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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

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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 (IVa_1) 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 (IVa_1) 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 esters[4] 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, VI[1] 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 IVa_1 with acetic anhydride–pyridine gave *N*-(2-acetoxyethyl)-*N*-cyclohexyl-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide (IX) (Chart 3, Table III).

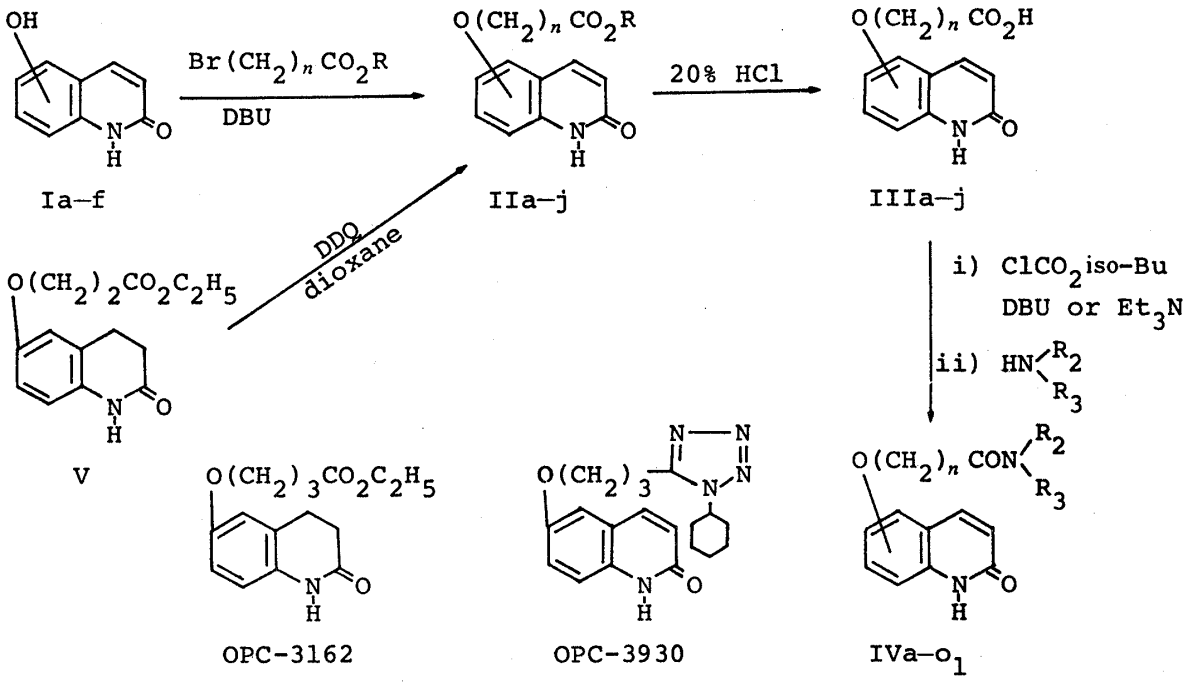
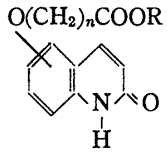


Chart 1

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_2CH_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_2CH_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_2CH_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_2CH_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_2CH_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.

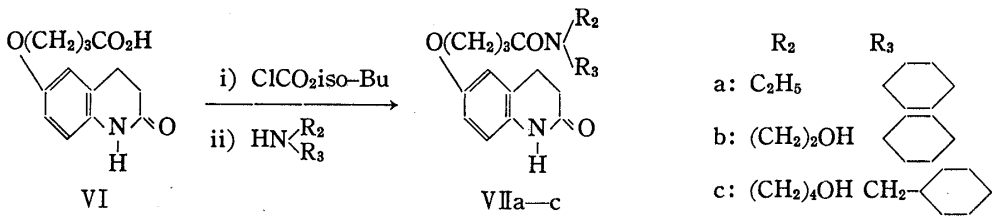
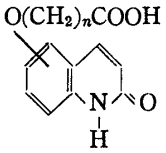


Chart 2

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	$C_{11}H_9NO_4$	60.27 (60.10	4.14 4.11	6.39 6.42)
IIIb	6	2	92	272—273.5	MeOH	$C_{12}H_{11}NO_4$	61.80 (61.80	4.75 4.76	6.01 6.14)
IIIc	6	3	95	262—265	DMF–H_2O	$C_{13}H_{13}NO_4$	63.15 (63.30	5.30 5.28	5.67 5.70)
IIId	6	4	85	245—247	DMF	$C_{14}H_{15}NO_4$	64.36 (64.39	5.79 5.79	5.36 5.40)
IIIe	6	5	95	215—217	DMF	$C_{15}H_{17}NO_4$	65.44 (65.36	6.22 6.16	5.09 5.10)
IIIf	3	3	93	237—239	DMF–H_2O	$C_{13}H_{13}NO_4$	63.15 (63.27	5.30 5.58	5.67 5.73)
IIIg	4	3	60	300	DMF	$C_{13}H_{13}NO_4$	63.15 (63.10	5.30 5.22	5.67 5.81)
IIIh	5	3	90	241—243	EtOH–H_2O	$C_{13}H_{13}NO_4$	63.15 (63.15	5.30 5.35	5.67 5.70)
IIIi	7	3	96	275—278.5	DMF	$C_{13}H_{13}NO_4$	63.15 (62.87	5.30 5.41	5.67 5.76)
IIIj	8	3	96	258—261.5	DMF	$C_{13}H_{13}NO_4$	63.15 (63.39	5.30 5.32	5.67 5.82)

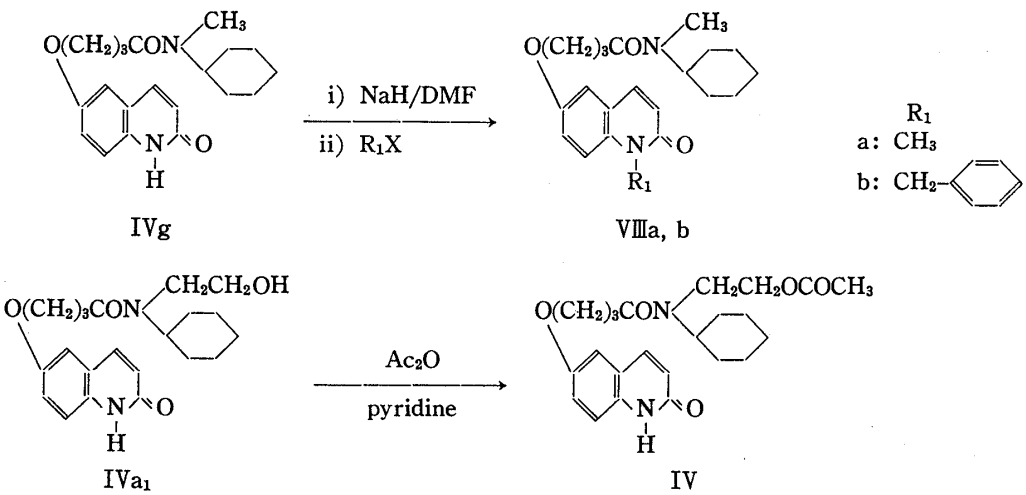
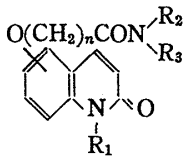
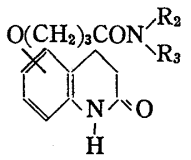


Chart 3

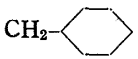
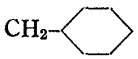
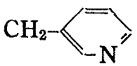
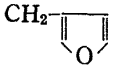
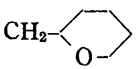
TABLE III. *N*,*N*-Disubstituted-(1,2-dihydro-2-oxoquinolyloxy or 2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)alkanoic Acid Amide Derivatives and Their Inhibition of Blood Platelet Aggregation

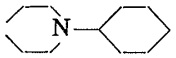
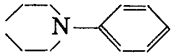


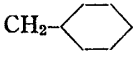
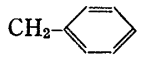
(IVa—o1, VIIIa, b, x)



(VIIa—c)

Compd. No.	Position	*n*	R_1	R_2	R_3	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (IC_{50}, μM) ADP	Collagen
IVa	6	3	H	H	H	23	241—242	MeOH–H_2O	$C_{13}H_{14}N_2O_3$	63.42 (63.48	5.71 5.73	11.38 11.19)	495	254
IVb	6	3	H	CH_3	H	17	201—202	$CHCl_3$	$C_{14}H_{16}N_2O_3$	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	$C_{15}H_{18}N_2O_3$	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	$C_{17}H_{22}N_2O_3 \cdot 1/4H_2O$	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	$C_{20}H_{20}N_2O_3$	71.41 (71.20	5.99 6.09	8.33 8.23)	12.6	6.3
IVf	6	3	H	CH_3		80	163—163.5	MeOH–H_2O	$C_{21}H_{22}N_2O_3$	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_2O	$C_{20}H_{26}N_2O_3$	70.15 (70.19	7.65 7.79	8.18 8.30)	4.2	2.1
IVh	6	3	H	CH_2CH_3		59	166.5—168	$CHCl_3$–petr. ether	$C_{22}H_{30}N_2O_3$	71.32 (71.02	8.16 8.24	7.56 7.52)	ne[a]	ne
IVi	6	3	H	CH_3		55	169.5—171	$CHCl_3$–petr. ether	$C_{20}H_{21}N_3O_3 \cdot 1/4H_2O$	67.49 (67.32	6.09 6.06	11.81 11.75)	11.3	6.7
IVj	6	3	H	CH_3		77	125.5—127.5	$CHCl_3$–petr. ether	$C_{19}H_{20}N_2O_4$	67.04 (67.03	5.92 5.87	8.23 8.22)	29.4	15.1
IVk	6	3	H	CH_3		75	150—151.5	$CHCl_3$–petr. ether	$C_{20}H_{26}N_2O_4$	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	$C_{18}H_{22}N_2O_3$	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 (%) Calcd (Found) C	H	N	Inhibition (IC_{50}, μM) ADP	Collagen
IVm	6	3	H			25	184.5—186	MeOH–H_2O	$C_{23}H_{31}N_3O_3$	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	$C_{23}H_{25}N_3O_3$	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	$C_{19}H_{24}N_2O_3$	69.49 (69.30	7.37 7.64	8.53 8.66)	ne	69.3
IVp	6	3	H	CH_2CH_3		73	173—174	EtOH–H_2O	$C_{21}H_{28}N_2O_3$	70.76 (70.70	7.92 7.88	7.86 7.94)	4.2	2.1
IVq	6	3	H	$CH_2CH_2CH_3$		70	182—184.5	EtOAc	$C_{22}H_{30}N_2O_3$	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	$C_{22}H_{30}N_2O_3$	71.32 (71.51	8.16 8.19	7.56 7.53)	38.6	20.2
IVs	6	3	H	$(CH_2)_3CH_3$		39	159—160	EtOH	$C_{23}H_{32}N_2O_3$	71.84 (71.91	8.39 8.25	7.29 7.34)	42.0	14.7
IVt	6	3	H	$(CH_2)_4CH_3$		65	156.5—157.5	EtOAc	$C_{24}H_{34}N_2O_3$	72.33 (72.35	8.60 8.58	7.03 6.81)	323	54.6
IVu	6	3	H	$(CH_2)_5CH_3$		58	129—132	Benzene–ligroin	$C_{25}H_{36}N_2O_3$	72.78 (72.63	8.80 8.92	6.79 6.52)	96.6	111
IVv	6	3	H	$(CH_2)_6CH_3$		32	100—103	Ligroin	$C_{26}H_{38}N_2O_3$	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	$C_{25}H_{28}N_2O_3 \cdot 1/4H_2O$	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	$C_{26}H_{30}N_2O_3$	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	$C_{25}H_{34}N_2O_3$	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	$C_{26}H_{36}N_2O_3$	72.78 (72.70	8.57 8.51	6.53 6.52)	29.4	8.8
IVa$_1$	6	3	H	$(CH_2)_2OH$		55	163—165.5	MeOH–H_2O	$C_{21}H_{28}N_2O_4$	67.72 (67.64	7.58 7.55	7.52 7.35)	1.4	0.5
IVb$_1$	6	3	H	$(CH_2)_4OH$		19	153—155	iso-PrOH–EtOAc	$C_{24}H_{32}N_2O_4 \cdot 1/4H_2O$	68.21 (68.24	8.09 7.97	6.92 6.77)	1.9	1.9
IVc$_1$	6	1	H	CH_2CH_3		55	159.5—162	Benzene	$C_{19}H_{24}N_2O_3$	69.49 (69.63	7.37 7.68	8.53 8.39)	483	44.1

IVd$_1$	6	2	H	CH_2CH_3		16	149—150	EtOAc–petr. ether	$C_{20}H_{26}N_2O_3$	69.24 (69.50	7.70 7.63	8.07 8.07)	54.6	6.5
IVe$_1$	6	4	H	CH_2CH_3		47	142—142.5	EtOAc–petr. ether	$C_{22}H_{30}N_2O_3 \cdot 1/4H_2O$	70.47 (70.50	8.20 7.98	7.47 7.43)	4.2	0.5
IVf$_1$	6	5	H	CH_2CH_3		48	128—130	EtOAc–petr. ether	$C_{23}H_{32}N_2O_3$	71.84 (71.88	8.39 8.34	7.29 7.28)	37.0	27.3
IVg$_1$	6	3	H	CH_2CH_3		17	150—152	Benzene–petr. ether	$C_{18}H_{22}N_2O_3$	68.77 (68.60	7.05 7.19	8.91 8.64)	50.4	21.0
IVh$_1$	6	3	H	CH_2CH_3		51	158—160	$CHCl_3$–petr. ether	$C_{20}H_{26}N_2O_3$	70.15 (70.37	7.65 7.70	8.18 8.20)	9.7	2.1
IVi$_1$	6	3	H	CH_2CH_3		22	145—147	Benzene–petr. ether	$C_{22}H_{30}N_2O_3 \cdot 1/4H_2O$	70.46 (70.73	8.20 8.04	7.47 7.29)	5.5	2.1
IVj$_1$	6	3	H	CH_2CH_3		34	143—144.5	Benzene–petr. ether	$C_{23}H_{32}N_2O_3$	71.84 (71.52	8.39 8.24	7.29 7.29)	7.6	2.1
IVk$_1$	3	3	H	CH_2CH_3		72	201—202	$CHCl_3$–petr. ether	$C_{21}H_{28}N_2O_3$	70.76 (70.65	7.92 7.86	7.86 7.92)	ne	ne
IVl$_1$	4	3	H	CH_2CH_3		49	176—178	$CHCl_3$–petr. ether	$C_{21}H_{28}N_2O_3 \cdot 1/4H_2O$	69.88 (69.88	7.96 7.79	7.76 7.66)	ne	ne
IVm$_1$	5	3	H	CH_2CH_3		67	165—168	Benzene–petr. ether	$C_{21}H_{28}N_2O_3$	70.76 (70.58	7.92 7.98	7.86 7.75)	ne	ne
IVn$_1$	7	3	H	CH_2CH_3		90	98—101	EtOAc–petr. ether	$C_{21}H_{28}N_2O_3$	70.76 (70.44	7.92 8.10	7.86 7.47)	420	42.0
IVo$_1$	8	3	H	CH_2CH_3		73	160.5—161.5	EtOAc	$C_{21}H_{28}N_2O_3$	70.76 (70.71	7.98 7.91	7.75 7.78)	ne	ne
VIIa	6	3	H	CH_2CH_3		77	128—129	MeOH–H_2O	$C_{21}H_{30}N_2O_3$	70.36 (69.97	8.44 8.49	7.82 7.87)	6.3	16.0
VIIb	6	3	H	$(CH_2)_2OH$		41	139—141	$CHCl_3$–petr. ether	$C_{21}H_{30}N_2O_4$	67.35 (67.02	8.08 8.25	7.48 7.20)	18.1	8.8
VIIc	6	3	H	$(CH_2)_4OH$		62	109—111	EtOAc–iso-Pr_2O	$C_{24}H_{36}N_2O_4$	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	$C_{21}H_{28}N_2O_3$	70.76 (70.80	7.92 7.80	7.86 7.86)	ne	134
VIIIb	6	3		CH_3		46	107.5—108.5	Benzene–ligroin	$C_{27}H_{32}N_2O_3$	74.97 (75.18	7.46 7.36	6.48 6.41)	ne	ne
IX	6	3	H	$(CH_2)_2OAc$		77	137—139	$CHCl_3$–iso-Pr_2O	$C_{23}H_{30}N_2O_5$	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

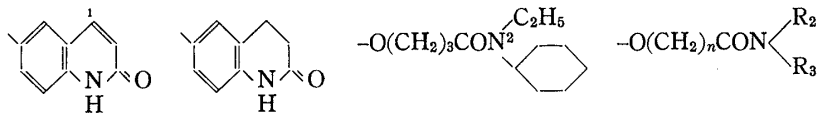
The inhibitory activities of the synthesized compounds on blood platelet aggregation *in vitro* are summarized in Table III. Their structure–activity relationships may be expressed as follows.

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:

IVp>VIIa and $IVa_1 \gg$VIIb].

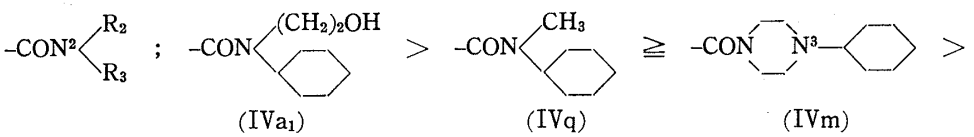
Second, the 6-substituted isomer (IVp) exhibited the greatest potency among the positional isomers for the given side chain in iii. The 7-substituted isomer (IVn_1) was a little less active, while the 3-, 4-, 5- and 8- substituted isomers (IVk_1, l_1, m_1, o_1,) were completely inactive. Therefore, further comparisons of the effects of various substituents were made within the 6-substituted isomer series.

Substitution on the N^1-position of the nucleus (VIIIa, b) resulted in substantial loss of the activity, so the proton at the N^1-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 (IVe_1)>2 (IVd_1)>5 (IVf_1)>1 (IVc_1).

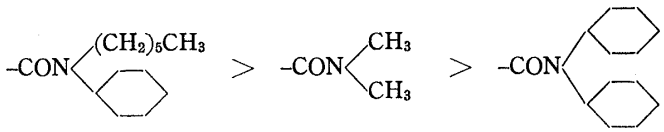


i ii iii iv

The order as regards amide groups was tertiary amide (IVc)>secondary (IVb)>primary amide (IVa). The effect of N^2-substituent was in the following order.



(IVa_1) (IVq) (IVm)



(IVt) (IVc) (IVy)

The best compound (IVa_1) has a hydroxy group as R_2 and a cyclohexyl group as R_3. The derivatives (IVg, IVp, IVh_1, IVi_1, IVj_1) having an alkyl group as R_2 and a cycloalkyl group as R_3 showed high potency, whereas the compounds (IVc, IVd, IVy) in which both R_2 and R_3 were alkyls or cycloalkyls showed decreased activity. On the other hand, compounds (IVm, n) derived from N^3-monosubstituted piperazines also showed high potency. Methyl and ethyl groups (IVg, IVp) were better than longer alkyl groups (IVq—v) as R_2.

Among the compounds synthesized, *N*-cyclohexyl-*N*-(2-hydroxyethyl)-4-(1,2-dihydro-2-oxo-6-quinolyloxy)butyramide (IVa_1) 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)propionate[1)] 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 ν_{max}^{KBr} cm^{-1}: 3160 (NH), 1730 ($COOCH_3$), 1655 (CONH), 1625 (C=C). NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $-COOCH_2-C\underline{H}_3$), 2.76 (2H, t, J=6 Hz, $-OCH_2C\underline{H}_2-$), 4.15 (2H, q, J=7 Hz, $-COOC\underline{H}_2CH_3$), 4.23 (2H, t, J=6 Hz, $-OC\underline{H}_2-CH_2-$), 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, N$\underline{H}$). 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 ν_{max}^{KBr} cm^{-1}: 3160 (NH), 1730 (CO_2Me), 1655 (CONH), 1620 (C=C). NMR ($CDCl_3$) δ: 2.12 (2H, m, $-OCH_2C\underline{H}_2CH_2-$), 2.53 (2H, t, J=6 Hz, $-C\underline{H}_2CO_2CH_3$), 3.70 (3H, s, $-CO_2C\underline{H}_3$), 4.02 (2H, t, J=6 Hz, $-OC\underline{H}_2-$), 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, N$\underline{H}$). 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 ν_{max}^{KBr} cm^{-1}: 3140 (NH), 1700 (COOH), 1640 (CONH), 1610 (C=C). NMR (CF_3COOD) δ: 1.94 (2H, m, $-OCH_2C\underline{H}_2CH_2-$), 2.38 (2H, t, J=6 Hz, $-C\underline{H}_2COOH$), 3.96 (2H, t, J=6 Hz, $-OC\underline{H}_2CH_2-$), 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—o_1 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 ν_{max}^{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, $-OCH_2C\underline{H}_2C\underline{H}_2-$), 2.81 (3H, s, N–$C\underline{H}_3$), 3.23—3.73 (0.5H, br, methine proton of cyclohexyl ring), 4.02 (2H, t, J=6 Hz, $-OC\underline{H}_2CH_2-$), 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—o_1 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 VIIIa, b. *N*-Cyclohexyl-*N*-methyl-4-(1,2-dihydro-1-methyl-2-oxo-6-quinolyloxy)butyramide (VIIIa)——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 VIIIa (3.2 g, 90%) as colorless needles, mp 118.5—119.5°C. IR ν_{max}^{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, $-OCH_2C\underline{H}_2C\underline{H}_2-$) 2.81 (3H, s, $-OCH_2CH_2CH_2CONC\underline{H}_3$), 3.63 (3H, s, $-CN^1-C\underline{H}_3$), 3.30—4.63 (1H, m, methine proton of cyclohexyl ring), 4.03 (2H, t, J=6 Hz, $-OC\underline{H}_2CH_2-$), 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 VIIIb was obtained by the same procedure as described for VIIIa, 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 $CHCl_3$–$isoPr_2O$ gave IX (1.28 g, 77%) as colorless granules, mp 137—139°C. IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1740 (–CH_2OCOCH_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, –COC<u>H</u>$_3$), 2.16 (2H, m, –$OCH_2C\underline{H}_2CH_2$–), 2.57 (2H, t, J=6 Hz, –C<u>H</u>$_2$CO–) 3.45 (2H, t, J=7 Hz, –$NC\underline{H}_2CH_2O$–), 3.33—4.40 (1H, m, methine proton of cyclohexyl ring), 3.95—4.30 (4H, m, –$NCH_2C\underline{H}_2OCOCH_3$ and –$OC\underline{H}_2CH_2CH_2$–), 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 paper[1] using rabbit citrated platelet-rich plasma (PRP). The inhibitory activity data are shown in Table III.

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