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Studies on 2-Oxoquinoline Derivatives as Blood Platelet Aggregation Inhibitors. I. Alkyl 4-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrates and Related Compounds

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Many alkyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrates and related compounds were synthesized and tested for inhibitory activity against blood platelet aggregation *in vitro*. Among them, ethyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate was found to have the most potent inhibitory activity. The structure–activity relationships are discussed.

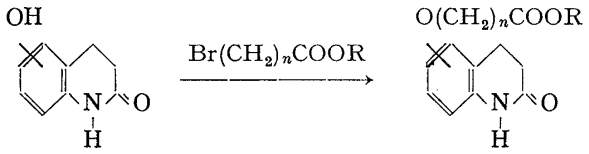
Keywords——alkyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate; inhibitor of blood platelet aggregation; ethyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate; structure–activity relationship; turbidimetric method

Introduction

Recently, in view of the important contribution of platelet functions to thrombus formation, many compounds have been synthesized in a search for inhibitors of platelet aggregation.[1] Among the reported inhibitors, we were interested in lactams of 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazoline-2-ones, which have potent inhibitory effects, and have been trying to synthesize various new agents possessing the 2-oxoquinoline nucleus.

We recently succeeded in the synthesis of some practically useful agents such as 5-(3-*tert*-butylamino-2-hydroxypropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline as a β-adrenergic blocking agent[2] and 1,2-dihydro-5-(1-hydroxy-2-isopropylaminobutyl)-8-hydroxy-2-oxoquinoline as a β-adrenergic stimulating agent.[3]

The purpose of this work was to synthesize many alkyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy) alkanoates and related compounds for testing for inhibitory activity *in vitro*. We describe here the synthesis of various 2-oxoquinoline derivatives possessing high inhibitory activity towards blood platelet aggregation and we discuss their structure–activity relationships.



Ia—b

	position
a:	5
b:	6
c:	7
d:	8

IIa—f

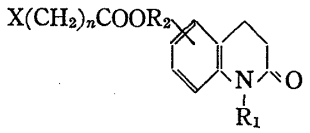
	position	n	R
a:	5	3	CH_2CH_3
b:	6	1	CH_2CH_3
c:	6	3	CH_3
d:	6	3	CH_2CH_3
e:	7	3	CH_2CH_3
f:	8	3	CH_2CH_3

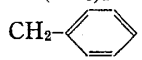
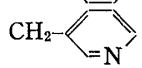
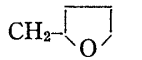
Chart 1

Synthesis

Alkyl (2-oxo-1,2,3,4-tetrahydroquinolyloxy) alkanoates (IIa—f) were easily synthesized from 5-, 6-, 7- and 8-hydroxy-2-oxo-1,2,3,4-tetrahydroquinolines (Ia—d)[4] with ethyl and methyl bromoalkanoates in the presence of sodium hydroxide in dimethyl formamide (DMF) at 45°C according to the usual method[5] (Chart 1, Table I). Ethyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)crotonate (III) was also prepared

TABLE I. Alkyl (2-Oxo-1,2,3,4-tetrahydroquinolyloxy)alkanoate Derivatives and Their Inhibition of Blood Platelet Aggregation



Compd. No.	Position	X	n	R_1	R_2	Yield (%)	mp (°C) [bp (°C)]	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Inhibition (IC_{50} μM) ADP	Inhibition (IC_{50} μM) Collagen
IIa	5	O	3	H	CH_2CH_3	56	114—116	$C_{15}H_{19}NO_4$	64.94	6.91	5.05	65.06	6.88	5.20	18	12
IIb	6	O	1	H	CH_2CH_3	82	129—131.5	$C_{13}H_{15}NO_4$	62.64	6.07	5.62	62.58	5.95	5.56	11	8.8
IIc	6	O	3	H	CH_3	49	104—106	$C_{14}H_{17}NO_4$	63.87	6.51	5.32	63.63	6.54	5.23	5.3	3.1
IId	6	O	3	H	CH_2CH_3	72	121—121.5	$C_{15}H_{19}NO_4$	64.96	6.91	5.05	64.93	7.00	5.11	3.4	2.9
IIe	7	O	3	H	CH_2CH_3	56	72—74	$C_{15}H_{19}NO_4$	64.96	6.91	5.05	65.04	6.85	4.99	890	19
IIf	8	O	3	H	CH_2CH_3	62	126—128	$C_{15}H_{19}NO_4$	64.96	6.91	5.05	64.78	6.90	4.98	>1000	97
VI	6	O	2	H	CH_2CH_3	63	136—137	$C_{14}H_{17}NO_4$	63.86	6.51	5.32	63.58	6.41	5.23	10	3.7
VII	6	O	3	H	H	88	218—220	$C_{13}H_{15}NO_4$	62.64	6.07	5.62	62.65	6.15	5.57	>1000	>1000
VIIIa	6	O	3	H	$CH_2CH_2CH_3$	51	88—89	$C_{16}H_{21}NO_4$	65.96	7.27	4.81	65.81	7.25	4.80	3.6	4.6
VIIIb	6	O	3	H	$(CH_2)_3CH_3$	58	61—63	$C_{17}H_{23}NO_4$	66.87	7.59	4.59	66.48	7.24	4.64	3.8	4.5
VIIIc	6	O	3	H	$CH(CH_3)_2$	75	104—105	$C_{16}H_{21}NO_4$	65.95	7.27	4.81	65.80	7.31	5.01	4.1	1.1
VIIId	6	O	3	H		63	96—97	$C_{20}H_{21}NO_4$	70.78	6.24	4.13	70.48	6.15	4.12	7.9	25
VIIIe	6	O	3	H		46	87.5—89.5	$C_{19}H_{20}N_2O_4$	67.04	5.92	8.23	66.67	5.81	8.10	4.0	3.9
VIIIf	6	O	3	H		59	62.5—64	$C_{18}H_{23}NO_5$	64.85	6.95	4.20	64.92	6.85	4.26	3.0	2.6
IX	6	O	3	CH_3	CH_2CH_3	76	[197—199/0.7]	$C_{16}H_{21}NO_4$	65.95	7.27	4.81	65.68	7.40	5.17	640	56
X	6	O	3	H	$C(CH_3)_3$	25	107.5—108	$C_{17}H_{23}NO_4$	66.86	7.59	4.59	67.03	7.90	4.76	8.9	8.8
XIVa	6	O	4	H	CH_2CH_3	87	115—118	$C_{16}H_{21}NO_4$	65.96	7.27	4.81	65.99	7.53	4.86	15	3.2
XIVb	6	O	6	H	CH_2CH_3	55	103—105	$C_{18}H_{25}NO_4$	67.69	7.89	4.39	67.85	8.10	4.52	>1000	>1000
XXII	6	CO	3	H	CH_2CH_3	72	149—151	$C_{16}H_{19}NO_4$	66.42	6.62	4.84	66.27	6.68	4.75	58	29
XXIII	6	CH(OH)	3	H	CH_2CH_3	73	83—84	$C_{16}H_{21}NO_4$	65.96	7.27	4.81	65.86	7.21	4.83	450	34
XXVI	6	CH_2	3	H	CH_2CH_3	48	60—61	$C_{16}H_{21}NO_3$	69.79	7.69	5.09	69.43	7.69	5.15	45	25
XXXII	6	S	3	H	CH_2CH_3	49	82—83	$C_{15}H_{19}NO_3S$	61.41	6.53	4.77	61.52	6.44	4.68	26	25
XXXIII	6	SO_2	3	H	CH_2CH_3	8	115—117	$C_{15}H_{19}NO_5S$	55.37	5.89	4.30	55.31	5.83	4.29	400	29

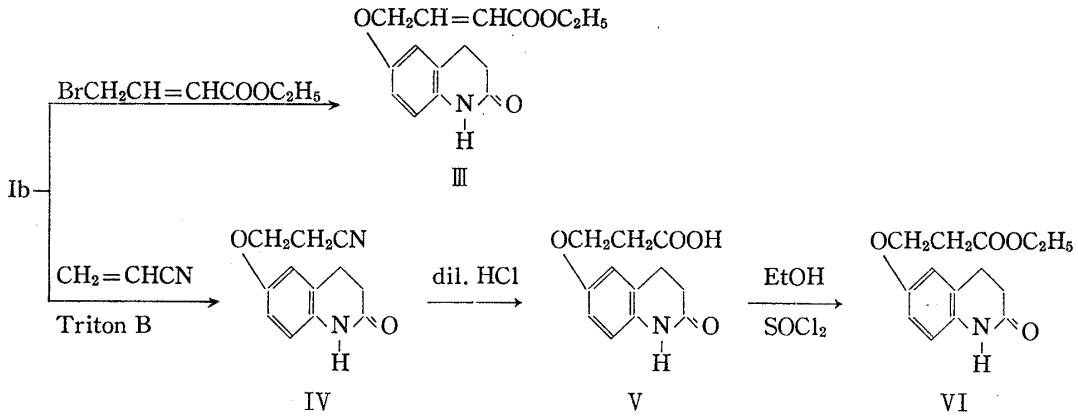
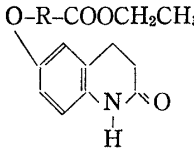


Chart 2

TABLE II. Ethyl (2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)alkanoate Derivatives and Their Inhibition of Blood Platelet Aggregation



Compd. No.	R	Yield (%)	mp (°C) [bp (°C)]	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (IC_{50}, μM) ADP	Collagen
III	$CH_2CH=CH$	57	151—152	$C_{15}H_{17}NO_4$	65.44 (65.31	6.22 6.15	5.09 5.01)	8.6	12
XIVc	$CH_2CH(CH_3)CH_2$	54	95—97	$C_{16}H_{21}NO_4$	65.95 (65.92	7.27 7.35	4.81 4.89)	54	9
XIVd	$CH_2CH_2CH(CH_3)$	45	[206—208/0.6]	$C_{16}H_{21}NO_4$	65.95 (65.87	7.27 7.50	4.81 5.05)	20	5.8

from Ib and ethyl 4-bromocrotonate[6] in the same manner (Chart 2, Table II).

Ethyl 3-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)propionate (VI), however, could not be obtained by the same procedure, and it was obtained in the following way. 3-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)propionitrile (IV) was readily prepared from Ib and acrylonitrile in the presence of Triton B, though the yield was unsatisfactory (26.5%). Attempts to hydrolyze the nitrile group of N under alkaline conditions were unsuccessful because only the retro-Michael reaction took place and Ib was recovered, but hydrolysis with hydrochloric acid under reflux proceeded quite smoothly to give 3-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy) propionic acid (V) in excellent yield. Esterification of V in ethanol and thionyl chloride gave VI (Chart 2, Table I).

The structure–activity relationships of II indicated that 2-oxoquinolines substituted at the 6-position were most promising (*vide infra*), and hence our synthetic work on various derivatives of 2-oxoquinolines was concentrated on 6-substituted compounds.

Various esters (VIII) of 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyric acid (VII) other than the ethyl and methyl esters (II) were first synthesized *via* VII itself; namely, hydrolysis of IId with methanolic sodium hydroxide gave VII, which was esterified with various alcohols in the presence of thionyl chloride or *p*-toluenesulfonic acid (*p*-Tos OH), whereas the *tert*-butyl ester (X) was obtained by treatment of VII with isobutylene using conc. H_2SO_4 as a catalyst. Methylation of IId with methyliodide gave the *N*-methyl compound (IX) (Chart 3, Table I).

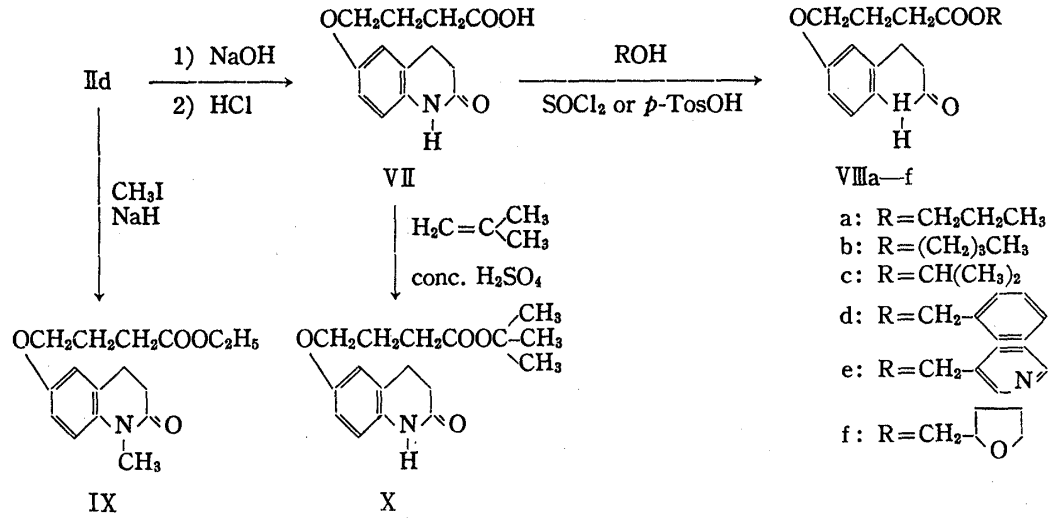


Chart 3

Some ethyl esters (XIV) having straight or branched chains of different lengths were next synthesized. For example, ethyl 3-methyl-4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (XIVc) was synthesized as follows. Treatment of Ib with 1-bromo-3-chloro-2-methylpropane in the presence of sodium ethoxide in ethanol gave 6-(3-chloro-2-methylpropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XIc), which was converted to the nitrile (XIIc) by treatment with sodium cyanide in DMF, followed by hydrolysis with refluxing 2 N sodium hydroxide to give the carboxylic acid (XIIIc). Esterification of XIIIc readily gave XIVc. Similarly, XIVa,b,d were also synthesized (Chart 4, Tables I and II).

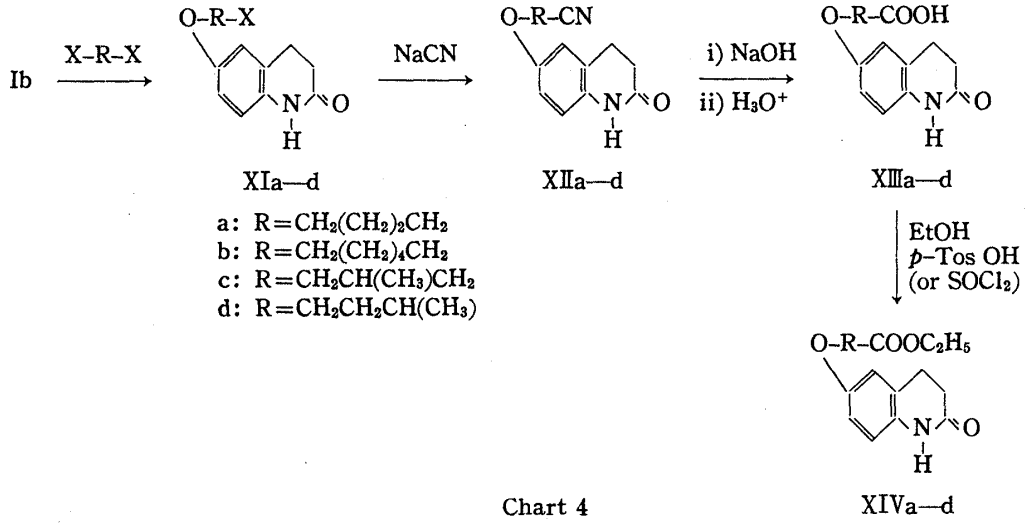


Chart 4

The following compounds (XV—XX), which have another group in place of the ester group in the side chain of IId, were synthesized as shown in Chart 5. Thus, treatment of Ib with some halides gave alkylation products (XVa, b, XVI, XVIII). 6-(3-Hydroxypropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XVI) was acylated with propionic anhydride to give XVII, while the ketal (XVIII) was hydrolyzed to a ketone (XIX), followed by reduction with sodium borohydride to give the alcohol (XX) (Chart 5, Table III).

Chart 6 shows the synthesis of some ester derivatives (XXII, XXIII, XXVI) having an alkanoate side chain directly bonded, not *via* an oxygen atom, to the tetrahydroquinoline ring. The Friedel–Crafts acylation of 2-oxo-1,2,3,4-tetrahydroquinoline with glutaric anhydride in the presence of aluminium chloride gave 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolylcarbonyl)butyric

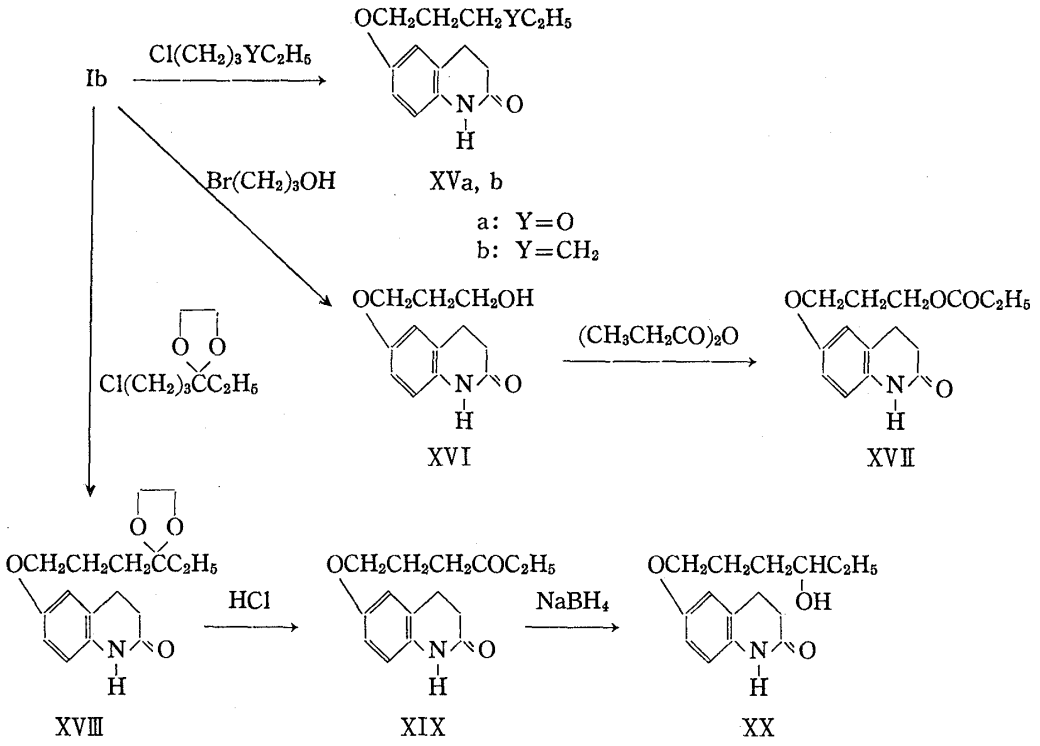
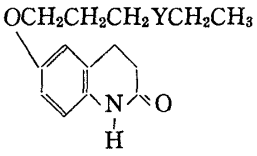


Chart 5

TABLE III. 6-Alkyloxy-2-oxo-1,2,3,4-tetrahydroquinoline Derivatives and Their Inhibition of Blood Platelet Aggregation



Compd. No.	Y	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (IC_{50}, μM) ADP	Collagen
XVa	O	22	87—88.5	$C_{14}H_{19}NO_3$	67.44 (67.06)	7.68 7.76	5.62 5.66)	45	28
XVb	CH_2	16	91—93	$C_{15}H_{21}NO_2$	72.84 (72.44)	8.56 8.51	5.66 5.82)	45	25
XVII	OCO	36	113—115	$C_{15}H_{19}NO_4$	64.96 (64.68)	6.91 6.95	5.05 5.08)	380	33
XVIII		70	92—94	$C_{17}H_{23}NO_4$	66.86 (66.48)	7.59 7.53	4.59 4.72)		
XIX	CO	35	115—116	$C_{15}H_{19}NO_3$	68.94 (68.75)	7.33 7.45	5.36 5.55)	>1000	30
XX	CH(OH)	73	92—93.5	$C_{15}H_{21}NO_3$	68.42 (68.17)	8.04 7.83	5.32 5.47)	>1000	69
XXVIII	S	55	92.5—94.5	$C_{14}H_{19}NO_2S$	63.37 (63.24)	7.22 7.06	5.28 5.25)	>1000	29
XXIX	SO_2	9	185—187	$C_{14}H_{19}NO_4S$	56.55 (56.75)	6.44 6.07	4.71 4.78)	>1000	35

acid (XXI), which was esterified to XXII, followed by catalytic reduction over palladium charcoal in ethanol to give the hydroxy ester (XXIII). Reduction of XXI with sodium borohydride easily gave the hydroxy alkanoic acid (XXIV), which was further reduced

catalytically over palladium black in the presence of perchloric acid to give the valeric acid derivative (XXV). Esterification of XXV gave the corresponding ethyl ester (XXVI) (Chart 6, Table I).

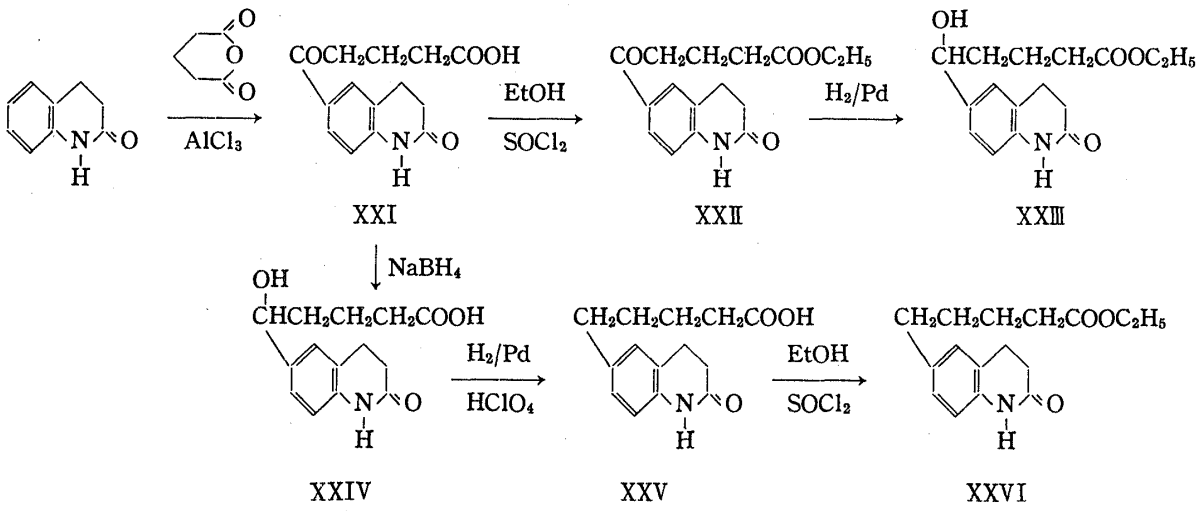


Chart 6

Some sulfur-containing derivatives (XXVIII, XXIX, XXXII, XXXIII) were then synthesized as shown in Charts 7 and 8 (Tables I and III). Compound Ib was again chloroalkylated with 1-bromo-3-chloropropane in the same manner as with XIc to give 6-(3-chloropropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XXVII), which was easily converted to the ethylthio derivative (XXVIII) by treatment with sodium ethanethiolate in aqueous DMF at 70—80°C. Oxidation of XXVIII with hydrogen peroxide in acetic acid gave the sulfone (XXIX), though in very poor yield (Chart 7). Another sulfone (XXXIII) having a sulfur atom directly attached at the 6-position of the 2-oxoquinoline ring was also synthesized as follows. Treatment of 2-oxo-1,2,3,4-tetrahydroquinoline with chlorosulfonic acid gave the chlorosulfone (XXX), which was reduced with zinc powder in sulfonic acid, followed by

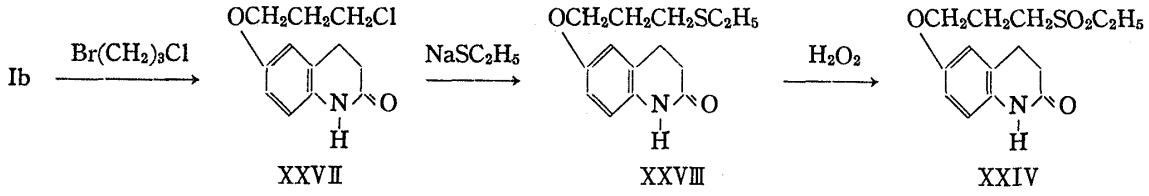


Chart 7

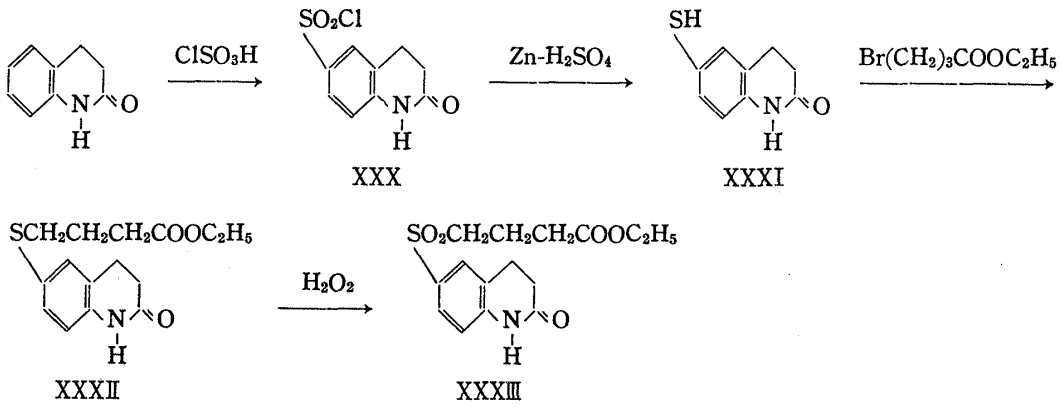


Chart 8

XXXIVa—d

	n	R
XI:	2	C_2H_5
IId:	3	C_2H_5
XIVa:	4	C_2H_5
VII:	3	H

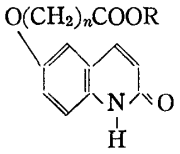
	n	R
a:	2	C_2H_5
b:	3	C_2H_5
c:	4	C_2H_5
d:	3	H

Chart 9

alkylation with ethyl 4-bromobutyrate to provide the sulfide (XXXII). Oxidation of XXXII with hydrogen peroxide as described above gave the sulfone (XXXIII), though also in very poor yield.

Finally, (1,2-dihydro-2-oxo-6-quinolyloxy)alkanoic acid derivatives (XXXIVa—d) were synthesized by dehydrogenation of (2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)alkanoic acid derivatives (VI, IId, XIVa, VII) with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as shown in Chart 9 (Table IV).

TABLE IV. Ethyl (1,2-Dihydro-2-oxo-6-quinolyloxy) alkanoate Derivatives and Their Inhibition of Blood Platelet Aggregation



Compd. No.	n	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (IC_{50}, μM) ADP	Collagen
XXXIVa	2	CH_2CH_3	40	164—166	$C_{14}H_{15}NO_4$	64.36 (64.11	5.79 5.65	5.36 5.36)	8.5	2.1
XXXIVb	3	CH_2CH_3	22	130—132	$C_{15}H_{17}NO_4$	65.44 (65.41	6.22 6.29	5.09 5.18)	3.1	0.85
XXXIVc	4	CH_2CH_3	35	131—133	$C_{16}H_{19}NO_4$	66.42 (66.05	6.62 6.71	4.84 4.87)	11	2.6
XXXIVd	3	H	85	257—258	$C_{13}H_{13}NO_4$	63.15 (62.89	5.30 5.25	5.67 5.71)	>1000	>1000

Structure-Activity Relationships

On the basis of the data obtained by *in vitro* screening, the structure–activity relationships of 2-oxoquinoline derivatives may be expressed as follows.

The initial study of these compounds as inhibitors of blood platelet aggregation involved an evaluation of the positional isomers in the 2-oxo-1,2,3,4-tetrahydroquinoline series. The results showed that when the side chain substitution was maintained as $-OCH_2CH_2CH_2COOC_2H_5$, the 6-substituted isomer (IId) exhibited the highest potency, and the 5-substituted isomer (IIa) was a little less active, while the 7- and 8-substituted isomers (IIe and IIf) were much less active. Therefore, further comparison of the activities of various substituents was made within the 6-substituted derivative series.

The N^1-substitution effects were first examined, and it was found that the nonsubstituted derivative (IId) was more active than the N^1-methyl derivative (IX). The effect of the number of methylene groups (n) in $-O(CH_2)_nCOOR$ was next examined, and the order of potency was found to be $n=3$ (IId)$>$2 (VI), 4 (XIVa)$\geqq$1 (IIb)$\gg$6 (XIVb). Compounds XIVc and XIVd having a branched chain and III having a unsaturated chain were even less active.

The observed potency order for the linked groups between the nucleus and side chain was O (IId)$>$S (XXXII)$\geqq CH_2$ (XXVI)$\geqq$CO (XXII)$>SO_2$ (XXXIII)$\geqq$CH(OH) (XXIII).

The potency order for Y groups (located in side chain, $-O(CH_2)_3YCH_2CH_3$) was COO (IId)$\gg$O (XVa)=CH_2 (XVb)>OCO (XVII)>CO (XIX), CH(OH) (XX), S(XXVIII), SO_2(XXIX).

As regards the nucleus, since the potency order was XXXIVb$\geqq$IId, 2-oxo-1,2,3,4-tetrahydroquinoline was a little less active than 1,2-dihydro-2-oxoquinoline, but the difference between the two nuclei was very small.

Among the compounds, ethyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (OPC-3162) and ethyl 4-(1,2-dihydro-2-oxo-6-quinolyoxy)butyrate were found to have the most potent inhibitory activities.

Experimental

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

Preparations of IIa—f and III. Ethyl 4-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (IId)——A solution of 19.6 g of Ib and 6.2 g of NaOH in 200 ml of water was evaporated to dryness under reduced pressure. Next, 200 ml of EtOH was added to the residue, then the solvent was evaporated off *in vacuo* again. A solution of 30 g of ethyl 4-bromobutyrate[7] in 50 ml of DMF was added to a suspension of the residue in 160 ml of DMF over a period of 1 h with stirring at room temperature, and the mixture was stirred at 40—45°C for 3 h, then the reaction mixture was poured into 1.5 l of saturated NaCl aq. solution. The precipitated crystals were collected by filtration and recrystallized from EtOH to give IId (23.9 g, 71.8%) as colorless prisms, mp 121.0—121.5°C. NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $-COOCH_2C\underline{H}_3$), 1.94—2.30 (2H, m, $-OCH_2C\underline{H}_2CH_2-$), 2.38—3.10 (6H, m, $-C\underline{H}_2C\underline{H}_2-$, $-OCH_2CH_2C\underline{H}_2-$), 3.97 (2H, t, J=5.5 Hz, $-OC\underline{H}_2CH_2CH_2-$), 4.19 (2H, q, J=7 Hz, $-COOC\underline{H}_2CH_3$), 6.68—6.89 (3H, m, aromatic H), 9.71 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table I.

Compounds IIa—c, IIe, f and III were obtained by the same procedure as described for IId, and the yield, mp and elemental analysis data are shown in Tables I and II.

3-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)propionitrile (IV)——Triton B (2 ml) was added dropwise with stirring and ice-water cooling to a suspension of 11.4 g of Ib in 30 ml of acrylonitrile. The reaction mixture was stirred under reflux for 3 h, then cooled. The precipitated crystals were collected by filtration, washed with Et_2O, and added to 100 ml of 5% NaOH. The insoluble crystals were collected by filtration and recrystallized successively from EtOH and CH_3CN to give IV (4.0 g, 26.5%) as colorless needles, mp 116—118.5°C. IR ν_{max}^{KBr} cm^{-1}: 3210 (NH), 2260 (CN), 1670 (C=O). NMR ($CDCl_3$) δ: 2.33—3.00 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 2.81 (2H, t, J=6 Hz, $-CH_2C\underline{H}_2CN$), 4.10 (2H, t, J=6 Hz, $-C\underline{H}_2CH_2CN$), 6.53—6.87 (3H, m, aromatic H), 9.69 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.56; H, 5.67; N, 13.02.

3-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)propionic Acid (V)——A suspension of 5.0 g of IV in 25 ml of conc. HCl and 25 ml of water was refluxed for 3 h on an oil bath, then poured into ice-water. The insoluble materials were collected by filtration and washed with water, then recrystallized from DMF to give V (5.0 g, 91.9%) as colorless needles, mp 188—190.5°C. IR ν_{max}^{KBr} cm^{-1}: 3370 (NH), 1740 (COOH), 1650 (CONH). NMR (DMSO-d_6) δ: 2.25—3.00 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 2.63 (2H, t, J=6 Hz, $-CH_2C\underline{H}_2COOH$), 4.07 (2H, t, J=6 Hz, $-C\underline{H}_2CH_2-COOH$), 6.53—6.83 (3H, m, aromatic H), 9.80 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.11; H, 5.58; N, 6.06.

Ethyl 3-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)propionate (VI)——$SOCl_2$ (1 ml) was added dropwise with stirring to a suspension of 3.0 g of V in 60 ml of EtOH at 0—10°C. After being stirred at 50—60°C for 3 h, the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 100 ml of $CHCl_3$ and the solution was washed successively with water, 1% NaOH and water, then dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel; eluent, $CHCl_3$–MeOH=100: 1) and recrystallized from AcOEt–Et_2O to give VI (2.1 g, 62.5%) as colorless needles, mp 136—137°C. IR ν_{max}^{KBr} cm^{-1}: 3220 (NH), 1735 (COOEt), 1680 (CONH). NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $-COOCH_2C\underline{H}_3$), 2.40—3.00 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 2.70 (2H, t, J=6 Hz, $-CH_2C\underline{H}_2-COOC_2H_5$), 4.11 (2H, q, J=7 Hz, $-COOC\underline{H}_2CH_3$), 4.13 (2H, t, J=6 Hz, $-C\underline{H}_2CH_2COOC_2H_5$), 6.51—6.83 (3H, m, aromatic H), 9.20 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table I.

4-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyric Acid (VII)——A solution of 5.6 g of IId and 1.2 g of NaOH in 80 ml of MeOH was refluxed for 1.5 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 100 ml of H_2O and then acidified with dil. HCl. The resulting precipitates were collected by filtration, washed with water, and recrystallized from EtOH to give VII (4.4 g, 87.4%) as colorless needles, mp 218—220°C. The elemental analysis data are shown in Table I.

Alkyl 4-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (XIIIa—f)——Compounds VIIIa—f were obtained by the same procedure as described for VI, and the yield, mp and elemental analysis data are shown in Table I.

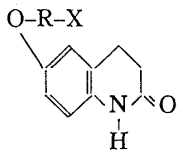
Ethyl 4-(1-Methyl-2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (IX)——A solution of 2.5 g of IId in 25 ml of DMF was treated with 0.5 g of 50% NaH (dispersion in oil) with stirring under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h, then 0.7 g of CH_3I was added and the whole was stirred at 35—40°C for 5 h, then poured into saturated NaCl. The solution was extracted with $CHCl_3$, and the extract was washed with water, and dried over Na_2SO_4. After removal of the solvent, the oily residue was distilled to give IX (2.0 g, 76.4%) as a colorless oil, bp 197—199°C/0.7 mmHg. The elemental analysis data are shown in Table I.

***tert*-Butyl 4-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (X)**——A suspension of 1.0 g of VII in 100 ml of CH_2Cl_2 was treated with 1.0 ml conc. H_2SO_4, and then isobutylene was bubbled into the mixture with stirring at room temperature for 36 h. After removal of the insoluble material, $CHCl_3$ (50 ml) was added to the filtrate. The $CHCl_3$ solution was washed successively with water, 30 ml of 5% $NaHCO_3$ and water, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, $CHCl_3$) and recrystallized from $CHCl_3$–pet. ether to give X (0.31 g, 25.3%) as colorless needles, mp 107.5—108°C. NMR ($CDCl_3$) δ: 1.49 (9H, s, $-C(C\underline{H}_3)_3$), 1.90—2.30 (2H, m, $-OCH_2C\underline{H}_2CH_2-$), 2.31—3.13 (6H, m, $-C\underline{H}_2C\underline{H}_2-$, $-OCH_2CH_2C\underline{H}_2-$), 3.97 (2H, t, $J=6$ Hz, $-OC\underline{H}_2CH_2-$), 6.8 (3H, br s, aromatic H), 9.47 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table I.

Preparation of XIa—d. 6-(3-Chloro-2-methylpropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XIc)——1-Bromo-3-chloro-2-methylpropane (38 g) was added dropwise to a solution of 32 g of Ib and 17 g of NaOEt in 200 ml of EtOH with stirring under reflux. The reaction mixture was refluxed for 12 h and then poured into 1.5 l of 0.5 N NaOH. The precipitated crystals were collected by filtration and washed with water. Recrystallization from EtOH gave XIc (34 g, 68.3%) as colorless needles, mp 103—105°C. NMR ($CDCl_3$) δ: 1.15 (3H, d, $J=7$ Hz, $>CHC\underline{H}_3$), 2.45—3.12 (5H, m, $-C\underline{H}_2C\underline{H}_2-$, $>C\underline{H}CH_3$), 3.65 (2H, d, $J=6$ Hz, $-C\underline{H}_2Cl$), 3.87 (2H, d, $J=6$ Hz, $-OC\underline{H}_2CH<$), 6.79 (3H, br s, aromatic H), 9.69 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table V.

Compounds XIa, b and XId were obtained by the same procedure as described for XIc, and the yield, mp and elemental analysis data are shown in Table V.

TABLE V. 6-(ω-Bromoalkoxy)-2-oxo-1,2,3,4-tetrahydroquinoline Derivatives

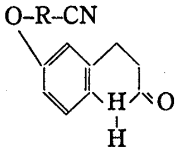


Compd. No.	R	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XIa	$CH_2(CH_2)_2CH_2$	Br	52	139—141	$C_{13}H_{16}BrNO_2$	52.36 (52.22	5.41 5.31	4.70 4.82)
XIb	$CH_2(CH_2)_4CH_2$	Br	47	118—119	$C_{15}H_{20}BrNO_2$	55.22 (55.07	6.17 6.15	4.29 4.42)
XIc	$CH_2CH(CH_3)CH_2$	Cl	68	103—105	$C_{13}H_{16}ClNO_2$	61.54 (61.26	6.36 6.42	5.52 5.37)
XId	$CH_2CH_2CH(CH_3)$	Br	61	105—106	$C_{13}H_{16}BrNO_2$	52.36 (52.09	5.41 5.23	4.70 4.57)

Preparation of XIIa—d. 6-(3-Cyano-2-methylpropyl)-2-oxo-1,2,3,4-tetrahydroquinoline (XIIc)——A mixture of 10 g of XIc, 4 g of NaCN and 2 g of NaI in 100 ml of DMF was heated at 120—130°C for 15 h with stirring. The reaction mixture was poured into 1 l of water. The precipitated crystals were collected by filtration and washed with water. Recrystallization from EtOH gave XIIc (7.3 g, 75.8%) as colorless needles, mp 125—127°C. NMR ($CDCl_3$) δ: 1.15 (3H, d, $J=7$ Hz, $>CHC\underline{H}_3$), 2.45—3.12 (5H, m, $-C\underline{H}_2C\underline{H}_2-$, $>C\underline{H}CH_3$), 3.65 (2H, d, $J=6$ Hz, $-C\underline{H}_2CN$), 3.87 (2H, d, $J=6$ Hz, $-OC\underline{H}_2CH<$). 6.79 (3H, br s, aromatic H), 9.69 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table VI.

Compounds XIIa, b and XIId were obtained by the same procedure as described for XIIc, and the yield, mp and elemental analysis data are shown in Table VI.

Table VI. 6-(ω-Cyanoalkoxy)-2-oxo-1,2,3,4-tetrahydroquinoline Derivatives

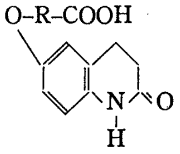


Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XIIa	$CH_2(CH_2)_2CH_2$	89	151—153	$C_{14}H_{16}N_2O_2$	68.83 (68.71	6.60 6.47	11.47 11.62)
XIIb	$CH_2(CH_2)_4CH_2$	69	122—125	$C_{16}H_{20}N_2O_2$	70.56 (70.30	7.40 7.37	10.29 10.12)
XIIc	$CH_2CH(CH_3)CH_2$	76	125—127	$C_{14}H_{16}N_2O_2$	68.83 (68.88	6.60 6.56	11.47 11.43)
XIId	$CH_2CH_2CH(CH_3)$	74	102—104	$C_{14}H_{16}N_2O_2$	68.83 (68.65	6.60 6.44	11.47 11.17)

Preparation of XIIIa—d. 3-Methyl-4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyric Acid (XIIIc)—— A suspension of 11.4 g of XIIc in 120 ml of 2 N NaOH was refluxed for 17 h. After cooling, the reaction solution was acidified with 1 N HCl. The resulting precipitates were collected by filtration and dissolved in 100 ml of 5% NaOH. After removal of the insoluble material, the filtrate was acidified with 1 N HCl. The resulting precipitates were collected by filtration and recrystallized from EtOH–H_2O to give XIIIc (5.6 g, 45.6%) as colorless needles, mp 173—174°C. NMR (DMSO-d_6) δ: 1.02 (3H, d, J=6.5 Hz, >CHC$\underline{H}_3$), 2.17—3.03 (7H, m, –C$\underline{H}_2$C$\underline{H}_2$–, –C$\underline{H}$(CH$_3$)C$\underline{H}_2$COO–), 3.77 (2H, d, J=5 Hz, –OC$\underline{H}_2$CH), 6.70—6.87 (3H, m, aromatic H), 9.89 (1H, br s, –N$\underline{H}$–). The elemental analysis data are shown in Table VII.

Compounds XIIIa, b and XIIId were obtained by the same procedure as described for XIIIc, and the yield, mp and elemental analysis data are shown in Table VII.

Table VII. ω-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyloxy) alkanoic Acid Derivatives



Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XIIIa	$CH_2(CH_2)_2CH_2$	56	185—187	$C_{14}H_{17}NO_4$	63.86 (63.75	6.51 6.63	5.32 5.14)
XIIIb	$CH_2(CH_2)_4CH_2$	43	179—181	$C_{16}H_{21}NO_4$	65.95 (65.67	7.27 7.26	4.81 4.86)
XIIIc	$CH_2CH(CH_3)CH_2$	46	173—174	$C_{14}H_{17}NO_4$	63.86 (63.64	6.51 6.38	5.32 5.27)
XIIId	$CH_2CH_2CH(CH_3)$	19	201—203	$C_{14}H_{17}NO_4$	63.86 (63.72	6.51 6.54	5.32 5.34)

Preparation of XIVa—d. Ethyl 3-Methyl-4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (XIVc)—— A solution of 4.0 g of XIIIc and 40 mg of *p*-TosOH in 40 ml of EtOH was refluxed for 4.5 h. After removal of the solvent, the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed successively with 30 ml of cold 5% Na_2CO_3 and water, and dried over Na_2SO_4. After removal of the $CHCl_3$, the residue was recrystallized from EtOH to give XIVc (2.4 g, 54.2%) as colorless needles, mp 95—97°C. NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6.5 Hz, >CHC$\underline{H}_3$), 1.35 (3H, t, J=7 Hz, –CH$_2$C$\underline{H}_3$), 2.11—3.24 (7H, m, –C$\underline{H}_2$C$\underline{H}_2$–, C$\underline{H}$CH$_3$,

$-C\underline{H}_2COO-$), 3.86 (2H, d, $J=5$ Hz, $-OC\underline{H}_2CH$), 4.21 (2H, q, $J=7$ Hz, $-COOC\underline{H}_2CH_3$), 6.79 (3H, s, aromatic H), 9.03 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table II.

Compounds XIVa, b and XIVd were obtained by the same procedure as described for XIVc, and the yield, mp and elemental analysis data are shown in Tables I and II.

Compounds XVa, b and XVIII were obtained by the same procedure as described for IId, and the yield, mp and elemental analysis data are shown in Table III.

6-(3-Hydroxypropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XVI)——A solution of 8.2 g of Ib and 2.0 g of NaOH in 80 ml of H_2O was stirred at room temperature for 30 min. To this solution, 0.3 g of KI and 8.4 g of $BrCH_2CH_2CH_2OH$ were added and the reaction mixture was stirred at 90—95°C for 5 h, then cooled. The precipitated crystals were collected by filtration and washed successively with 100 ml of dil. NaOH and water. Recrystallization from EtOH gave XVI (5.2 g, 47%) as colorless needles, mp 163—164°C. NMR (DMSO-d_6) δ: 1.57—1.93 (2H, m, $-OCH_2C\underline{H}_2CH_2O-$), 2.17—2.91 (4H, m, $-NHCOC\underline{H}_2C\underline{H}_2-$), 3.22 (1H, br s, $-CH_2O\underline{H}$), 3.33—3.63 (2H, m, $-C\underline{H}_2OH$), 3.88 (2H, t, $J=6$ Hz, $-OC\underline{H}_2CH_2-$), 6.64 (3H, br s, aromatic H), 9.73 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.10; H, 6.94; N, 6.37.

3-(2-Oxo-1,2,3,4-tetrahydroquinolyloxy)propyl Propionate (XVII)——A solution of 2.2 g of XVI and 2.6 g of propionic anhydride in 10 ml of pyridine was stirred with ice-water cooling for 1 h then at room temperature for 6 h. The reaction mixture was poured into 200 ml of ice-water. The precipitated crystals were collected by filtration and recrystallization from $CHCl_3$–petr. ether gave XVII (1.0 g, 36%) as colorless needles, mp 113—115°C. NMR ($CDCl_3$) δ: 1.09 (3H, t, $J=7.5$ Hz, $-OCOCH_2C\underline{H}_3$), 1.87—2.40 (4H, m, $-OCOC\underline{H}_2CH_3$, $-OCH_2C\underline{H}_2CH_2-$), 2.41—2.95 (4H, m, $-NHCOC\underline{H}_2C\underline{H}_2-$), 3.91 (2H, t, $J=6$ Hz, $-OC\underline{H}_2CH_2-$), 4.17 (2H, t, $J=6$ Hz, $-C\underline{H}_2OCO-$), 6.57—6.77 (3H, m, aromatic H), 9.18 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table III.

6-(4-Oxohexyloxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XIX)——A mixture of 1.0 g of XVIII in 20 ml of AcOH and 1 ml of conc. HCl was stirred at 90—95°C for 1 h. The mixture was cooled, then 50 ml of water was added, and the whole was extracted with three 50 ml portions of $CHCl_3$. The extracts were combined and washed successively with 20 ml of dil. NaOH and water, and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from EtOH–H_2O to give XIX (0.3 g, 35.1%) as colorless needles, mp 115—116°C. NMR ($CDCl_3$) δ: 1.14 (3H, t, $J=7.5$ Hz, $-COOCH_2C\underline{H}_3$), 1.85—3.05 (10H, m, $-C\underline{H}_2C\underline{H}_2-$, $-COC\underline{H}_2-$, $-OCH_2C\underline{H}_2C\underline{H}_2-$), 4.0 (2H, t, $J=6$ Hz, $-OC\underline{H}_2-$), 6.81 (3H, br s, aromatic H), 9.5 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table III.

6-(4-Hydroxyhexyloxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XX)——A solution of 1.5 g of XIX in 250 ml of EtOH was treated with 0.5 g of $NaBH_4$ at room temperature with stirring. After being stirred for 2 h, the reaction solution was acidified with dil. HCl and evaporated to dryness under reduced pressure. The residue was extracted with 100 ml of $CHCl_3$, and the extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from $CHCl_3$–pet. ether to give XX (1.1 g, 72.8%) as colorless needles, mp 92.0—93.5°C. NMR ($CDCl_3$) δ: 0.96 (3H, t, $J=7$ Hz, $-CH(OH)CH_2C\underline{H}_3$), 1.26—2.06 (6H, m, $-OCH_2C\underline{H}_2C\underline{H}_2CH(OH)C\underline{H}_2CH_3$), 2.19 (1H, br s, $>CHO\underline{H}$), 2.41—3.13 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 3.42—3.76 (1H, m, $>C\underline{H}OH$), 3.95 (2H, t, $J=5.5$ Hz, $-OC\underline{H}_2CH_2-$), 6.76 (3H, br s, aromatic H), 9.31 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table III.

4-(2-Oxo-1,2,3,4-tetrahydro-6-quinolylcarbonyl)butyric Acid (XXI)——A mixture of 4.4 g of 2-oxo-1,2,3,4-tetrahydroquinoline, 5.1 g of glutaric anhydride and 27.0 g of $AlCl_3$ in 50 ml of 1,2-dichloroethane was stirred at 30—40°C for 3 h, and then poured into 200 ml of ice-water. The precipitated crystals were collected by filtration and washed with water, then dissolved in 50 ml of 10% NaOH. After removal of the insoluble material, the filtrate was adjusted to about pH 3.0 with dil. HCl. The resulting precipitates were collected by filtration again and washed with water. Recrystallization from 50% EtOH gave XXI (2.7 g, 34.6%) as light yellow needles, mp 244—245°C. NMR (DMSO-d_6) δ: 1.59—2.0 (2H, m, $-CH_2C\underline{H}_2CH_2CO-$), 2.12—3.08 (8H, m, $-C\underline{H}_2C\underline{H}_2-$, $-COC\underline{H}_2CH_2C\underline{H}_2CO-$), 6.85 (1H, d, $J=9$ Hz, aromatic 8-H), 7.62—7.80 (2H, m, aromatic 5,7-H), 10.29 (1H, br s, $-N\underline{H}-$), 12.92 (1H, br s, $-COO\underline{H}$). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.75; N, 5.36. Found: C, 64.27; H, 6.01; N, 5.42.

Ethyl 4-(2-Oxo-1,2,3,4-tetrahydro-6-quinolylcarbonyl)butyrate (XXII)——Compound XXII was obtained by the procedure described for VI, and the yield, mp and elemental analysis data are shown in Table I.

Ethyl 5-Hydroxy-5-(2-oxo-1,2,3,4-tetrahydro-6-quinolyl)valerate (XXIII)——A mixture of 1.0 g of ethyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolylcarbonyl)butyrate (XXII) and 0.1 g of Pd-black in 100 ml of EtOH was stirred at 40—50°C under atmospheric pressure of hydrogen for 8 h. The mixture was cooled, the catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from $CHCl_3$–petr. ether to give XXIII (0.74 g, 73.4%) as colorless needles, mp 83—84°C. NMR ($CDCl_3$) δ: 1.2 (3H, t, $J=7.5$ Hz, $-COOCH_2C\underline{H}_3$), 1.53—1.79 (2H, m, $-CH_2C\underline{H}_2CH_2COO-$), 2.13—2.98 (8H, m, $-NHCOC\underline{H}_2C\underline{H}_2-$, $-C\underline{H}_2CH_2C\underline{H}_2COO-$), 4.02 (2H, q, $J=9$ Hz, $-COOC\underline{H}_2CH_3$), 4.53 (1H, m, $-C\underline{H}-$(OH)–), 6.65 (1H, d, $J=9$ Hz, aromatic 8-H), 6.91—7.09 (2H, m, aromatic 5,7-H), 8.7 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table I.

5-Hydroxy-5-(2-oxo-1,2,3,4-tetrahydro-6-quinolyl)valeric Acid (XXIV)——Compound XXIV was obtained by the procedure described for XX. Colorless needles, mp 124—126°C (from H_2O). NMR (DMSO-d_6) δ: 1.33—1.77 (4H, m, $-CH(OH)C\underline{H}_2C\underline{H}_2CH_2-$), 2.03—2.93 (6H, m, $-C\underline{H}_2C\underline{H}_2-$, $-C\underline{H}_2COOH$), 4.24—4.47

(1H, m, $-C\underline{H}(OH)CH_2-$), 6.69 (1H, d, $J=9$ Hz, aromatic 8-H), 7.01 (2H, m, aromatic 5,7-H), 9.88 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.88; H, 6.46; N, 5.32. Found: C, 63.64; H, 6.51; N, 5.38.

5-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyl)valeric Acid (XXV)——A mixture of 1.0 g of XXIV, 0.5 ml of 70% $HClO_4$ and 0.3 g of Pd-black in 50 ml of AcOH was stirred at 60—65°C under atmospheric pressure of hydrogen. The mixture was cooled to room temperature, the catalyst and the insoluble material were removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give XXV (0.3 g, 31.9%) as colorless needles, mp 181—182°C. NMR (DMSO-d_6) δ: 1.33—1.77 (4H, m, $-CH(OH)C\underline{H}_2-$, $C\underline{H}_2CH_2CO-$), 2.03—2.93 (6H, m, $-C\underline{H}_2C\underline{H}_2-$, $-C\underline{H}_2COOH$), 4.24—4.47 (1H, m, $-C\underline{H}(OH)CH_2-$), 6.69 (1H, d, $J=9$ Hz, aromatic 8-H), 7.01 (2H, m, aromatic 5,7-H), 9.88 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.15; H, 7.17; N, 5.72.

Ethyl 5-(2-Oxo-1,2,3,4-tetrahydro-6-quinolyl)valerate (XXVI)——Compound XXVI was obtained by the procedure described for VI, and the yield, mp and elemental analysis data are shown in Table I.

6-(3-Chloropropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XXVII)——A solution of 4.2 g of Ib and 1.6 g of KOH in 80 ml of iso-PrOH and 10 ml of water, was stirred with 4.3 g of 1-bromo-3-chloropropane under reflux for 4 h, then the reaction mixture was concentrated *in vacuo*. The residue was poured into water, and the precipitated crystals were collected by filtration. Recrystallization from EtOH gave XXVII (3.3 g, 53.5%) as colorless needles, mp 133—135°C. NMR (DMSO-d_6) δ: 1.90—2.30 (2H, m, $-CH_2C\underline{H}_2CH_2-$), 2.30—2.90 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 3.72 (2H, t, $J=6$ Hz, $-C\underline{H}_2Cl$), 3.98 (2H, t, $J=6$ Hz, $-OC\underline{H}_2-$), 6.50—6.90 (3H, m, aromatic H), 9.83 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.11; H, 5.86; N, 5.83.

6-(3-Ethylthiopropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XXVIII)——A solution of 2.3 g of XXVII in 70 ml of DMF was added to a solution of 0.7 g of ethylmercaptan and 0.8 g of NaOH in 10 ml of water and the mixture was stirred at 70—80°C for 3 h. The reaction mixture was poured into water and the precipitated crystals were collected by filtration. Recrystallization from ligroin gave XXVIII (1.4 g, 55.0%) as colorless needles, mp 92.5—94.5°C. NMR (DMSO-d_6) δ: 1.16 (3H, t, $J=7$ Hz, $-SCH_2C\underline{H}_3$), 1.70—2.10 (2H, m, $-CH_2C\underline{H}_2CH_2-$), 2.20—2.90 (8H, m, $-C\underline{H}_2C\underline{H}_2-$, $-C\underline{H}_2SC\underline{H}_2-$), 3.92 (2H, t, $J=6$ Hz, $-OC\underline{H}_2-$), 6.50—6.70 (3H, m, aromatic H), 9.82 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table III.

6-(3-Ethylsulfonylpropoxy)-2-oxo-1,2,3,4-tetrahydroquinoline (XXIX)——A 2 ml aliquot of 30% H_2O_2 was added to a solution of 1.0 g of XXVIII in 30 ml of AcOH with stirring at room temperature, and the mixture was stirred overnight. The reaction mixture was poured into saturated NaCl aq. solution and extracted with $CHCl_3$. The extracts were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from EtOH to give XXIX (0.1 g, 8.9%) as colorless needles, mp 185—187°C. NMR (DMSO-d_6) δ: 1.22 (3H, t, $J=7$ Hz, $-SCH_2C\underline{H}_3$), 1.90—2.30 (2H, m, $-CH_2-C\underline{H}_2CH_2-$), 2.30—2.90 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 2.90—3.30 (4H, m, $C\underline{H}_2SC\underline{H}_2-$), 3.98 (2H, t, $J=6$ Hz, $-OC\underline{H}_2-$), 6.50—6.90 (3H, m, aromatic H), 9.82 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table III.

6-Chlorosulfonyl-2-oxo-1,2,3,4-tetrahydroquinoline (XXX)——2-Oxo-1,2,3,4-tetrahydroquinoline (26.7 g) was added in portions to a mixture of 90 ml of chlorosulfonic acid and 120 ml of CCl_4 with stirring and ice-water cooling. The reaction mixture was stirred at room temperature for 3 h, and then poured into water. The precipitated crystals were collected by filtration, washed with water, and dried over Na_2SO_4. Recrystallization from $CHCl_3$ gave XXX (27 g, 60.6%) as colorless plates, mp 209—212°C (dec.). NMR (DMSO-d_6) δ: 2.30—3.00 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 6.82 (1H, d, $J=9$ Hz, aromatic 8-H), 7.38 (1H, dd, $J_1=9$ Hz, $J_2=1.5$ Hz, aromatic 7-H), 7.42 (1H, d, $J=1.5$ Hz, aromatic 5-H), 10.13 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for $C_9H_8ClNO_3S$: C, 44.00; H, 3.28; N, 5.70. Found: C, 43.68; H, 3.21; N, 5.58.

6-Mercapto-2-oxo-1,2,3,4-tetrahydroquinoline (XXXI)——Compound XXX (9.4 g) was added slowly to a solution of 26 ml of conc. H_2SO_4 in 140 ml of H_2O with stirring and cooling ice-water. Next, 26 g of Zn powder was added in portions to the reaction mixture with stirring at room temperature, and the whole was stirred at 60—70°C for 5 h. The insoluble material was collected by filtration, washed with water, and then dissolved in 100 ml of 0.5 N NaOH aq. solution. After the insoluble material had been removed by filtration, the filtrate was acidified with dil. HCl. The resulting precipitates were collected by filtration and recrystallized from water to give XXXI (3.7 g, 68.6%) as colorless needles, mp 163.5—166°C. NMR (DMSO-d_6) δ: 2.20—2.90 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 5.40 (1H, br s, $-S\underline{H}$), 6.72 (1H, d, $J=9$ Hz, aromatic 8-H), 7.02 (1H, dd, $J_1=9$ Hz, $J_2=1.5$ Hz, aromatic 7-H), 7.06 (1H, d, $J=1.5$ Hz, aromatic 5-H), 9.97 (1H, br s, $-N\underline{H}-$). *Anal.* Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.12; H, 4.81; N, 7.89.

6-(3-Ethoxycarbonylpropylthio)-2-oxo-1,2,3,4-tetrahydroquinoline (XXXII) and 6-(3-Ethoxycarbonylpropylsulfonyl)-2-oxo-1,2,3,4-tetrahydroquinoline (XXXIII)——Compounds XXXII and XXXIII were obtained by the same procedure as described for IId and XXIX, respectively, and the elemental analysis data, mp and yield are shown in Table I.

Preparation of XXXIVa—d. Ethyl 4-(1,2-Dihydro-2-oxo-6-quinolyloxy)butyrate (XXXIVb)——A mixture of 1.4 g of IId and 1.7 g of DDQ in 28 ml of dioxane was stirred under reflux for 15 h. After removal of the insoluble material, the filtrate was evaporated to dryness *in vacuo*. The residue was extracted with $CHCl_3$, then the extracts were washed successively with 20 ml of saturated $NaHCO_3$ aq. solution and water, and dried over Na_2SO_4. After removal of $CHCl_3$, the residue was recrystallized from EtOH to give XXXIVb (0.3 g, 21.6%) as colorless needles, mp 130—132°C. NMR ($CDCl_3$) δ: 1.23 (3H, t, $J=7$ Hz, $-COOCH_2C\underline{H}_3$),

1.92—2.27 (2H, m, $-OCH_2C\underline{H}_2CH_2-$), 2.48 (2H, t, $J=6$ Hz, $-C\underline{H}_2COO-$), 3.97 (2H, t, $J=6$ Hz, $-OC\underline{H}_2CH_2-$), 4.09 (2H, q, $J=7$ Hz, $-COOC\underline{H}_2CH_3$), 6.53 (1H, d, $J=10$ Hz, aromatic 3-H), 6.89 (1H, d, $J=3$ Hz, aromatic 5-H), 7.05 (1H, dd, $J_1=6$ Hz, $J_2=3$ Hz, aromatic 7-H), 7.35 (1H, d, $J=6$ Hz, aromatic 8-H), 7.55 (1H, d, $J=10$ Hz, aromatic 4-H), 12.90 (1H, br s, $-N\underline{H}-$). The elemental analysis data are shown in Table IV.

Compounds XXXIVa and XXXIVc, d were obtained by the same procedure as described for XXXIVb, and the yield, mp and elemental analysis data are shown in Table IV.

Inhibition of Blood Platelet Aggregation——Rabbit citrated platelet-rich plasma (PRP) containing 5×10^6 platelets/μl was prepared from the blood obtained by cannulation of the carotid artery. Platelet aggregation was studied by the turbidimetric method[8] with an aggregometer (platelet aggregation tracer, Nicho Bioscience Co., Ltd.). Test compound or the control solution (20 μl) was added to 0.2 ml of the PRP and incubated at 37°C with stirring for 1 min before the addition of aggregating agents (20 μl). Aggregating agents such as collagen (Collagen reagent Horm®, Hormon-Chemie) and adenosine diphosphate (ADP) (Sigma Chemical Co.) were prepared as follows: collagen was diluted further with SKF Horm buffer (Hormon-Chemie) to a concentration of 200 μg/ml immediately prior to use, and ADP was dissolved in 0.9% saline at a concentration of 75 μM, then kept frozen until used. The extent of aggregation was expressed in terms of the maximum change of transmission expressed as a percentage, taking the difference of light transmission between PRP and platelet-poor plasma (PPP) as 100%. Percent inhibition of aggregation by a test compound was calculated by dividing the percent aggregation by that observed in the control run, then multiplying by 100.

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References

1) F. Ishikawa and Y. Watanabe, *Chem. Pharm. Bull.*, **28**, 1307 (1980); F. Ishikawa, Y. Watanabe, and J. Saegusa, *Chem. Pharm. Bull.*, **28**, 1357 (1980); F. Ishikawa. A. Kosasayama, H. Yamaguchi, Y. Watanabe, J. Saegusa, S. Shibamura, K. Sakuma, S. Ashida and Y. Abiko, *J. Med. Chem.*, **24**, 376 (1981); F. Ishikawa and H. Yamaguchi, *Chem. Pharm. Bull.*, **28**, 3172 (1980); U.S. Fleming and J.P. Buyniski, *Thrombosis Research*, **15**, 373 (1979); W.N. Beverung and R.A. Partyka, *J. Med. Chem.*, **18**, 224 (1975); A. Ohtsu, T. Tanaka, F. Kamimoto, K. Hoshina, S. Kurozumi, T. Naruchi and Y. Hashimoto, *J. Pharm. Dyn.*, **3**, 589 (1980); K. Imai, T. Ishida, H. Horiguchi, T. Ozawa, M. Ohno, S. Kawahara and M. Murakami, *Yakugaku Zasshi*, **96**, 578 (1976); G.P. Claxton, J.M. Grisar, E.M. Roberts and R.W. Fleming, *J. Med. Chem.*, **15**, 500 (1972); O. Ponari, E. Civardi, A.G. Dettori, A. Megha, R. Poti and G. Bulletti, *Arzneim.-Forsch.*, **26**, 1532 (1976); E.F. Elaslager, J.R. McLean, S.C. Rerricone, D. Potoczak, H. Veloso, D.F. Worth and R.H. Wheelock, *J. Med. Chem.*, **14**, 397 (1971); J.M. Grisar, G.P. Claxton, K.J. Stewart, R.D. Mackenzie and T. Kariya, *J. Med. Chem.*, **19**, 1195 (1976); K.E. Fahrenholtz, M.Z. Silverzweig, N. Germane, H.J. Crowley, B.A. Simko and C. Dalton, *J. Med. Chem.*, **22**, 948 (1979).
2) K. Nakagawa, N. Murakami, S. Yoshizaki, M. Tominaga, H. Mori, Y. Yabuuchi and S. Shintani, *J. Med. Chem.*, **17**, 529 (1974).
3) S. Yoshizaki, K. Tanimura, S. Tamada, Y. Yabuuchi and N. Nakagawa, *J. Med. Chem.*, **19**, 1138 (1976).
4) Y. Tamura, M. Terashima, Y. Higuchi and K. Ozaki, *Chem. Ind.* (London), **1970**, 1935; F. Mayer. L. van Zutphan and H. Rhilips, *Chem. Ber.*, **60**, 858 (1927); J.D. London and J. Ogg, *J. Chem. Soc.*, **1955**, 739; N. Shigematsu, *Chem. Pharm. Bull.*, **9**, 970 (1961).
5) M. Taniguchi and Y. Satomura, *Agric. Biol. Chem.*, **34**, 506 (1970).
6) J.W.E. Glattfield and E. Rietz, *J. Am. Chem. Soc.*, **62**, 974 (1940).
7) W.S. Wadsworth, JR. and W.D. Emmons, "Organic Synthesis," Coll. Vol. V, ed. by H.E. Baumgarten, John Wiley and Sons, Inc., New York, London, Sydney, Toronto, 1973, p. 545.
8) G.V.R. Born, *J. Physiol.* (London), **162**, 67 (1962).