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Studies on 2-Oxoquinoline Derivatives as Blood Platelet Aggregation Inhibitors. II. 6-[3-(1-Cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline and Related Compounds

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A series of ω-(1-substituted-5-tetrazolylalkoxy)-2-oxoquinolines was synthesized and tested for inhibitory activity towards collagen- and adenosine diphosphate (ADP)-induced aggregation of rabbit blood platelets *in vitro*. These compounds were prepared by the reaction of 1-substituted-5-(ω-chloroalkyl)-tetrazoles and hydroxy-2-oxoquinolines in the presence of a base. Among them, 6-[3-(1-cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline (IVb) was found to have the most potent inhibitory activity. The structure–activity relationships are discussed.

Keywords——ω-(1-substituted-5-tetrazolyl)alkoxy-2-oxoquinoline; 6-[3-(1-cyclohexyl 5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline; inhibition of blood platelet aggregation; structure–activity relationship

Introduction

In the course of our studies on 2-oxoquinolines as blood platelet aggregation inhibitors, it has been found that ethyl (2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butyrate (OPC-3162)

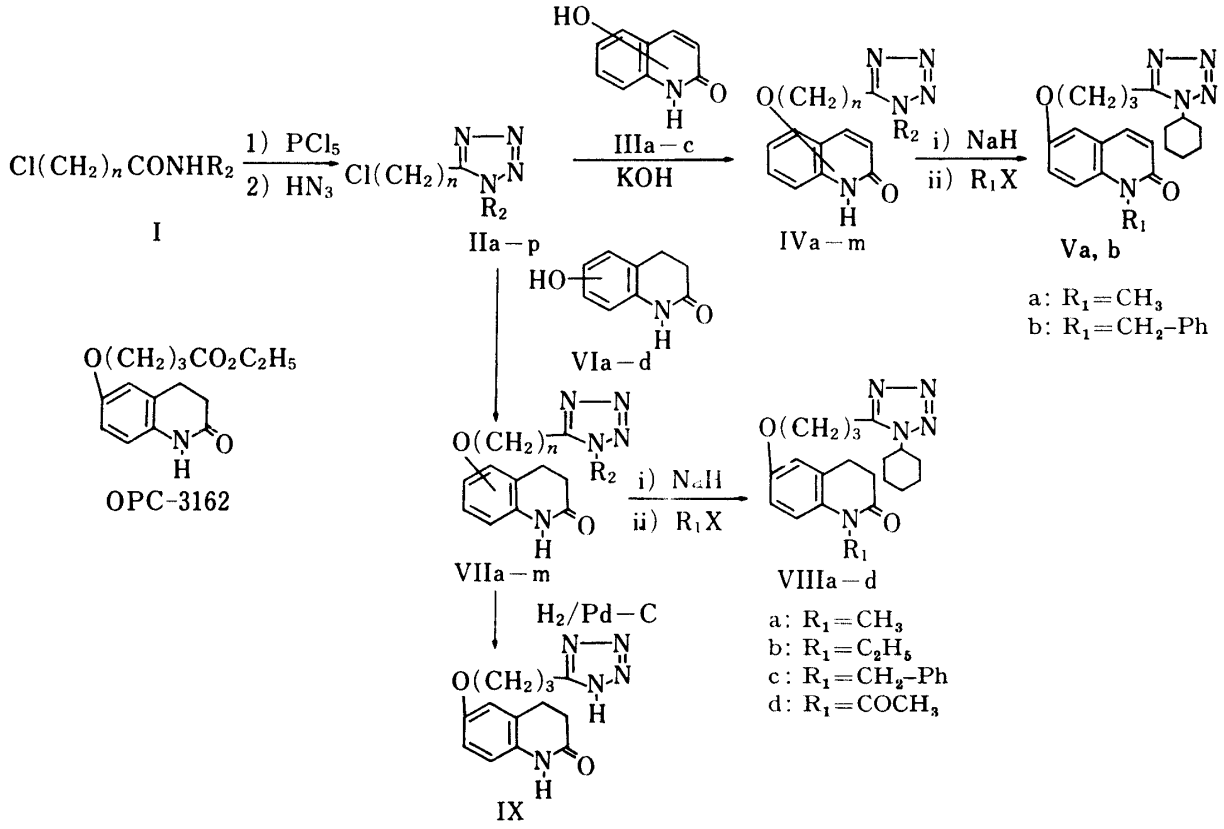
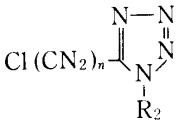


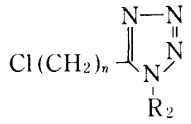
Chart 1

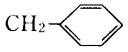
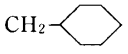
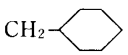
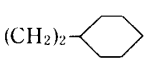
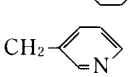
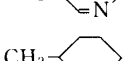
TABLE I-1. 1-Substituted-5-(ω-chloroalkyl)tetrazole Derivatives



Compd. No.	n	R_2	Yield (%)	mp (℃)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
IIa	1		80	101—103.5	$CHCl_3$-Petr. ether	$C_8H_{13}ClN_4$	47.88 (48.13	6.53 6.55	27.82 27.54)
IIb	3		82	82—85	iso-PrOH-H_2O	$C_{10}H_{17}ClN_4$	52.51 (52.34	7.49 7.72	24.50 24.71)
IIc	4		87	48—49	iso-PrOH-H_2O	$C_{11}H_{19}ClN_4$	54.42 (54.56	7.89 7.52	23.08 23.24)
IId	5		78	60—62	$CHCl_3$-Petr. ether	$C_{12}H_{21}ClN_4$	56.13 (56.31	8.24 8.40	21.82 22.09)
IIj	3		86	42—43.5	iso-PrOH-H_2O	$C_{11}H_{19}ClN_4$	54.42 (54.56	7.89 7.91	23.08 23.51)

TABLE I-2. 1-Substituted-5-(ω-chloroalkyl)tetrazole Derivatives[a]



Compd. No.	n	R_2	Yield (%)	^{1}H-NMR δ[b] ($CDCl_3$)
IIe	3		62	2.29 (2H, quint, 6Hz), 3.05 (2H, t, 6Hz), 3.63 (2H, t, 6Hz), 7.25—7.80 (5H, m)
IIf	3		83	2.19 (2H, quint, 6Hz), 2.93 (2H, t, 6Hz), 3.58 (2H, t, 6Hz), 5.54 (2H, s), 7.00—7.57 (5H, m)
IIg	3	CH_2CH_3	50	1.52 (3H, t, 7Hz), 2.26 (2H, quint, 6Hz), 3.02 (2H, t, 6Hz), 3.68 (2H, t, 6Hz), 4.36 (2H, quint, 7Hz)
IIh	3	$CH(CH_3)_2$	87	1.59 (6H, d, 7Hz), 2.27 (2H, quint, 6Hz), 3.00 (2H, t, 6Hz), 3.66 (2H, t, 6Hz), 4.71 (1H, quint, 7Hz)
IIi	3		51	1.46—2.67 (10H, m), 3.06 (2H, t, 6Hz), 3.70 (2H, t, 6Hz), 4.80 (1H, br quint, 6Hz)
IIk	3		64	1.30—2.60 (14H, m), 2.33 (2H, quint, 6H), 3.00 (2H, t, 7Hz), 3.65 (2H, t, 6Hz), 4.17—4.70 (1H, m)
III	3		90	0.60—2.70 (11H, m), 2.34 (2H, quint, 6Hz), 3.04 (2H, t, 6Hz), 3.72 (2H, t, 6Hz), 4.14 (2H, quint, 6Hz)
IIm	4		87	0.75—2.50 (11H, m), 2.86 (2H, t, 6Hz), 3.57 (2H, t, 6Hz), 4.07 (2H, d, 7Hz)
IIn	4		82	0.60—2.50 (13H, m), 2.80 (2H, t, 6Hz), 3.56 (2H, t, 6Hz), 4.23 (2H, t, 8Hz)
IIo	4		75	1.56—2.16 (4H, m), 2.83 (2H, t, 6Hz), 3.50 (2H, t, 6Hz), 5.56 (2H, s), 7.21—7.70 (2H, m), 8.53—8.70 (2H, m)
IIp	4		91	1.00—2.50 (10H, m), 2.93 (2H, t, 6Hz), 3.06—4.55 (5H, m), 3.57 (2H, t, 6Hz)

a) The compounds given in Table I-2 could not be distilled.
b) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in parentheses. Tetramethylsilane was used as external standard.

TABLE II. ω-(1-Substituted-5-tetrazolylalkoxy)-1,2,-dihydro-2-oxoquinoline Derivatives and Their Inhibition of Blood Platelet Aggregation

Compd. No.	Position	n	R_1	R_2	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (IC_{50}, μM) ADP	Collagen
IVa	6	1	H		89	278—281	DMF	$C_{17}H_{19}N_5O_2$	62.75 (62.81)	5.89 (6.00)	21.53 (21.80)	> 250	> 250
IVb	6	3	H		50	211—212	$CHCl_3$	$C_{19}H_{23}N_5O_2$	64.57 (64.40)	6.56 (6.35)	19.82 (19.84)	9.7	7.3
IVc	6	4	H		37	177.5—178.5	iso-PrOH	$C_{20}H_{25}N_5O_2$	65.37 (65.46)	6.86 (6.95)	19.06 (19.09)	21	16
IVd	6	3	H	CH_2CH_3	10	179—181.5	$CHCl_3$	$C_{15}H_{17}N_5O_2$	60.19 (59.86)	5.70 (5.57)	23.40 (23.22)	95	73
IVe	6	3	H	$CH(CH_3)_2$	56	202—203	$CHCl_3$	$C_{16}H_{19}N_5O_2$	61.32 (61.48)	6.11 (6.05)	22.35 (22.27)	70	49
IVf	6	3	H		53	173—174	$CHCl_3$-Petr. ether	$C_{19}H_{17}N_5O_2$	65.69 (65.64)	4.93 (4.81)	20.16 (20.39)	21	38
IVg	6	3	H		46	152—154	EtOH-H_2O	$C_{20}H_{19}N_5O_2$	64.85 (64.85)	5.44 (5.34)	18.91 (19.11)	> 250	93
IVh	6	3	H		51	196.5—197.5	MeOH	$C_{18}H_{21}N_5O_2$	63.70 (63.42)	6.24 (6.29)	20.64 (20.84)	21	37
IVi	6	3	H		63	214—215	MeOH-H_2O	$C_{20}H_{25}N_5O_2$	65.37 (65.16)	6.86 (6.72)	19.06 (19.28)	21	12
IVj	6	3	H		40	220—220.5	EtOH	$C_{21}H_{27}N_5O_2$	66.12 (65.85)	7.13 (7.08)	18.36 (18.50)	200	210
IVk	6	3	H		52	175—175.5	EtOH	$C_{20}H_{25}N_5O_2$	65.37 (65.37)	6.86 (6.87)	19.06 (19.07)	19	21
IVl	3	3	H		74	208—209	$CHCl_3$-Acetone	$C_{19}H_{23}N_5O_2$	64.57 (64.35)	6.56 (6.43)	19.82 (19.86)	> 250	> 250
IVm	4	3	H		34	247—249	$CHCl_3$-Petr. ether	$C_{19}H_{23}N_5O_2$	64.57 (64.44)	6.56 (6.57)	19.82 (19.96)	> 250	> 250
Va	6	3	CH_3		87	150—151.5	Acetone	$C_{20}H_{25}N_5O_2$	65.37 (65.56)	6.86 (6.83)	19.06 (18.90)	> 250	> 250
Vb	6	3			36	139—140	Benzene-iso-Pr_2O	$C_{26}H_{29}N_5O_2$	70.40 (70.47)	6.59 (6.62)	15.79 (15.81)	> 250	> 250
Adenosine												21	84

showed the most potent inhibitory activity towards blood platelet aggregation, as described in the preceding paper.[1] This compound, however, has little practical utility because it is readily hydrolyzed *in vivo* to the corresponding inactive carboxylic acid. Therefore, the present work was undertaken to find active compounds which are stable *in vivo*. On the basis of the structure-activity relationships described in the preceding paper,[1] variously substituted 2-oxoquinolines were examined and some tetrazole derivatives were found to be stable as well as active *in vivo*.

TABLE III. ω-(1-Substituted-5-tetrazolyloxy)-2-oxo-1,2,3,4,-tetrahydroquinoline Derivatives and Their Inhibition of Blood Platelet Aggregation

Compd. No.	Position	n	R_1	R_2	Yield (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Inhibition (IC_{50}, μM) ADP	Collagen
VIIa	6	3	H		63	154.5—155.5	$CHCl_3$–Petr. ether	$C_{19}H_{25}N_5O_2$	64.20 (64.39)	7.09 (7.13)	19.71 (19.89)	21	16
VIIb	6	4	H		74	158—159	MeOH-H_2O	$C_{20}H_{27}N_5O_2$	65.01 (65.11)	7.37 (7.33)	18.96 (19.16)	24	32
VIIc	6	5	H		40	174—176	MeOH-Petr. ether	$C_{21}H_{29}N_5O_2$	65.77 (65.60)	7.54 (7.54)	18.49 (18.49)	> 250	> 250
VIId	6	3	H		61	159—160.5	EtOH	$C_{19}H_{19}N_5O_2$	65.31 (65.37)	5.48 (5.35)	20.05 (20.10)	56	> 250
VIIe	6	3	H	CH_2–	24	136.5—138	EtOAc	$C_{20}H_{21}N_5O_2$	66.10 (66.08)	5.82 (5.70)	19.27 (19.01)	31	210
VIIf	6	3	H	CH_2–	54	137—138	EtOH	$C_{20}H_{27}N_5O_2$	65.01 (64.74)	7.37 (7.39)	18.96 (18.90)	24	46
VIIg	6	4	H	CH_2–	44	141—143	Acetone	$C_{21}H_{29}N_5O_2$	65.77 (65.39)	7.62 (7.48)	18.26 (18.04)	29	114
VIIh	6	4	H	$(CH_2)_2$–	8	137.5—139	MeOH-H_2O	$C_{22}H_{31}N_5O_2$	66.47 (66.50)	7.86 (7.57)	17.62 (17.61)	41	> 250
VIIi	6	4	H	CH_2–	53	135—136.5	$CHCl_3$–Acetone	$C_{20}H_{22}N_6O_2$	63.47 (63.27)	5.86 (5.91)	22.21 (22.29)	23	> 250
VIIj	6	4	H	CH_2–	39	120—121	MeOH	$C_{20}H_{27}N_5O_3$	62.32 (62.06)	7.06 (6.85)	18.17 (18.20)	23	24
VIIk	5	3	H		57	220—221.5	$CHCl_3$–Hexane	$C_{19}H_{25}N_5O_2$	64.20 (64.05)	7.09 (7.34)	19.71 (19.93)	> 250	> 250
VIII	7	3	H		52	171.5—173.5	EtOH	$C_{19}H_{25}N_5O_2$	64.20 (64.04)	7.09 (7.22)	19.71 (20.01)	68	180
VIIm	8	3	H		43	164.5—166	$CHCl_3$–EtOAc	$C_{19}H_{25}N_5O_2$	64.20 (64.28)	7.09 (7.27)	19.71 (20.06)	> 250	> 250
VIIIa	6	3	CH_3		85	102—103	Benzene-Hexane	$C_{20}H_{27}N_5O_2$	65.01 (65.28)	7.37 (7.54)	18.96 (19.12)	73	> 250
VIIIb	6	3	C_2H_5		77	106.5—108.5	Benzene-*iso*-Pr_2O	$C_{21}H_{29}N_5O_2$	65.77 (65.89)	7.62 (7.82)	18.26 (17.89)	140	> 250
VIIIc	6	3	CH_2–		53	140.5—141.5	EtOAc-Hexane	$C_{26}H_{31}N_5O_2$	70.08 (69.90)	7.01 (15.93)	15.72	> 250	> 250
VIIId	6	3	$COCH_3$		15	124—126.5	$CHCl_3$–Petr. ether	$C_{21}H_{27}N_5O_3$	63.45 (63.14)	8.85 (6.73)	17.62 (17.55)	210	> 250
IX	6	3	H	H	80	242—244	MeOH	$C_{13}H_{15}N_5O_2$	57.13 (57.03)	5.53 (5.50)	25.63 (25.81)	> 250	> 250

Tetrazoles used in medicinal chemistry are usually limited to 5-monosubstituted compounds, which are known as bioisosteres of the corresponding carboxylic acids.[2] 1,5-Disubstituted tetrazoles, except for some analogues of cephalosporin, however, have hardly been investigated. We report here the synthesis and the biological activity of some 2-oxoquinoline derivatives having a 1,5-disubstituted tetrazole moiety in the side chain.

Synthesis

2-Oxoquinoline derivatives (IVa—m, Va, b, VIIa—m, VIIIa—d and IX) were synthesized

by the pathway shown in Chart 1.

A benzene solution of I[3] was treated with phosphorus pentachloride (1 eq), followed by addition of hydrogen azide (1.5—2 eq). The solution was allowed to stand overnight at room temperature and then refluxed for 2 h to give a 1-substituted-5-(ω-chloroalkyl)tetrazole (IIa—p) in a high yield.[4] The solid compounds (IIa—d, j) were easily purified by recrystallization (Table I-1), but purification of the oily compounds (IIe—i, k—p) by distillation was unsuccessful because of their thermal instability. Their structures were nevertheless confirmed unequivocally by means of their nuclear magnetic resonance (NMR) and mass spectra.

Condensation of II with hydroxy-1,2-dihydro-2-oxoquinolines (IIIa—c)[5] and hydroxy-2-oxo-1,2,3,4-tetrahydroquinolines (VIa—d)[6] in the presence of potassium hydroxide in the usual way gave 1,2-dihydro-2-oxoquinoline derivatives (IVa—m) and 2-oxo-1,2,3,4-tetrahydroquinoline derivatives (VIIa—m), respectively (Tables II and III).

Alkylation of the sodium salts of 2-oxoquinoline derivatives (IVb, VIIa) with alkyl halides gave N^1-substituted derivatives (Va, b, VIIIa—c). Similarly, acetylation of VIIa with acetyl chloride gave N-acetylated derivative (VIIId) (Table II and III).

Finally, the nonsubstituted derivative (IX) at the 1-position in the tetrazole was prepared from the benzyl derivative (VIId) by hydrogenation using Pd-C as a catalyst (Table III).[7]

Structure–Activity Relationships

The results of *in vitro* screening tests are shown in Tables II and III. Their structure–activity relationships may be summarized as follows. First, comparison of the potency showed IVb>VIIa, IVc>VIIb, IVf>VIId and IVk>VIIf, so that 1,2-dihydro-2-oxoquinoline derivatives possess higher activity than 2-oxo-1,2,3,4-tetrahydroquinoline derivatives. Second, the 6-substituted isomers (IVb, VIIa) showed the highest potency among the positional isomers when the side chain was kept to i. The 7-substituted isomer (VIIl) was less, while the 3-, 4-, 5- and 8-substituted isomers (IVl, IVm, VIIm) were much less active. Therefore, further comparisons of the effects of various substituents were made within the 6-substituted isomer series. Substitution on the 1-position of the nucleus (Va, b, VIIa—d) resulted in loss of the activity, so the proton at the 1-position of the nucleus is essential. The order of potency according to methylene number (n) in the side chain ii was found to be n=3 (IVb, VIIa)>4 (IVc, VIIb)$\gg$1 (IVa), 5 (VIIc). When the effects of substituents on the tetrazole group at the 1-position were compared, the cyclohexyl group (IVb) was the most active and the nonsubstituted compound (IX) showed low activity. Therefore, the substituents on the tetrazole group at the 1-position are also essential for potent activity.

i ii

Among the compounds, 6-[3-(1-cyclohexyl-5-tetrazolyl)propoxy]-1,2-dihydro-2-oxoquinoline (IVb, OPC-3930) showed the most potent activity, which was almost equal to the activity of OPC-3162. This compound was certainly stable *in vivo*. However, 6-[4-(1-cyclohexyl-5-tetrazolyl)butoxy]-1,2,3,4-tetrahydro-2-oxoquinoline (VIIb, OPC-13013), though rather less active than IVb, has additional favorable effects such as cerebral vasodilating activity with little systemic tachycardia or systemic blood pressure change. Therefore, VIIb is now being tested clinically.

Experimental

All melting points are uncorrected. Infrared (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. Mass spectra (MS) were obtained on a Hitachi RMU-6MG spectrometer.

Preparation of IIa—p. 5-(4-Chlorobutyl)-1-cyclohexyltetrazole (IIc)——To a solution of 1.75 g of 5-chloro-*N*-cyclohexylvaleramide in 15 ml of benzene, 1.9 g of PCl_5 was added slowly under cooling with ice-water. The mixture was stirred at room temperature for 1 h, then a solution of 1.4 M of HN_3 in 11 ml of benzene was added with stirring at room temperature. The reaction mixture was stirred overnight and then refluxed for 2 h. After removal of the solvent under reduced pressure, the residue was poured into ice-water, and extracted with $CHCl_3$. The extract was washed successively with water, dil. $NaHCO_3$ and water, and dried over Na_2SO_4. After removal of the $CHCl_3$ by evaporation, the residue was recrystallized from iso-PrOH–water to give IIc (1.7 g, 87%) as colorless needles, mp 48—49°C. NMR ($CDCl_3$) δ: 1.10—2.17 (14H, m, methylene protons of cyclohexyl ring, $ClCH_2C\underline{H}_2C\underline{H}_2CH_2$–), 2.92 (2H, t, J=6 Hz, $ClCH_2CH_2CH_2$-$C\underline{H}_2$–), 3.60 (2H, t, J=6 Hz, $ClC\underline{H}_2C\underline{H}_2$–), 4.23 (1H, m, methine proton of cyclohexyl ring). MS *m/e*: 207 (M^+-Cl), 125 (M^+-(Cl+cyclohexane)), 55 (=CH $CH_2CH_2CH_2^+$, base peak). The elemental analysis data are shown in Table I-1.

Compounds IIa, b and IId—p were obtained by the same procedure as described for IIc; the yields and physiological data are listed in Tables I-1 and I-2.

Preparation of IVa—m and VIIa—m. 6-[4-(1-Cyclohexyl-5-tetrazoly)butoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (VIIb)——A solution of IIc (5.7 g) in 15 ml of iso-PrOH was added dropwise to a solution of 3.2 g of 6-hydroxy-2-oxo-1,2,3,4-tetrahydroquinoline and 1.4 g of KOH in 20 ml of iso-PrOH, under reflux. After being stirred under reflux for 4 h, the reaction mixture was evaporated to dryness *in vacuo*. The residue was extracted with $CHCl_3$, and the extract was washed successively with 1 N NaOH, dil. HCl and water, and dried over Na_2SO_4. After removal of the $CHCl_3$, the residue was purified by column chromatography (silica gel; eluent, $CHCl_3$–MeOH=30: 1) and recrystallized from MeOH–water to give VIIb (6.0 g, 74%) as colorless needles, mp 158—159°C. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1670 (CONH). NMR ($CDCl_3$) δ: 1.10—2.40 (14H, m, methylene protons of cyclohexyl ring, $-OCH_2C\underline{H}_2C\underline{H}_2CH_2$–), 2.43—3.10 (4H, m, $-NHCOC\underline{H}_2C\underline{H}_2$–), 2.93 (2H, t, J=6 Hz, $-O(CH_2)_3C\underline{H}_2$–), 3.96 (2H, t, J=6 Hz, $-OC\underline{H}_2C\underline{H}_2$–), 4.15 (1H, m, methine proton of cyclohexyl ring), 6.53—6.90 (3H, m, aromatic protons), 9.57 (1H, br s, NH). MS *m/e*: 369 (M^+), 125 (=$CHCH_2CH_2CH_2$–  , base peak). The elemental analysis data are shown in Table III.

Compounds IVa—m, VIIa and VIIc—m were obtained by the same procedure as described for VIIb; the yields, mp and elemental analysis data are listed in Tables II and III.

Preparation of Va, b and VIIIa—d. 1-Benzyl-6-[3-(1-cyclohexyl-5-tetrazolyl)propoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (VIIIc)——A 3 g portion of 6-[3-(1-cyclohexyl-5-tetr zolyl)propoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (VIIa) was added to a suspension of 0.5 g of NaH in 15 ml of dimethylformamide (DMF) and dissolved at 50—60°C. The mixture was stirred at room temperature for 1 h, then 1.2 g of $PhCH_2Cl$ was added dropwise with stirring at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was washed with water and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was crystallized with Et_2O. The crystals were dissolved in MeOH again and decolorized with activated charcoal. Recrystallization from MeOH gave VIIIc (2.3 g, 61.2%) as colorless needles, mp 140.5—141.5°C. IR ν_{max}^{KBr} cm^{-1}: 1670 (CONH). NMR ($CDCl_3$) δ: 1.07—2.10 (10H, m, methylene protons of cyclohexyl ring), 2.26 (2H, m, $-OCH_2C\underline{H}_2CH_2$–), 2.55—3.09 (6H, m, $-NCOC\underline{H}_2C\underline{H}_2$–, $-OCH_2CH_2C\underline{H}_2$–), 3.91 (2H, t, J=6 Hz, $-OC\underline{H}_2CH_2CH_2$–), 3.73—4.27 (1H, m, methine proton of cyclohexyl ring), 5.06 (2H, s, N–$C\underline{H}_2$Ph), 6.40—6.77 (3H, m, aromatic protons), 6.90—7.37 (6H, m, aromatic protons). The elemental analysis data are shown in Table III.

Compounds Va, b and VIIIa, b, d were obtained by the same procedure as described for VIIIc; the yields, mp and elemental analysis data are given in Tables II and III.

6-[3-(5-Tetrazolyl)propoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (IX)——A mixture of 1.5 g of 6-[3-(1-benzyl-5-tetrazolyl)propoxy]-2-oxo-1,2,3,4-tetrahydroquinoline (VIIe) and 0.3 g of 10% Pd-C in 200 ml of MeOH was stirred at 60—70°C under an initial pressure of 2 atm of hydrogen for 5 h, then cooled to room temperature. The catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH to give IX (0.85 g, 80%) as colorless prisms, mp 242—244°C. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1650 (CONH). NMR (DMSO-d_6) δ: 1.97—3.23 (8H, m, $-OCH_2$-$C\underline{H}_2C\underline{H}_2$–, $-NHCOC\underline{H}_2C\underline{H}_2$), 3.99 (2H, t, J=6 Hz, $-OC\underline{H}_2CH_2$–), 6.53—6.90 (3H, m, aromatic protons), 9.89 (1H, br s, N$\underline{H}$). The elemental analysis data are given in Table III.

Inhibition of Blood Platelet Aggregation *in Vitro*——The inhibition of blood platelet aggregation was determined by the same method as described in the previous paper.[1]

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