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Studies on 2-Oxoquinoline Derivatives as Blood Platelet Aggregation Inhibitors.

III. *N*-Cyclohexyl-*N*-(2-hydroxyethyl)-4-(1,2-dihydro-2-oxo-6-quinolyloxy)-butyramide and Related Compounds

TAKAO NISHI, FUJIO TABUSA, TATSUYOSHI TANAKA, HIRAKI UEDA, TAKEFUMI SHIMIZU,
TOSHIMI KANBE, YUKIO KIMURA and KAZUYUKI NAKAGAWA*

*Tokushima Research Institute, Otsuka Pharmaceutical Co., Ltd., Kagasuno
463-10, Kawauchi-cho, Tokushima-shi 771-01, Japan*

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A series of *N,N*-disubstituted- ω -(1,2-dihydro-2-oxoquinolyloxy)alkanecarboxamides was synthesized and tested for inhibitory activity towards collagen- and ADP-induced aggregation of rabbit blood platelet *in vitro*. These compounds were prepared by the reaction of ω -(1,2-dihydro-2-oxoquinolyloxy)alkanoic acid and various amines by the mixed anhydride method. Among them, *N*-cyclohexyl-*N*-(2-hydroxyethyl)-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide (IVa₁) was found to have the most potent inhibitory activity. The structure-activity relationships are discussed.

Keywords—*N,N*-disubstituted- ω -(1,2-dihydro-2-oxoquinolyloxy)alkanecarboxamide derivative; *N*-cyclohexyl-*N*-(2-hydroxyethyl)-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide; inhibition of blood platelet aggregation; structure-activity relationship

Introduction

In the preceding two papers,^{1,2)} we reported that ethyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (OPC-3162) and 6-[3-(1-cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline (OPC-3930) showed potent inhibitory activity towards blood platelet aggregation. As a continuation of our search for much more active compounds, we report here the synthesis and testing of 2-oxoquinolines having a disubstituted amide group in their side chain. *N*-Cyclohexyl-*N*-(2-hydroxyethyl)-4-(1,2-dihydro-6-quinolyloxy)butyramide (IVa₁) was found to have very potent inhibitory activity towards blood platelet aggregation, being about five times more potent than OPC-3162 and OPC-3930. This paper deals with the synthesis, biological activity and structure-activity relationships of *N,N*-disubstituted ω -(1,2-dihydro-2-oxoquinolyloxy)alkanecarboxamides.

Synthesis

Condensation of hydroxy-1,2-dihydro-2-oxoquinolines (Ia-f)³⁾ with ω -bromoalkanoic acid esters⁴⁾ in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) afforded the corresponding ester derivatives (IIa, c-j) in good yield. However, ethyl 3-(1,2-dihydro-2-oxo-6-quinolyloxy)propionate (IIb) could not be prepared by the same procedure, and hence it was obtained by dehydrogenation of ethyl 3-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)propionate (V) using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Chart 1, Table I).

Hydrolysis of IIa-j with 20% hydrochloric acid gave the corresponding carboxylic acids (IIIa-j) (Table II). Various amide derivatives (IVa-o, VIIa-c) were prepared from IIIa-j, VI¹⁾ and various amines by the ordinal mixed anhydride method using isobutyl chloroformate (Charts 1 and 2, Table III).

Alkylation of IVg with alkyl halides gave the corresponding *N*¹-alkyl derivatives (VIIIa, b), and acetylation of IVa₁ with acetic anhydride-pyridine gave *N*-(2-acetoxyethyl)-*N*-cyclohexyl-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide (IX) (Chart 3, Table III).

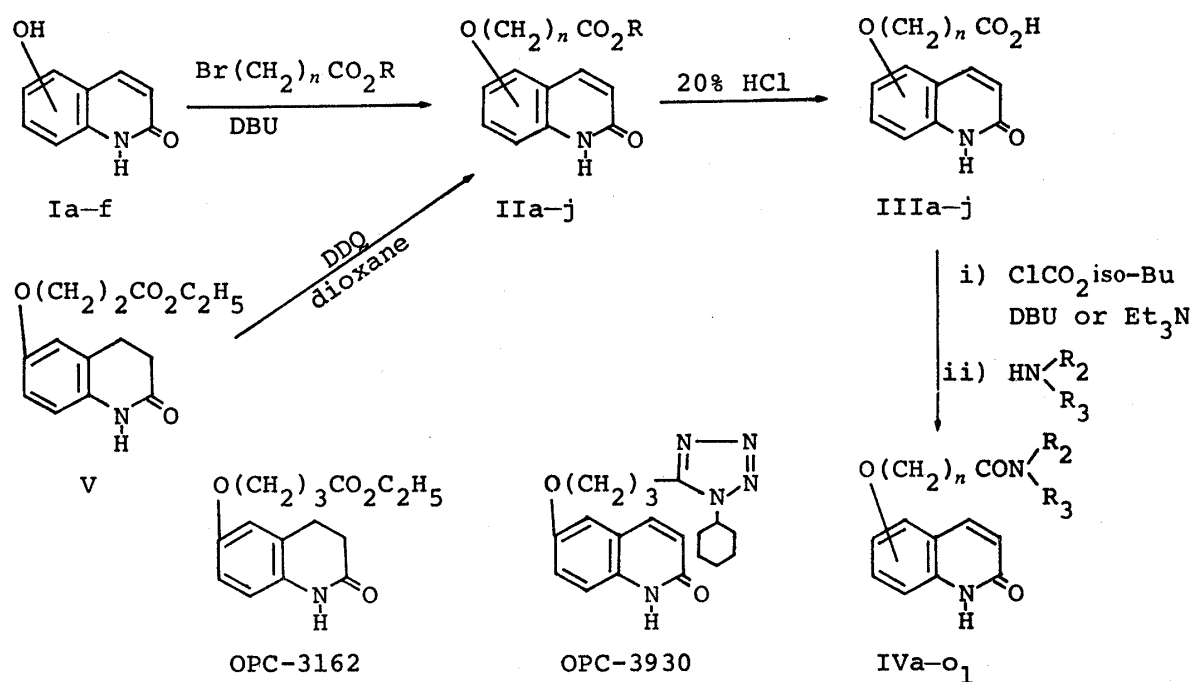


TABLE I. Alkyl (1,2-Dihydro-2-oxoquinolyloxy)alkanoate Derivatives

Compd. No.	Position	n	R	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%)		
								Calcd (Found)		
								C	H	N
IIa	6	1	CH ₃	91	204—206	MeOH	C ₁₂ H ₁₁ NO ₄	61.80 (61.61)	4.75 4.80	6.01 5.94
IIb	6	2	CH ₂ CH ₃	40 ^{a)}	164—166	MeOH	C ₁₄ H ₁₅ NO ₄	64.36 (64.11)	5.79 5.65	5.36 5.36
IIc	6	3	CH ₃	74	150.5—152	MeOH	C ₁₄ H ₁₅ NO ₄	64.36 (64.30)	5.79 5.77	5.36 5.30
IId	6	4	CH ₂ CH ₃	86	131—133	CHCl ₃ — EtOAc	C ₁₆ H ₁₉ NO ₄	66.42 (66.05)	6.62 6.71	4.84 4.87
IIe	6	5	CH ₂ CH ₃	88	107.5—109	CHCl ₃ — EtOAc	C ₁₇ H ₂₁ NO ₄	67.31 (67.23)	6.98 7.14	4.62 4.54
IIf	3	3	CH ₃	83	144—145.5	CHCl ₃ — petr. ether	C ₁₄ H ₁₅ NO ₄	64.36 (64.36)	5.79 5.81	5.36 5.33
IIg	4	3	CH ₂ CH ₃	83	133—135	EtOH	C ₁₅ H ₁₇ NO ₄	65.44 (65.39)	6.22 6.31	5.09 5.12
IIh	5	3	CH ₂ CH ₃	76	171—173	EtOH	C ₁₅ H ₁₇ NO ₄	65.44 (65.26)	6.22 6.31	5.09 5.36
IIi	7	3	CH ₃	78	134.5—136	CHCl ₃ — petr. ether	C ₁₄ H ₁₅ NO ₄	64.36 (64.46)	5.79 5.72	5.36 5.39
IIj	8	3	CH ₃	86	138.5—140	iso-PrOH	C ₁₄ H ₁₅ NO ₄	64.36 (64.13)	5.79 5.94	5.36 5.38

a) The yield obtained by DDQ oxidation.

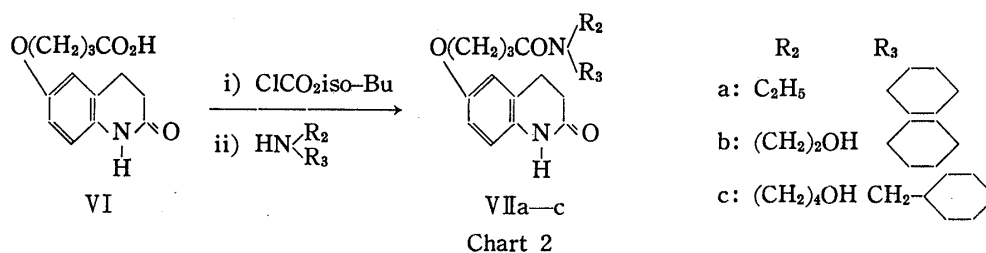


TABLE II. (1,2-Dihydro-2-oxoquinolyloxy)alkanoic Acid Derivatives

Compd. No.	Position	n	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%)		
							Calcd (Found)		
							C	H	N
IIIa	6	1	98	288—290.5	DMF	$\text{C}_{11}\text{H}_9\text{NO}_4$	60.27 (60.10)	4.14 (4.11)	6.39 (6.42)
IIIb	6	2	92	272—273.5	MeOH	$\text{C}_{12}\text{H}_{11}\text{NO}_4$	61.80 (61.80)	4.75 (4.76)	6.01 (6.14)
IIIc	6	3	95	262—265	DMF-H ₂ O	$\text{C}_{13}\text{H}_{13}\text{NO}_4$	63.15 (63.30)	5.30 (5.28)	5.67 (5.70)
IIId	6	4	85	245—247	DMF	$\text{C}_{14}\text{H}_{15}\text{NO}_4$	64.36 (64.39)	5.79 (5.79)	5.36 (5.40)
IIIe	6	5	95	215—217	DMF	$\text{C}_{15}\text{H}_{17}\text{NO}_4$	65.44 (65.36)	6.22 (6.16)	5.09 (5.10)
IIIf	3	3	93	237—239	DMF-H ₂ O	$\text{C}_{13}\text{H}_{13}\text{NO}_4$	63.15 (63.27)	5.30 (5.58)	5.67 (5.73)
IIIg	4	3	60	300	DMF	$\text{C}_{13}\text{H}_{13}\text{NO}_4$	63.15 (63.10)	5.30 (5.22)	5.67 (5.81)
IIIh	5	3	90	241—243	EtOH-H ₂ O	$\text{C}_{13}\text{H}_{13}\text{NO}_4$	63.15 (63.15)	5.30 (5.35)	5.67 (5.70)
IIIi	7	3	96	275—278.5	DMF	$\text{C}_{13}\text{H}_{13}\text{NO}_4$	63.15 (62.87)	5.30 (5.41)	5.67 (5.76)
IIIj	8	3	96	258—261.5	DMF	$\text{C}_{13}\text{H}_{13}\text{NO}_4$	63.15 (63.39)	5.30 (5.32)	5.67 (5.82)

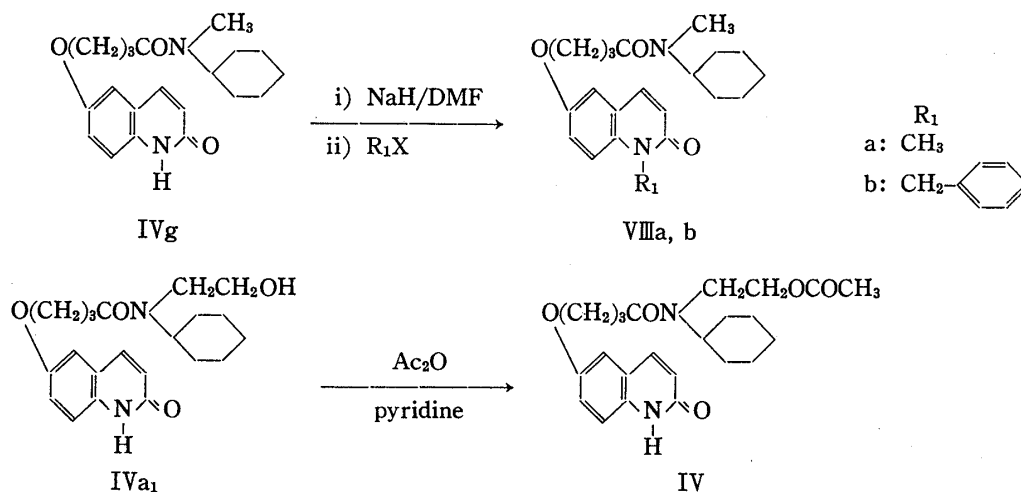
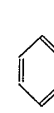
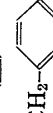
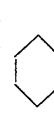
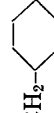
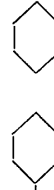


TABLE III. *N,N*-Disubstituted-(1,2-dihydro-2-oxoquinolinyloxy or 2-oxo-1,2,3,4-tetrahydro-6-quinolinyloxy)alkanoic Acid Amide Derivatives and Their Inhibition of Blood Platelet Aggregation

(IVa—o, VIIIa, b, x)

(VIIa—c)

Compd. No.	Position	<i>n</i>	<i>R</i> ₁	<i>R</i> ₂	<i>R</i> ₃	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%)				Inhibition (IC ₅₀ , μM)	
										Calcd	Found	C	H	N	ADP
IVa	6	3	H	H	H	23	241—242	MeOH—H ₂ O	C ₁₃ H ₁₄ N ₂ O ₃	63.42 (63.48)	5.71 5.73	11.38 11.19	495	254	
IVb	6	3	H	CH ₃	H	17	201—202	CHCl ₃	C ₁₄ H ₁₆ N ₂ O ₃	64.60 (64.28)	6.20 6.06	10.76 10.39	134	139	
IVc	6	3	H	CH ₃	CH ₃	66	163—163.5	CHCl ₃ — petr. ether	C ₁₅ H ₁₈ N ₂ O ₃	65.67 (65.57)	6.61 6.98	10.21 10.48	160	103	
IVd	6	3	H	CH ₃	CH(CH ₃) ₂	86	123—124	CHCl ₃ — petr. ether	C ₁₇ H ₂₂ N ₂ O ₃ ·1/4H ₂ O	66.53 (66.58)	7.39 7.25	9.13 9.09	50.4	77.7	
IVe	6	3	H	CH ₃		58	187—189	CHCl ₃ — petr. ether	C ₂₀ H ₂₀ N ₂ O ₃	71.41 (71.20)	5.99 6.09	8.33 8.23	12.6	6.3	
IVf	6	3	H	CH ₃	CH ₂ — 	80	163—163.5	MeOH—H ₂ O	C ₂₁ H ₂₂ N ₂ O ₃	71.98 (71.68)	6.33 6.26	8.00 7.78	11.8	21.0	
IVg	6	3	H	CH ₃		75	186—188	MeOH—H ₂ O	C ₂₀ H ₂₀ N ₂ O ₃	70.15 (70.19)	7.65 7.79	8.18 8.30	4.2	2.1	
IVh	6	3	H	CH ₂ CH ₃	CH ₂ — 	59	166.5—168	CHCl ₃ — petr. ether	C ₂₂ H ₃₀ N ₂ O ₃	71.32 (71.02)	8.16 8.24	7.56 7.52	ne ^{a)}	ne	
IVi	6	3	H	CH ₃	CH ₂ — 	55	169.5—171	CHCl ₃ — petr. ether	C ₂₀ H ₂₁ N ₃ O ₃ ·1/4H ₂ O	67.49 (67.32)	6.09 6.06	11.81 11.75	11.3	6.7	
IVj	6	3	H	CH ₃	CH ₂ — 	77	125.5—127.5	CHCl ₃ — petr. ether	C ₁₉ H ₂₀ N ₂ O ₄	67.04 (67.03)	5.92 5.87	8.23 8.22	29.4	15.1	
IVk	6	3	H	CH ₃	CH ₂ — 	75	150—151.5	CHCl ₃ — petr. ether	C ₂₀ H ₂₀ N ₂ O ₄	67.02 (66.89)	7.41 7.32	7.82 7.77	11.3	6.7	
IVl	6	3	H			83	170—172	CHCl ₃ — petr. ether	C ₁₈ H ₂₂ N ₂ O ₃	68.77 (68.69)	7.05 7.13	8.91 8.60	63.0	23.1	

Compd. No.	Position	n	R ₁	R ₂	R ₃	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%)				Inhibition (IC ₅₀ , μM)	
										Calcd (Found)	C	H	N	ADP	Collagen
IVm	6	3	H			25	184.5—186	MeOH-H ₂ O	C ₂₃ H ₃₁ N ₃ O ₃	69.49 (69.42)	7.86 (7.88)	10.57 (10.38)		4.6	6.1
IVn	6	3	H			40	202.5—203.5	DMF	C ₂₃ H ₂₅ N ₃ O ₃	70.57 (70.39)	6.44 (6.47)	10.73 (10.73)		5.9	10.5
IVo	6	3	H	H		81	251—252	DMF	C ₁₉ H ₂₄ N ₂ O ₃	69.49 (69.30)	7.37 (7.64)	8.53 (8.66)		ne	69.3
IVp	6	3	H	CH ₂ CH ₃		73	173—174	EtOH-H ₂ O	C ₂₁ H ₂₈ N ₂ O ₃	70.76 (70.70)	7.92 (7.88)	7.86 (7.94)		4.2	2.1
IVq	6	3	H	CH ₂ CH ₂ CH ₃		70	182—184.5	EtOAc	C ₂₂ H ₃₀ N ₂ O ₃	71.32 (71.57)	8.16 (7.95)	7.56 (7.81)		27.3	2.1
IVr	6	3	H	CH(CH ₃) ₂		47	174—175	Benzene-petr. ether	C ₂₂ H ₃₀ N ₂ O ₃	71.32 (71.51)	8.16 (8.19)	7.56 (7.53)		38.6	20.2
IVs	6	3	H	(CH ₂) ₃ CH ₃		39	159—160	EtOH	C ₂₃ H ₃₂ N ₂ O ₃	71.84 (71.91)	8.39 (8.25)	7.29 (7.34)		42.0	14.7
IVt	6	3	H	(CH ₂) ₄ CH ₃		65	156.5—157.5	EtOAc	C ₂₄ H ₃₄ N ₂ O ₃	72.33 (72.35)	8.60 (8.58)	7.03 (6.81)		323	54.6
IVu	6	3	H	(CH ₂) ₅ CH ₃		58	129—132	Benzene-ligroin	C ₂₅ H ₃₆ N ₂ O ₃	72.78 (72.63)	8.80 (8.92)	6.79 (6.52)		96.6	111
IVv	6	3	H	(CH ₂) ₆ CH ₃		32	100—103	Ligroin	C ₂₆ H ₃₈ N ₂ O ₃	73.20 (73.32)	8.98 (8.85)	6.57 (6.41)		58.8	46.2
IVw	6	3	H			69	180—181.5	CHCl ₃ -petr. ether	C ₂₅ H ₂₈ N ₂ O ₃ · 1/4H ₂ O	73.41 (73.08)	7.02 (6.97)	6.85 (6.85)		27.7	16.4
IVx	6	3	H	CH ₂ - 		87	185.5—187	Benzene-ligroin	C ₂₆ H ₃₀ N ₂ O ₃	74.61 (74.82)	7.23 (7.21)	6.69 (6.49)		4.2	2.1
IVy	6	3	H			44	228.5—230.5	MeOH	C ₂₅ H ₃₄ N ₂ O ₃	73.14 (73.10)	8.35 (8.33)	6.82 (6.75)		ne	252
IVz	6	3	H	CH ₂ - 		40	172—173.5	EtOAc-petr. ether	C ₂₆ H ₃₆ N ₂ O ₃	72.78 (72.70)	8.57 (8.51)	6.53 (6.52)		29.4	8.8
IVa ₁	6	3	H	(CH ₂) ₂ OH		55	163—165.5	MeOH-H ₂ O	C ₂₁ H ₂₈ N ₂ O ₄	67.72 (67.64)	7.58 (7.55)	7.52 (7.35)		1.4	0.5
IVb ₁	6	3	H	(CH ₂) ₄ OH		19	153—155	iso-PrOH-EtOAc	C ₂₄ H ₃₂ N ₂ O ₄ · 1/4H ₂ O	68.21 (68.24)	8.09 (7.97)	6.92 (6.77)		1.9	1.9
IVc ₁	6	1	H	CH ₂ CH ₃		55	159.5—162	Benzene	C ₁₉ H ₂₄ N ₂ O ₃	69.49 (69.63)	7.37 (7.68)	8.53 (8.39)		483	44.1

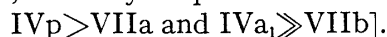
IVd ₁	6	2	H	CH ₂ CH ₃		16	149—150	EtOAc- petr. ether	C ₂₀ H ₂₈ N ₂ O ₃	69.24 (69.50)	7.70 7.63	8.07 8.07	54.6	6.5
IVe ₁	6	4	H	CH ₂ CH ₃		47	142—142.5	EtOAc- petr. ether	C ₂₂ H ₃₀ N ₂ O ₃ ·1/4H ₂ O	70.47 (70.50)	8.20 7.98	7.47 7.43	4.2	0.5
IVf ₁	6	5	H	CH ₂ CH ₃		48	128—130	EtOAc- petr. ether	C ₂₃ H ₃₂ N ₂ O ₃	71.84 (71.88)	8.39 8.34	7.29 7.28	37.0	27.3
IVg ₁	6	3	H	CH ₂ CH ₃		17	150—152	Benzene- petr. ether	C ₁₃ H ₂₂ N ₂ O ₃	68.77 (68.60)	7.05 7.19	8.91 8.64	50.4	21.0
IVh ₁	6	3	H	CH ₂ CH ₃		51	158—160	CHCl ₃ - petr. ether	C ₂₀ H ₂₈ N ₂ O ₃	70.15 (70.37)	7.65 7.70	8.18 8.20	9.7	2.1
IVi ₁	6	3	H	CH ₂ CH ₃		22	145—147	Benzene- petr. ether	C ₂₂ H ₃₀ N ₂ O ₃ ·1/4H ₂ O	70.46 (70.73)	8.20 8.04	7.47 7.29	5.5	2.1
IVj ₁	6	3	H	CH ₂ CH ₃		34	143—144.5	Benzene- petr. ether	C ₂₃ H ₃₂ N ₂ O ₃	71.84 (71.52)	8.39 8.24	7.29 7.29	7.6	2.1
IVk ₁	3	3	H	CH ₂ CH ₃		72	201—202	CHCl ₃ - petr. ether	C ₂₁ H ₂₈ N ₂ O ₃	70.76 (70.65)	7.92 7.86	7.86 7.92	ne	ne
IVl ₁	4	3	H	CH ₂ CH ₃		49	176—178	CHCl ₃ - petr. ether	C ₂₁ H ₂₈ N ₂ O ₃ ·1/4H ₂ O	69.88 (69.88)	7.96 7.79	7.76 7.66	ne	ne
IVm ₁	5	3	H	CH ₂ CH ₃		67	165—168	Benzene- petr. ether	C ₂₁ H ₂₈ N ₂ O ₃	70.76 (70.58)	7.92 7.98	7.86 7.75	ne	ne
IVn ₁	7	3	H	CH ₂ CH ₃		90	98—101	EtOAc- petr. ether	C ₂₁ H ₂₈ N ₂ O ₃	70.76 (70.44)	7.92 8.10	7.86 7.47	420	42.0
IVo ₁	8	3	H	CH ₂ CH ₃		73	160.5—161.5	EtOAc	C ₂₁ H ₂₈ N ₂ O ₃	70.76 (70.71)	7.98 7.91	7.75 7.78	ne	ne
VIla	6	3	H	CH ₂ CH ₃		77	128—129	MeOH-H ₂ O	C ₂₁ H ₃₀ N ₂ O ₃	70.36 (69.97)	8.44 8.49	7.82 7.87	6.3	16.0
VIlb	6	3	H	(CH ₂) ₂ OH		41	139—141	CHCl ₃ - petr. ether	C ₂₁ H ₃₀ N ₂ O ₄	67.35 (67.02)	8.08 8.25	7.48 7.20	18.1	8.8
VIlc	6	3	H	(CH ₂) ₂ OH		62	109—111	EtOAc- iso-Pr ₂ O	C ₂₄ H ₃₈ N ₂ O ₄	69.20 (69.49)	8.71 8.68	6.73 6.73	6.7	2.9
VIIIa	6	3	CH ₃	CH ₃		90	118.5—119.5	Benzene- ligroin	C ₂₁ H ₂₈ N ₂ O ₃	70.76 (70.80)	7.92 7.80	7.86 7.86	ne	134
VIIIb	6	3	CH ₂ - 	CH ₃		46	107.5—108.5	Benzene- ligroin	C ₂₇ H ₃₂ N ₂ O ₃	74.97 (75.18)	7.46 7.36	6.48 6.41	ne	ne
IX	6	3	H	(CH ₂) ₂ OAc		77	137—139	CHCl ₃ - iso-Pr ₂ O	C ₂₃ H ₃₀ N ₂ O ₅	66.64 (66.69)	7.30 7.22	6.76 6.79	1.4	0.5
Adenosine													21	84

a) ne means no effect.

Structure-Activity Relationships

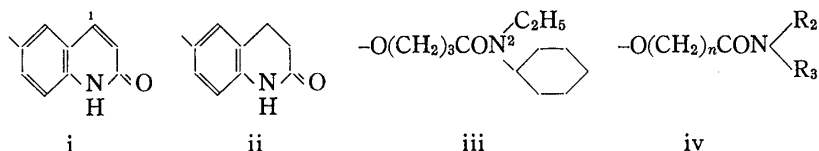
The inhibitory activities of the synthesized compounds on blood platelet aggregation *in vitro* are summarized in Table III. Their structure-activity relationships may be expressed as follows.

First, as regards the nucleus, 1,2-dihydro-2-oxoquinoline derivatives (i) were more active than 2-oxo-1,2,3,4-tetrahydroquinoline derivatives (ii) [relative potencies:

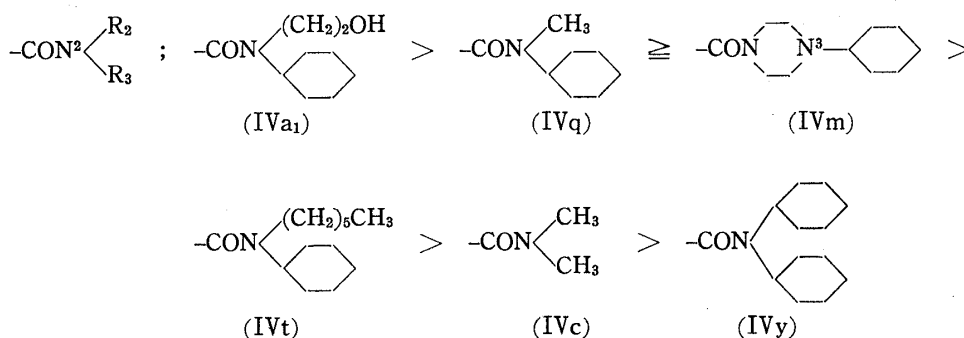


Second, the 6-substituted isomer (IVp) exhibited the greatest potency among the positional isomers for the given side chain in iii. The 7-substituted isomer (IVn₁) was a little less active, while the 3-, 4-, 5- and 8- substituted isomers (IVk₁, l₁, m₁, o₁) were completely inactive. Therefore, further comparisons of the effects of various substituents were made within the 6-substituted isomer series.

Substitution on the N¹-position of the nucleus (VIIIa, b) resulted in substantial loss of the activity, so the proton at the N¹-position is presumably essential. The order of the potency according to the difference of methylene number (*n*) in the side chain iv was found to be *n*=3 (IVp) > 4 (IVe₁) > 2 (IVd₁) > 5 (IVf₁) > 1 (IVc₁).



The order as regards amide groups was tertiary amide (IVc) > secondary (IVb) > primary amide (IVa). The effect of N²-substituent was in the following order.



The best compound (IVa₁) has a hydroxy group as R₂ and a cyclohexyl group as R₃. The derivatives (IVg, IVp, IVh₁, IVi₁, IVj₁) having an alkyl group as R₂ and a cycloalkyl group as R₃ showed high potency, whereas the compounds (IVc, IVd, IVy) in which both R₂ and R₃ were alkyls or cycloalkyls showed decreased activity. On the other hand, compounds (IVm, n) derived from N³-monosubstituted piperazines also showed high potency. Methyl and ethyl groups (IVg, IVp) were better than longer alkyl groups (IVq—v) as R₂.

Among the compounds synthesized, *N*-cyclohexyl-*N*-(2-hydroxyethyl)-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide (IVa₁) has the most potent inhibitory activity; it is five times more active than OPC-3162 and OPC-3930 reported in the preceding papers.^{1,2)}

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO IRA-2 spectrometer. NMR spectra were recorded on a Varian EM-390 NMR spectrometer using tetramethylsilane as an internal standard.

Ethyl 3-(1,2-Dihydro-2-oxo-6-quinolyloxy)propionate (IIb)—A suspension of 2 g of ethyl 3-(1,2,3,4-

tetrahydro-2-oxo-6-quinolyloxy)propionate¹¹ in 60 ml of dioxane was treated with 3.5 g of DDQ, and the reaction mixture was refluxed for 6 h on an oil bath. After removal of the solvent under reduced pressure, 100 ml of CHCl_3 was added to the residue. After removal of the insoluble materials, the CHCl_3 extract was washed successively with dil. NaOH and water, and dried over MgSO_4 . After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, CHCl_3 -MeOH=100:1) and the product was recrystallized from MeOH to give IIb (0.8 g, 40%) as colorless needles, mp 164–166°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3160 (NH), 1730 (COOCH_3), 1655 (CONH), 1625 (C=C). NMR (CDCl_3) δ : 1.25 (3H, t, $J=7$ Hz, $-\text{COOCH}_2\text{CH}_3$), 2.76 (2H, t, $J=6$ Hz, $-\text{OCH}_2\text{CH}_2-$), 4.15 (2H, q, $J=7$ Hz, $-\text{COOCH}_2\text{CH}_3$), 4.23 (2H, t, $J=6$ Hz, $-\text{OCH}_2\text{CH}_2-$), 6.65 (1H, d, $J=9$ Hz, aromatic 3-H), 6.9–7.43 (3H, m, aromatic 5,7,8-H), 7.67 (1H, d, $J=9$ Hz, aromatic 4-H), 12.79 (1H, br s, NH). The elemental analysis data are shown in Table I.

Preparation of IIa and IIc–j. Methyl 4-(1,2-Dihydro-2-oxo-6-quinolyloxy)butyrate (IIc)—Methyl 4-bromobutyrate (6.8 g) was added dropwise to a solution of 5 g of 1,2-dihydro-6-hydroxy-2-oxoquinoline (Id) and 7 g of DBU in 75 ml of iso-PrOH with stirring under reflux, and the mixture was refluxed for 4 h. The solvent was evaporated off *in vacuo*, and the residue was extracted with CHCl_3 . The CHCl_3 extract was washed successively with 0.5 N NaOH, dil. HCl and H_2O , and dried over Na_2SO_4 . After removal of the solvent, the residue was recrystallized from MeOH to give IIc (6.0 g, 74%) as colorless needles, mp 150.5–152°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3160 (NH), 1730 (CO_2Me), 1655 (CONH), 1620 (C=C). NMR (CDCl_3) δ : 2.12 (2H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2-$), 2.53 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{CO}_2\text{CH}_3$), 3.70 (3H, s, $-\text{CO}_2\text{CH}_3$), 4.02 (2H, t, $J=6$ Hz, $-\text{OCH}_2-$), 6.69 (1H, d, $J=9$ Hz, aromatic 3-H), 6.90–7.52 (3H, m, aromatic 5,7,8-H), 7.71 (1H, d, $J=9$ Hz, aromatic 4-H), 12.88 (1H, br s, NH). The elemental analysis data are shown in Table I.

Compounds IIa and IId–j were obtained by the same procedure as described for IIc, and the yield, mp and elemental analysis data are shown in Table I.

Preparation of IIIa–j. 4-(1,2-Dihydro-2-oxo-6-quinolyloxy)butyric Acid (IIIc)—A suspension of 6 g of IIc in 60 ml of 20% HCl was stirred at 85–90°C for 2 h, then cooled. The precipitated crystals were collected by filtration and washed with water. Recrystallization from DMF–water gave IIIc (5.4 g, 95%) as colorless granules, mp 262–265°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3140 (NH), 1700 (COOH), 1640 (CONH), 1610 (C=C). NMR (CF_3COOD) δ : 1.94 (2H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2-$), 2.38 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{COOH}$), 3.96 (2H, t, $J=6$ Hz, $-\text{OCH}_2\text{CH}_2-$), 6.43 (1H, d, $J=9$ Hz, aromatic 3-H), 6.97–7.30 (3H, m, aromatic 5,7,8-H), 7.76 (1H, d, $J=9$ Hz, aromatic 4-H), 11.45–12.05 (1H, br, NH). The elemental analysis data are shown in Table II.

Compounds IIIa, b and IIId–j were obtained by the same procedure as described for IIIc, and the yield, mp and elemental analysis data are shown in Table II.

Preparation of IVa–o₁ and VIIa–c. *N*-Cyclohexyl-*N*-methyl-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide (IVg)—Isobutyl chloroformate (1.42 ml) was added dropwise to a solution of 2.47 g of IIIc and 1.7 g of DBU in 60 ml of CHCl_3 with stirring and ice-water cooling, and the reaction mixture was stirred at room temperature for 1 h. Next, 1.4 g of *N*-methylcyclohexylamine was added dropwise with stirring at room temperature, and the whole mixture was stirred at room temperature for 3 h. The resulting solution was washed successively with 0.5 N NaOH, dil. HCl and water, and dried over Na_2SO_4 . After removal of the solvent under reduced pressure, the residue was recrystallized from MeOH– H_2O to give IVg (2.56 g, 75%) as colorless needles, mp 186–188°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3170 (NH), 1660, 1630 (CON). NMR (CDCl_3) δ : 0.77–1.96 (10H, m, methylene protons of cyclohexyl ring), 1.96–2.73 (4H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2-$), 2.81 (3H, s, $\text{N}-\text{CH}_3$), 3.23–3.73 (0.5H, br, methine proton of cyclohexyl ring), 4.02 (2H, t, $J=6$ Hz, $-\text{OCH}_2\text{CH}_2-$), 4.17–4.67 (0.5H, br, methine proton of cyclohexyl ring), 6.61 (1H, d, $J=9$ Hz, aromatic 3-H), 6.78–7.47 (3H, m, aromatic 5,7,8-H), 7.64 (1H, d, $J=9$ Hz, aromatic 4-H), 12.76 (1H, br s, NH). The elemental analysis data are shown in Table III.

Compounds IVa–f, IVh–o₁ and VIIa–c were obtained by the same procedure as described for IVg, and the yield, mp and elemental analysis data are shown in Table III.

Preparation of VIIa, b. *N*-Cyclohexyl-*N*-methyl-4-(1,2-dihydro-1-methyl-2-oxo-6-quinolyloxy)butyramide (VIIa)—A solution of 3.4 g of IVg in 200 ml of DMF was treated with 0.5 g of NaH (50% dispersion in mineral oil) at room temperature, and the reaction mixture was stirred until the evolution of H_2 gas ceased. Then 0.75 ml of CH_3I was added dropwise at room temperature and the whole mixture was stirred at room temperature for 1 h. After removal of the solvent, the residue was extracted with CHCl_3 . The CHCl_3 extract was washed with water and dried over Na_2SO_4 . After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, CHCl_3 -MeOH=50:1). Recrystallization from benzene–ligroin gave VIIa (3.2 g, 90%) as colorless needles, mp 118.5–119.5°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1655 and 1635 (C=O), 1600 (C=C). NMR (CDCl_3) δ : 0.80–1.97 (10H, m, methylene protons of cyclohexyl ring), 1.97–2.73 (4H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2-$), 2.81 (3H, s, $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CONCH}_3$), 3.63 (3H, s, $-\text{CN}^1\text{-CH}_3$), 3.30–4.63 (1H, m, methine proton of cyclohexyl ring), 4.03 (2H, t, $J=6$ Hz, $-\text{OCH}_2\text{CH}_2-$), 6.59 (1H, d, $J=9$ Hz, aromatic 3-H), 6.86–7.33 (3H, m, aromatic 5,7,8-H), 7.48 (1H, d, $J=9$ Hz, aromatic 4-H). The elemental analysis data are shown in Table III.

Compound VIIb was obtained by the same procedure as described for VIIa, and the yield, mp and elemental analysis data are shown in Table III.

N-(2-Acetoxyethyl)-*N*-cyclohexyl-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide (IX)—Acetic anhydride (0.75 ml) was added dropwise to a solution of 1.5 g of IVa in 10 ml of dry pyridine with stirring at room

temperature, and the reaction mixture was stirred overnight. CHCl_3 was added to the reaction mixture, and the CHCl_3 extract was washed successively with saturated aq. NaHCO_3 , saturated aq. KHSO_4 and water, then dried over Na_2SO_4 . After removal of the solvent *in vacuo*, the residue was purified by column chromatography (silica gel; eluent, CHCl_3 - MeOH =30:1). Recrystallization from CHCl_3 -iso Pr_2O gave IX (1.28 g, 77%) as colorless granules, mp 137–139°C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3150 (NH), 1740 ($-\text{CH}_2\text{OCOCH}_3$), 1650 and 1640 (CON), 1620 (C=C). NMR (CDCl_3) δ : 0.76–1.95 (10H, m, methylene protons of cyclohexyl ring), 2.03 (3H, d, $J=3$ Hz, $-\text{COCH}_3$), 2.16 (2H, m, $-\text{OCH}_2\text{CH}_2\text{CH}_2-$), 2.57 (2H, t, $J=6$ Hz, $-\text{CH}_2\text{CO}-$), 3.45 (2H, t, $J=7$ Hz, $-\text{NCH}_2\text{CH}_2\text{O}-$), 3.33–4.40 (1H, m, methine proton of cyclohexyl ring), 3.95–4.30 (4H, m, $-\text{NCH}_2\text{CH}_2\text{OCOCH}_3$ and $-\text{OCH}_2\text{CH}_2\text{CH}_2-$), 6.68 (1H, d, $J=9$ Hz, aromatic 3-H), 6.90–7.50 (3H, m, aromatic 5,7,8-H), 7.71 (1H, d, $J=9$ Hz, aromatic 4-H), 12.97 (1H, br s, NH). The elemental analysis data are shown in Table III.

Inhibition of Blood Platelet Aggregation—Inhibition of blood platelet aggregation was determined by the same method as described in the preceding paper¹⁾ using rabbit citrated platelet-rich plasma (PRP). The inhibitory activity data are shown in Table III.

References

- 1) T. Nishi, K. Yamamoto, T. Shimizu, T. Kanbe, Y. Kimura and K. Nakagawa, *Chem. Pharm. Bull.*, **31**, 8 (1983).
- 2) T. Nishi, F. Tabusa, T. Tanaka, T. Shimizu, T. Kanbe, Y. Kimura and K. Nakagawa, *Chem. Pharm. Bull.*, accepted.
- 3) R.R. Holmes, J. Conrady, J. Guthrie and R. McKay, *J. Am. Chem. Soc.*, **76**, 2400 (1954); W.C. Fleming and G.R. Pettit, *J. Org. Chem.*, **36**, 3490 (1971); G.R. Pettit, W.C. Fleming and K.D. Paull, *J. Org. Chem.*, **33**, 1089 (1968); B. Eistert and H. Salzer, *Chem. Ber.*, **96**, 1234 (1963); E. Ziegler and K. Gelfert, *Monatsh. Chem.*, **90**, 822 (1959).
- 4) C.G. Derick and R.W. Hess, *J. Am. Chem. Soc.*, **40**, 537 (1918); R. Merchant, J.N. Wickert and C.S. Marvel, *J. Am. Chem. Soc.*, **49**, 1828 (1927); G. Barger, R. Robinson and L.H. Smith, *J. Chem. Soc.*, **1937**, 718.