	Needles (ethanol)	278—279	$C_{13}H_9NO_4S$	56.72 (56.61)	3.30 (3.20)	5.09 (5.12)	1650 (COOH)	7.0—8.0 (6H, m, olefin-H, thiophene-H, arom-H), 8.2 (2H, d, J=8 Hz, arom-H)[c]	N	0.0
XXVI	$-COCHN_2$	53.0	Needles (benzene–tetrahydrofuran)	194—195 (dec.)	$C_{14}H_9N_3O_3S$	56.18 (55.86)	3.03 (3.16)	14.04 (13.74)	2080 (N_2)	—	—	—
XXVII	$-CH=C(SCH_3)(SOCH_3)$	50.0	Needles (ethanol)	182—183	$C_{16}H_{15}NO_3S_3$	52.58 (52.74)	4.14 (4.21)	3.83 (3.80)	1060 (S–O)	7.86 (1H, s, CH=C)[b]	D	0.4
XXVIII-99	$-CH=C(CN)_2$	95.0	Leaves (acetone–benzene)	256	$C_{16}H_9N_3O_2S$	62.53 (62.08)	2.95 (2.81)	13.67 (13.55)	2200 (CN)	8.60 (1H, s, CH=C)[b]	—	—
XXVIII-100	$-CH=C(COOEt)_2$	80.0	Needles (ethanol)	135	$C_{20}H_{19}NO_6S$	59.84 (59.76)	4.77 (4.75)	3.49 (3.51)	1710 (COOEt)	7.96 (1H, s, CH=C)[b]	—	—
XXVIII-101	$-CH=C(COOH)_2$	81.0	Needles (acetone–tetrahydrofuran)	248 (dec.)	$C_{16}H_{11}NO_6S$	55.65 (55.41)	3.21 (3.17)	4.06 (3.91)	1700 (COOH)	7.90 (1H, s, CH=C)[c]	N	0.0

a) See Experimental section.
b) NMR solvent was $CDCl_3$.
c) NMR solvent was DMSO-d_6.

nitrile, diethyl malonate and malonic acid to yield XXVIII-99, 100 and 101, respectively (Table XI).

Pharmacological Results and Discussion

Inhibitory effects of α-4-vinylphenylacetic acids (A and B), 5-styryl-2-thienylacetic acids (C) and their derivatives against collagen-induced rabbit platelet aggregation were examined according to the method of Born and Cross.[18,19] Test samples dissolved in 0.02 N sodium hydroxide or dimethylsulfoxide were added into platelet-rich plasma to reach at a final concentration of 10^{-4} M. After preincubation for 3 min collagen was added and each degree of aggregation was measured by lowering of its optical density. Inhibition ratio (R_{ASP}) of each of the test samples to aspirin was calculated and a compound having $R_{ASP}=1$ indicates that it is as effective as aspirin. The results are shown in Table V, IX, X and XI. Compound (A-18) was slightly effective, and compounds (B-21 and B-27) were more effective than or as effective as aspirin. The inhibitory pattern of these three compounds compared with those of aspirin and Ibuprofen are shown in Fig. 1. All the compounds were ineffective against adenosine 5′-diphosphate-induced platelet aggregation as in case of aspirin and Ibuprofen. Nonsteroidal antiinflammatory agents(phenyl butazone, aspirin, indomethacin and Ibuprofen) control the release reaction of platelet, *i.e.* second phase aggregation, but they do not hinder the first phase aggregation induced by adenosine 5′-diphosphate.[20] Thus, antiinflammatory activity might be observed with the compounds(A-18, B-21 and B-27).

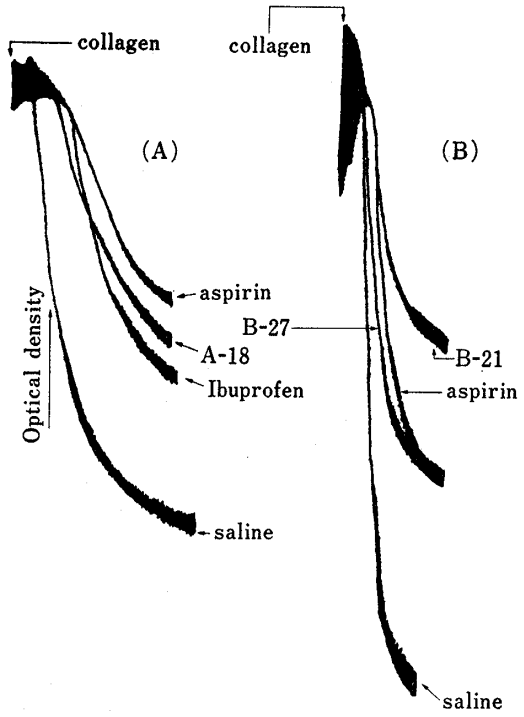


Fig. 1. Inhibition of Collagen-induced Rabbit Platelet Aggregation by Compounds (A-18, B-21 and B-27)

Rabbit platelet-rich plasma was pretreated with each of the test samples (10^{-4} M) at 37° for 3 min and it was challenged with collagen (100 μg/ml).

Experimental[21]

Compounds (I): 4-*p*-Nitrostyrylphenyl Methyl Ketone (I-2)——A solution of 7.62 g of $NaNO_2$ dissolved in a minimum amount of H_2O was added with stirring to an ice-cooled mixture of 14.8 g of *p*-aminoacetophenone, 30 ml of concentrated hydrochloric acid and 30 ml of H_2O. To the diazotized solution were added a solution of 20 g of *p*-nitrocinnamic acid in 130 ml of dimethylsulfoxide and subsequently a solution of 25.4 g of CH_3COONa and 20.6 g of $CuCl_2$ in a minimum amount of H_2O, whereby a gas evolved and the reaction proceeded. After the mixture was stirred in an ice-water bath for 24 hr, it was added to a large excess of H_2O. The precipitate separated was filtered, and dissolved in $CHCl_3$. The solution was washed with H_2O and dried over $MgSO_4$. The drying agent was filtered out and the solvent was removed *in vacuo*. The residue was purified through an alumina column using benzene–$CHCl_3$ (1: 1) as an eluent to yield I-2. Recrystallization from $CHCl_3$ gave 6.03 g (yield 20.44%) of I-2 as pale yellow needles, mp 194—197°. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O), 1320 (NO_2). NMR ($CDCl_3$+DMSO-d_6) δ: 2.6 (3H, s, $COCH_3$), 7.36 (2H, s, olefin-H), 7.36—8.33 (8H, m, Ar–H).

In the same manner compounds (I-3, 4, and 5) were synthesized. In case of 4 and 5, β-2-furylacrylic acid and β-2-thienylacrylic acid were dissolved in acetone instead of dimethylsulfoxide and in case of 3,*p*-

18) G.V. Born and M.J. Cross, *J. Physiol.*, **168**, 178 (1963).
19) K. Kikugawa, H. Suehiro, and M. Ichino., *J. Med. Chem.*, **16**, 1381 (1973).
20) K. Kikugawa, *Yakkyoku*, **25**, 1059 (1974).
21) NMR spectra were taken with an internal standard of tetramethylsilane.

acetoaminocinnamic acid was dissolved in pyridine and was added to the diazotized solution after addition of CH_3COONa and $CuCl_2$.

Compounds (II): Ethyl β-Methyl-β-4-styrylphenylglycidate (II-6)——A solution of *t*-BuOK in *t*-BuOH, prepared from 30 ml of *t*-BuOH and 0.94 g of K metal, was added to a mixture of 2.98 g 4-styryl phenylmethyl ketone (I-1) and 2.95 g of ethyl chloroacetate in 78 ml of anhydrous benzene dropwise over a period of 1.5 hr under a nitrogen atomosphere with stirring in a water bath. The reaction mixture was then stirred for 48 hr at room temperature and refluxed for 2 to 3 hr, followed by distillation under reduced pressure to remove the solvent. The residue was dissolved in 200 ml of ether and washed with H_2O. The organic layer was dried over Na_2SO_4. The drying agent was filtered out and the solvent was removed to afford a crystalline solid. Recrystallization from EtOH gave 3.22 g (yield 77.9%) of II-6 as white granules, mp 65—67°.

In the same manner, compound (II-7—9) were synthesized. Compound (8) obtained as an oil was purified on a silica gel column using benzene as an eluent.

Compounds (III): Sodium β-Methyl-β-4-styrylphenylglycidate (III-10)——An ethanolic solution of NaOEt, prepared from 0.37 g of Na metal and 30 ml of EtOH, was added to a solution of 5.0 g of ethyl glycidate (II-6) in 25 ml of EtOH at room temperature with stirring. To the resulting solution was added 0.12 ml of H_2O. After stirring for 24 hr, the white precipitate was filtered, washed with ethanol and dried to yield 4.75 g (yield 96.9%) of III-10 as white powder, mp 183—190° (dec.).

Similarly to the method described, compounds (III-11—13) were synthesized.

Compounds (IV): α-4-Styrylphenylpropionaldehyde (IV-14)——A suspension of 1.95 g of sodium β-methyl-β-4-styrylphenylglycidate (III-10) in 110 ml of H_2O was adjusted to pH 7 with dilute hydrochloric acid under stirring. The reaction mixture was refluxed for 3 hr under N_2 atomosphere. The precipitate separated was collected by filtration, washed with H_2O and dried to yield a crystalline solid. Recrystallization from *n*-hexane gave 1.30 g (yield 85.5%) of IV-14 as white needles, mp 105—107°.

Similarly to the method described, compounds (IV-15—17) were synthesized.

Compounds (V): 4-*p*-Acetoaminostyrylphenylacet-thiomorpholide (V-23)——A mixture of 2.0 g of phenyl methyl ketone (I-3), 0.57 g of sulfur and 1.5 g of morpholine was heated at 80° for 4 to 5 hr. The precipitate was collected and washed with small portions of CH_2Cl_2. Yellow crystals of V-23 were obtained in a yield of 89.7% (2.44 g). Recrystallization from ethyl acetate–acetone gave pure sample, mp 229—230°. *Anal.* Calcd. for $C_{22}H_{24}O_2S$: C, 69.44; H, 6.39; N, 7.36. Found: C, 69.33; H, 6.31; N, 7.22. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1670 (CONH), NMR (DMSO-d_6) δ: 2.06 (3H, s, CH_3CO), 3.23—4.00 (6H, m, methylene group neighbouring at nitrogen of the morpholine), 4.10—4.46 (4H, m, methylene group neighbouring at oxygen of the morpholine), 7.0—7.83 (10H, m, Ar–H), 9.96 (1H, s, CONH).

Similarly to the method described, 4-(2-thienyl) vinylphenylacet-thiomorpholide (V-24) was obtained in a yield of 91% as yellow needles, mp 168—170° (recrystallization from ethyl acetate). *Anal.* Calcd. for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25. Found: C, 65.23; H, 5.57; N, 4.41. IR ν_{max}^{KBr} cm^{-1}: 1480 (C=S). NMR ($CDCl_3$) δ: 3.16—4.00 (6H, m, methylene), 4.23—4.50 (4H, m, methylene), 6.93—7.66 (9H, m, olefin-H, Ar–H, thiophene-H).

Compounds (VII): 4-(*p*-Bromostyryl)benzoic Acid (VII-31)——An ethanolic solution of NaOEt, prepared from 0.08 g of Na metal and 100 ml of EtOH, was added to 1.0 g of methyl 4-(*p*-bromostyryl) benzoate (VI-29).[12] The resulting solution was refluxed for 6 hr. To the cooled mixture a minimum amount of H_2O was added and the mixture was stored in a refrigerator. Precipitate thus-formed were filtered, dissolved in an excess of 5% hydrochloric acid and the solution was refluxed for 5 hr with stirring. The precipitate from the reaction mixture was collected and dried. The white crystalline powder (VII-31) was obtained in a yield of 83.7% (0.8 g), mp 324—326°. *Anal.* Calcd. for $C_{15}H_{11}BrO_2$: C, 59.43; H, 3.66. Found: C, 59.36; H, 3.60. IR ν_{max}^{KBr} cm^{-1}: 1670 (COOH).

In a similar manner described, 4-(*p*-chlorostyryl)benzoic acid (VII-30) was obtained in a yield of 73.8% as white crystalline powder, mp 313—316°. *Anal.* Calcd. for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29. Found: C, 69.78; H, 4.30. IR ν_{max}^{KBr} cm^{-1}: 1670 (COOH).

Compounds (VIII): 4-Chloro-4′-diazoacetyl Stilbene (VIII-32)——4-(*p*-Chlorostyryl) benzoic acid (VII-30) (0.78 g) was treated with an excess of thionyl chloride under reflux for 7 hr and the mixture was distilled under reduced pressure to give light yellow crystals. They were dissolved in $CHCl_3$, and the solution were added dropwise to an ethereal solution of an excess of diazomethane. The resulting mixture was stirred for 24 hr to give precipitate which was collected and weighed 0.2 g (yield 26.2%). Recrystallization from benzene–*n*-hexane gave yellow crystals, mp 158° (dec.). *Anal.* Calcd. for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.83; H, 3.92; N, 9.63. IR ν_{max}^{KBr} cm^{-1}: 2100 (N_2), 1590 (CO). NMR ($CDCl_3$) δ: 5.87 (1H, s, CO–CH), 7.09 (2H, s, olefin-H), 7.38 (4H, s, Ar–H), 7.51 (2H, d, J=8 Hz, Ar–H), 7.75 (2H, d, J=8Hz, Ar–H).

In a similar manner described, compound (VIII-33) was obtained in a yield of 34.8%, mp 158° (dec.) (recrystallization from benzene–*n*-hexane). *Anal.* Calcd. for $C_{16}H_{11}BrN_2O$: C, 58.74 ; H, 3.39 ; N, 8.56. Found: C, 59.16; H, 3.58; N, 8.33. IR ν_{max}^{KBr} cm^{-1}: 2080 (N_2), 1585 (CO).

Compounds (IX): 4-*p*-Chlorostyrylphenylacetamide (IX-34)——Diazoacetyl stilbene (VIII-32) (0.2 g) in 20 ml of dioxane was boiled under reflux with 1.3 ml of aqueous ammonia (d=0.88) and 0.26 ml of 10% $AgNO_3$ in water for 1.5 hr. Precipitate was filtered off and an excess of H_2O was added to the filtrate to

yield the precipitate of the amide. It was crystallized from dioxane–H_2O (2: 1) to afford 0.13 g (yield 67.6%) of IX-34 as light yellow crystals, mp 255° (decomp.). *Anal.* Calcd. for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.70; H, 5.22; N, 5.31. IR ν_{max}^{KBr} cm^{-1}: 3340, 3150 (NH_2), 1640 (CO). NMR (CF_3COOH) δ: 3.92 (2H, s, CH_2), 7.11 (2H, s, olefin-H), 7.30 (2H, d, $J=9$ Hz, Ar-H), 7.40 (4H, s, Ar–H), 7.60 (2H, d, $J=9$ Hz, Ar–H).

In a similar manner described, 4-*p*-bromostyrylphenylacetamide (IX-35) was obtained in a yield of 70.1% as white leaves, mp 265° (dec.) (recrystallization from dioxane–H_2O). *Anal.* Calcd. for $C_{10}H_{14}BrNO$: C, 60.77; H, 4.46; N, 4.43. Found: C, 60.53; H, 4.31; N, 4.40.

Compounds (X): Methyl 4-*p*-Chlorostyrylphenylacetate (X-38)——To a suspension of 0.2 g of phenylacetic acid (A-36) in ether was added an excess amount of a solution of diazomethane in ether. The mixture was allowed to stand at room temperature for 1 hr. When an evolution of nitrogen gas subsided, the solvent was distilled off to give the residue. It was recrystallized from benzene–*n*-hexane (1: 2) to give 0.19 g (yield 90%) of X-38 as white needles, mp 104—106°. IR ν_{max}^{KBr} cm^{-1}: 1730 (COOH). NMR ($CDCl_3$) δ: 3.62 (2H, s, CH_2), 3.70 (3H, s, COOMe), 7.03 (2H, s, olefin-H), 7.2—7.6 (8H, m, Ar–H).

In a similar manner described, compounds (A-37 and B-27) were treated to give compounds (X-39 and 40).

Compounds (XI): Methyl α-4-*p*-Chlorostyrylphenylpropionate (XI-41)——A solution of 0.9 g of methyl phenylacetate (X-38) in 10 ml of dimethylformamide was added dropwise to a suspension of 0.18 g (50% NaH in a mineral oil) of NaH in 20 ml of dimethylformamide under a nitrogen stream at room temperature with stirring whereby the mixture became dark reddish. After 1 hr a solution of 15 g of MeI in 10 ml of dimethylformamide was added dropwise to the reaction mixture, which turned yellowish. The mixture was stirred for 10 min and poured into an ice-water mixture. The mixture was extracted with benzene and the extract was washed with H_2O and dried over $MgSO_4$. The solvent was distilled off to give crystals which were then recrystallized from *n*-hexane to afford 0.85 g (yield 90%) of pale yellow needles, mp 84—86°. IR ν_{max}^{KBr} cm^{-1}: 1730 (COOMe). NMR ($CDCl_3$) δ: 1.50 (3H, d, $J=7$ Hz, α-CH_3), 3.65 (3H, s, COOMe), 3.72 (1H, q, $J=7$ Hz, α-CH), 7.01 (2H, s, olefin-H), 7.25—7.5 (8H, m, Ar–H).

In a similar manner described, compounds (XI-42, 43, and 45) were synthesized. In case of synthesis of methyl α-4-(2-thienyl)vinylphenylpropionate (XI-43), methyl phenylacetate (X-40) was conducted using 4.62 molar excess of NaH. The resulting residue was purified by column chromatography on alumina (eluent: benzene) and successively by thin-layer chromatography on silica gel (solvent: benzene). The product was recrystallized from *n*-hexane, yield 24.4%, white needles, mp 61—62°. IR ν_{max}^{nujol} cm^{-1}: 1730 (COOMe). NMR ($CDCl_3$) δ: 1.50 (3H, $J=7$ Hz, α-CH_3), 3.56 (3H, s, $COCH_3$), 3.72 (1H, q, $J=7$ Hz, α-CH), 6.9—7.5 (9H, m, thiophene-H, Ar–H). Besides XI-43, methyl α-dimethyl-4-(2-thienyl)vinylphenylacetate (XI-44) was obtained as a by-product. NMR ($CDCl_3$) δ: 1.57 (6H, s, gem-CH_3), 3.63 (3H, s, OCH_3), 6.8—7.4 (9H, m, olefin–H, Ar–H). A ratio of the amount of XI-43 to XI-44 in an unseparated residue was 3: 1 when determined by NMR spectrum.

Compound (XI-45) was prepared by use of EtI in the presence of 1.2 molar excess of NaH. NMR spectrum of the product revealed that methyl and ethyl esters presented in a ratio of 1: 1.3.

4-*p*-Bromostyrylphenylacetonitrile (XII)——A mixture of 0.2 g of phenylacetamide (XI-35) and 1.0 g of polyphosphate ester dissolved in 10 ml of $CHCl_3$ was refluxed for 2 hr, and $CHCl_3$ was distilled. The resulting residue was adjusted to pH 7 with an aqueous solution of 30% sodium carbonate. The mixture was extracted with benzene and dried over Na_2SO_4. Benzene was distilled off to give the residue which was purified by column chromatography on silica gel to afford 0.1 g (yield 53%) of XII as leaves, mp 158—160° (recrystallization from benzene). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN). NMR ($CDCl_3$) δ: 3.73 (2H, s, CH_2), 7.04 (2H, s, olefin-H), 7.2—7.6 (8H, m, Ar–H).

Compounds (XIII): α-Methyl-4-*p*-bromostyrylphenylacetonitrile (XIII-50) and α-Dimethyl-4-*p*-bromostyrylphenylacetonitrile (XIII-51)——A solution of 0.16 g of phenylacetonitrile (XII) in 5 ml of dimethylformamide was added dropwise to a suspension of 26 mg (50% NaH in a mineral oil) of NaH in 5 ml of dimethylformamide under a nitrogen stream at room temperature with stirring, whereby the mixture became reddish purple. After 15 min a solution of 77 mg of MeI in 5 ml of dimethylformamide was added dropwise to the mixture. The mixture was stirred for 5 min and poured into an ice-water. The mixture was extracted with benzene and the extract was washed with H_2O and dried over $MgSO_4$. The solvent was distilled off to give the residue. The residue containing XIII-50 and XIII-51 was separated on a preparative thin-layer chromatography of silica gel (solvent: benzene) to afford 0.1 g (yield 59.7%) of XIII-50 as light yellow leaves, mp 128—129° (recrystallization from *n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 2220 (CN), NMR ($CDCl_3$) δ: 1.64 (3H, d, $J=7$ Hz, α-CH_3), 3.89 (1H, q, α-CH), 7.05 (2H, s, olefin-H), 7.2—7.6 (8H, m, Ar–H). Compound (XIII-51) was also isolated as yellow leaves, mp 113—115° (recrystallization from *n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 2220 (CN). NMR ($CDCl_3$) δ: 1.74 (6H, s, gem-CH_3), 7.05 (2H, s, olefin-H), 7.4—7.6 (8H, m, Ar–H).

Compounds (XV): 5-Phenylacetyl-2-thienylacetonitrile (XV-52)——To a mixture of 4.74 g of thienylacetonitrile (XIV)[13] and 7.06 g of phenylacetyl chloride in 60 ml of distilled $CHCl_3$, 13.27 g of anhydrous $AlCl_3$ powder was added gradually with cooling. The reaction mixture was stirred for 1 hr and poured into an ice-water. The aqueous mixture was extracted with $CHCl_3$. The extract was washed with H_2O and

dried over $MgSO_4$, and distilled to give the residue. It was recrystallized from ether–ethyl acetate to afford 7.2 g (yield 78%) of XV-52 as pale yellow granules, mp 68°.

In a similar manner, compounds (XV-53—59) were synthesized.

Compounds (XVI): 5-(2-*p*-Chlorophenyl-1-hydroxyethyl)-2-thienylacetonitrile (XVI-62)——To a solution of 4.0 g of 2-thienylacetonitrile (XV-54) in 50 ml of MeOH was gradually added 1.2 g of $NaBH_4$ with stirring. The reaction mixture was stirred at room temperature for 30 min and poured into H_2O. The aqueous solution was extracted with $CHCl_3$. The extract was washed with H_2O and dried over $MgSO_4$. The solvent was distilled off to give the residue which was recrystallized from *n*-hexane to afford 4.71 g (yield 77.9%) of XVI-62 as leaves, mp 77—78°.

In a similar manner, compounds (XVI-60, 61, 63—67) were synthesized.

Compounds (XVII): 5-Styryl-2-thienylacetonitrile (XVII-68)——To a solution of 0.5 g of the alcohol derivative (XVI-60) in 10 ml of dioxane was added 5 ml of 20% sulfuric acid. The resulting mixture was heated in a water bath for 30 min. Dioxane was distilled off under reduced pressure to give the residue which was recrystallized from *n*-hexane–benzene to afford 0.23 g (yield 51.5%) of XVII-68 as light yellow needles, mp 110—111°.

In a similar manner, compounds (XVII-69—75) were synthesized.

Compounds (XVIII): 5-(2-Phenyl-1-hydroxyethyl)-2-thienylacetic Acid (XVIII-77)——To a solution of 1.0 g of the acetonitrile derivative (XVI-60) in 10 ml of EtOH was added a solution of 1.15 g of KOH in 2 ml of H_2O, and the mixture was boiled for 24 hr. Dilute sulfuric acid was then added to the reaction mixture. The aqueous mixture was extracted with $CHCl_3$. The extract was washed with H_2O and dried over $MgSO_4$. The solvent was distilled off to give the residue which was recrystallized from benzene to afford 0.66 g (yield 62%) of XVIII-77 as light brown granules, mp 107.5°.

In a similar manner, compounds (XVIII-78—83) were synthesized.

5-*p*-Nitrostyryl-2-thienylacetamide (XIX)——To a solution of 0.8 g of the nitrile (XVII-75) in 10 ml of acetic acid was added 4.0 g of $TiCl_4$ at room temperature with stirring. After the addition of 2.0 ml of H_2O, the mixture was stirred for 4 hr. The resulting mixture was poured into water and the precipitate formed was collected, washed with H_2O and dried. The residue were recrystallized from EtOH to afford 0.75 g (yield 85%) of XIX as reddish orange crystals, mp 196—197°. *Anal.* Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72. Found: C, 58.26; H, 4.18; N, 9.36. IR ν_{max}^{KBr} cm^{-1}: 3350, 3150 (NH_2), 1640 ($CONH_2$). NMR (DMSO-d_6) δ: 3.66 (2H, s, CH_2), 6.83—8.0 (8H, m, NH_2, olefin-H, thiophene-H, Ar–H), 8.26 (2H, d, J=8 Hz, Ar–H).

***trans*-2-*p*-Nitrostyryl Thiophene (XX) and *cis*-α-*p*-Nitrophenyl-β-2-thienylacrylic Acid Piperidinium Salt (XXI)**——A mixture of 1.78 g of 2-formylthiophene, 2.9 g of *p*-nitrophenylacetic acid and 1 ml of piperidine was heated at 110° for 1 hr. The reaction mixture was triturated with $CHCl_3$. The residue was collected and washed with $CHCl_3$. The product was recrystallized from $CHCl_3$–EtOH to give 2.0 g of *trans*-2-*p*-nitrostyryl thiophene (XX) as yellow needles, mp 176—177°, which was consistent with a melting point previously described.[15] IR ν_{max}^{KBr} cm^{-1}: 1350, 1500 (NO_2). NMR ($CDCl_3$) δ: 7.4—8.3 (5H, m, thiophene-H, olefin-H), 7.53 (2H, d, J=8 Hz, Ar-H), 8.16 (2H, d, J=8 Hz, Ar–H).

From $CHCl_3$-soluble filtrate was obtained *cis*-α-*p*-nitrophenyl-β-2-thienylacrylic acid piperidinium salt (XXI), as yellow crystals in a yield of 1.36 g, mp 170—172° (recrystallization from ethyl acetate). *Anal.* Calcd. for $C_{18}H_{19}N_2O_4S$: C, 60.15; H, 5.33; N, 7.79. Found: C, 60.25; H, 5.63; N, 7.80. IR ν_{max}^{KBr} cm^{-1}: 1600—1520 (COO^-), 1330 (NO_2). NMR ($CDCl_3$) δ: 1.58 (6H, broad s, three methylenes of piperidine), 2.90 (4H, broad s, two methylenes of piperidine), 6.9—7.5 (4H, m, olefin-H, thiophene-H), 7.71 (2H, d, J=8 Hz, Ar–H), 8.2 (2H, d, J=8 Hz, Ar–H).

***cis*-α-*p*-Nitrophenyl-β-2-thienylacrylic Acid (XXII)**——To a solution of 1.0 g of XXI in 20 ml of H_2O was added an excess amount of concentrated hydrochloric acid. The precipitate thus-formed was filtered, dried and recrystallized from EtOH to give 0.72 g (yield 95%) of XXII as yellow columns, mp 184°.

***trans*-α-*p*-Nitrophenyl-β-2-thienylacrylic Acid (XXIII)**——Route 1: A mixture of 0.5 g of XXII and a piece of iodine in 10 ml of nitrobenzene was boiled under reflux for 30 min. Nitrobenzene was removed under reduced pressure to give the residue which was recrystallized from EtOH to afford 0.41 g of XXIII as light yellow needles, mp 235°.

Route 2: Triethylamine (1.24 ml) was added to a solution of 1.0 g of 2-formylthiophene and 1.6 g of *p*-nitrophenyl-acetic acid in 32 ml of acetic anhydride. The reaction mixture was refluxed at 140° to 150° for 8 hr. The reaction mixture was made alkaline with 5% NaOH. The mixture was washed with $CHCl_3$, and treated with concentrated hydrochloric acid. The precipitate thus-formed was collected and dried, 0.12 g (yield 5%). Recrystallization from EtOH gave pale yellow needles, mp 235°. IR- and NMR-spectrum of the samples prepared by two routes were identical and showed IR ν_{max}^{KBr} cm^{-1}: 1650 (COOH) and NMR (DMSO-d_6) δ: 6.9—7.66 (5H, m, Ar–H, thiophene-H), 8.2 (1H, s, olefin-H), 8.40 (2H, d, J=8 Hz, Ar–H).

***trans*-5-α-Nitrostyryl-2-formylthiophene (XXIV)**——To a Vielsmeyer reagent prepared from 6.89 g of N-methylformanilide and 7.8 g of $POCl_3$ was added gradually 10 g of thiophene derivative (XX). The reaction mixture was heated for 3 hr and poured into ice-water. The resulting yellow precipitate was collected. It was recrystallized from EtOH. Yellow needles of XXIV were obtained in a yield of 89.2% (10 g), mp 169—170°.

***trans*-5-*p*-Nitrostyryl-2-thienylcarboxylic Acid (XXV)**——Silver oxide prepared from 1.3 g of $AgNO_3$ and 0.46 g of NaOH was suspended in 30 ml of EtOH. To the suspension was added gradually 1.3 g of the aldehyde (XXIV) in a minimum amount of tetrahydrofuran and a solution of 0.15 g of NaOH in 5 ml of water with stirring at room temperature. The suspension was stirred for 24 hr and poured into H_2O. The resulting precipitate was filtered off and the filtrate was destilled. The precipitate formed was collected and dried to afford yellowish green needles. Recrystallization from EtOH gave 0.96 g (yield 70%) of XXV, mp 278—279°.

***trans*-5-*p*-Nitrostyryl-2-diazoacetyl Thiophene (XXVI)**——A mixture of 1.0 g of thiophene (XXV) and 0.65 g of thionyl chloride was boiled under reflux for 1 hr. Thionyl chloride was distilled off under reduced pressure. The residue was dissolved in distilled $CHCl_3$, and to the solution was added an excess amount of diazomethane in ether with stirring. After standing for a while, the solvent was distilled off under reduced pressure to give crude residue from which 0.57 g (yield 53%) of brown needles of XXVI, mp 194—195° (dec.) were obtained after recrystallization from benzen–tetrahydrofuran.

1-Methylsulfinyl-1-methylthio-2-(*trans*-5-*p*-nitrostyryl-2-thienyl)-ethylene (XXVII)——To a mixture of 1.19 g of methyl methylthiomethyl sulfoxide, 0.45 ml of 40% Triton B in MeOH and 50 ml of benzene was added 0.5 g of the aldehyde (XXIV). The mixture was stirred for 24 hr at room temperature and poured into H_2O. Reddish brown precipitate formed was collected, dried and recrystallized from EtOH. XXVII was obtained as reddish brown needles, 0.35 g (yield 50%), mp 182—183°.

***trans*-5-*p*-Nitrostyryl-2-thienylidene malononitrile (XXVIII-99)**——To a mixture of 1.0 g of thiophene aldehyde (XXIV) and 0.03 g of malononitrile in 20 ml of benzene was gradually added 0.04 g of triethylamine. The precipitate separated was filtered, dried and recrystallized from acetone–benzene to give 0.11 g (yield 95%) of XXVIII-99 as leaves, mp 256°.

Diethyl *trans*-5-*p*-nitrostyryl-2-thienylidene Malonate (XXVIII-100)——As soon as 0.07 ml of piperidine was added gradually to a mixture of 0.5 g of thiophene aldehyde (XXIV) and 0.29 g of diethyl malonate in 20 ml of EtOH, precipitate was formed. They were collected, dried and crystallized from EtOH to give 0.71 g (yield 80%) of XXVIII-100 as reddish orange needles, mp 135°.

5-*p*-Nitrostyryl-2-thienylidene Malonic Acid (XXVIII-101)——To a mixture of 0.3 g of thiophene aldehyde (XXIV) and 0.18 g of malonic acid in 20 ml of EtOH was added dropwise 0.02 ml of piperidine. The mixture was heated in a water bath for 1 hr and poured into hydrochloric acid. The resulting precipitate was collected, dried, and recrystallized from acetone-tetrahydrofuran to give 0.32 g (yield 81%) of XXVIII-101 as red needles, mp 248° (dec.).

Compounds (A and B)

***Via* Method 1: α-4-Styrylphenylpropionic Acid (A-18)**——An aqueous solution of 1.15 g of $AgNO_3$ in 30 ml of H_2O was added to a mixture of 1.0 g of the aldehyde (IV-14) in 10 ml of ethanol and 2 ml of tetrahydrofuran. To the resulting mixture was added dropwise a solution of 0.68 g of NaOH in 30 ml of H_2O at room temperature with stirring, and the mixture was stirred for 2 hr. The precipitate was filtered off, and the filtrate was distilled to removed the solvents. The residue was dissolved in H_2O and washed with ether. The aqueous layer was acidified with hydrochloric acid followed by extraction with ether. The extract was washed with H_2O, dried over $MgSO_4$, then distilled to remove the solvent. The residue was recrystallized from ether–*n*-hexane to afford 0.34 g (yield 31%) of A-18 as white needles, mp 181—183°. IR ν_{max}^{KBr} cm^{-1}: 1700 (COOH). NMR ($CDCl_3$) δ: 1.51 (3H, d, J=8 Hz, α-CH_3), 3.75 (1H, d, J=8 Hz, α-CH), 7.08 (2H, s, olefin-H), 7.18—7.75 (9H, m, Ar–H).

In the similar manner compound (A-19, B-20 and 21) were synthesized.

***Via* Method 2: Sodium 4-*p*-Aminostyrylphenylacetate (A-26)**——A mixture of 1.35 g of V-23, 150 ml of dioxane and 30 ml of 20% hydrochloric acid was heated at 90° to 95° for 24 hr with stirring, followed by distillation under reduced pressure to remove dioxane. Pale yellow matter precipitated was collected and dried. It was dissolved in 10 ml of EtOH and the solution was added to an ethanolic solution of NaOEt prepared from 0.23 g of Na metal and 5 ml of EtOH. The precipitate was removed by filtration and the filtrate was condensed to yield 0.35 g (25% yield) of A-26 as yellow-brown granules, mp 315—316°. IR ν_{max}^{KBr} cm^{-1}: 3500—2900 (NH_2), 1560 (COONa).

4-(2-Thienyl)vinylphenylacetic Acid (B-27)——An excess of 10% NaOH in water was added to a solution of 4.12 g of thiomorpholide (V-24) dissolved in 200 ml of dioxane. The resulting mixture was refluxed for 24 hr, and distilled under reduced pressure to removed dioxane. The resulting aqueous solution was acidified with 10% hydrochloric acid and extracted with ether. The extract was washed with water and dried over $MgSO_4$. The solvent was distilled to yield the residue which was recrystallized from ether–*n*-hexane to afford 1.0 g (yield 35%) of B-27 as pale yellow granules, mp 177—178°. IR ν_{max}^{KBr} cm^{-1}: 1700—1600 (COOH). NMR ($CDCl_3$) δ: 3.56 (2H, s, CH_2), 6.7—7.6 (9H, m, olefin-H, thiophene-H, Ar–H).

***Via* Method 3: 4-*p*-Chlorostyrylphenylacetic Acid (A-36)**——A mixture of 1.7 g of phenylacetamide (IX-34), 50 ml of concentrated hydrochloric acid and 50 ml of acetic acid was refluxed for 3 hr. The precipitate were filtered, washed with H_2O and recrystallized from benzene to give 1.42 g (yield 82.7%) of A-36 as light yellow leaves, mp 202—204°. IR ν_{max}^{KBr} cm^{-1}: 1725 (COOH). NMR (DMSO-d_6) δ: 3.59 (2H, s, CH_2), 7.1—7.8 (10H, m, olefin-H, Ar–H).

In a similar manner described, compound (IX-35) was treated to give A-37.

***Via* Method 4: α-4-*p*-Chlorostyrylphenylpropionic Acid (A-46)**——A mixture of 0.2 g of phenylpropionate (XI-41) in 20 ml of concentrated hydrochloric acid and 20 ml of acetic acid was heated under reflux for 2 hr. The mixture was poured into ice-water and the resulting mixture was extracted with benzene. The extract was washed with H_2O and dried over $MgSO_4$. The solvent distilled off to give a crystalline solid. Recrystallization from benzene gave 0.15 g (yield 78.7%) of A-46 as light yellow crystalline powder, mp 212—214°. IR ν_{max}^{KBr} cm^{-1}: 1695 (COOH). NMR (DMSO-d_6) δ: 1.40 (3H, d, J=7 Hz, α-CH_3), 3.69 (1H, q, J=7 Hz, α-CH), 7.22 (2H, s, olefin-H), 7.3—7.7 (8H, m, Ar–H).

In a similar manner described, compounds (A-47 and A-48) were synthesized. Hydrolysis of compound (XI-43) was conducted with 10% KOH in a water under reflux for 20 hr followed by acidification with concentrated hydrochloric acid to give compound (B-21). α-4-*p*-bromostyrylphenylpropionic acid (A-47) was obtained by treatment of compound (XIII-50) with a mixture of concentrated hydrochloric acid and acetic acid under reflux for 3 hr. The product was identical with the hydrolyzed product of XI-42 in respect to IR spectrum and melting point.

Compounds (C): 5-Styryl-2-thienylacetic Acid (C-84)——To a solution of 1.0 g of the alcohol (XVIII-77) in 20 ml of dioxane was added 5 ml of 50% sulfuric acid (or 50% phosphoric acid). The mixture was heated for 30 min in a water bath. Dioxane was distilled off under reduced pressure followed by addition of H_2O to give the precipitate. It was collected, washed with H_2O and dried.

Similarly, compounds (C-85—90) were synthesized.

Pharmacological Method: Platelet aggregation test was performed according to the previously reported method.[18,19] Platelet-rich citrated plasma (pH 7.7—7.9) obtained from a rabbit was immediately added to an equal volume of isotonic barbital buffer (pH 7.3). The buffered platelet-rich citrated plasma was stored near 20° for use within 8 hr. All glassware coming into contact with blood or platelet-rich citrated plasma was siliconized with Siliconizer N-A (Fuji Kobunshi Kogyo Co., Ltd.). Collagen was a lyophillized preparation from bovine achilles tendon (Sigma Chemical Co., Ltd.), and approximately 100 mg of collagen was placed in a glass homogenizer covered with 5 ml of saline and homogenized to a fine suspension with a Teflon covered piston at 2000 rpm for 2 to 3 hr. The supernatant suspension was removed and the concentration of the agent was 2.0 or 1.6 in optical density estimated at 420 nm. Adenosine 5′-diphosphate (Na_2) (Sigma Chemical Co., Ltd.) was dissolved in saline at 10^{-3} M. Each of the test samples was dissolved in 0.02 N NaOH (N) or dimethyl sulfoxide (D) at 10^{-2} M. A cuvette containing 1.0 ml of buffered platelet-rich citrated plasma preincubated at 37° for 3 min was treated with 10 μl of a test sample in 0.02 N NaOH (N) or dimethyl sulfoxide (D) at 37° for 3 min. A cuvett was then transferred into an EVANS EEL 169 aggregation meter and challenged with 100 μl of a solution of collagen or 10 μl of a solution of adenosine-5′-diphosphate (final concentration, 10^{-5} M) at 37°. Inhibition percentage of aggregation by a test compound was calculated by dividing the maximum deflection in the optical density curve by that observed with the control solvent (N or D), and then multiplying by 100. The inhibition percentages were not absolute as the sensitivity of platelets to aggregating agents varied from preparation to preparation. Accordingly, a relative potency (R_{ASP}) of inhibition of a compound to aspirin at the same concentration was a direct measure of potency of inhibition. Aspirin showed 30—70% inhibition (average, 55%) in solvent D and N, and Ibuprofen showed R_{ASP}=0.6 in solvent N.

Acknowledgement The authors express their deep gratitude to Dr. M. Ichino for his interest in this work and to Mr. T. Kawashima and his colaborators for physicochemical measurement.