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Studies on the Synthesis of Some Xanthonoid Derivatives Possessing Antiplatelet Effects

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Abstract—2,3- and 3,4-Dihydroxyxanthone react with ethyl 2,3-dibromopropanoate to form the new, substituted 1,4-benzodioxanes *3* and *4*, respectively. The regioisomers *3a* and *3b*; *4a* and *4b* were separated by column chromatography and characterized for evaluation of the antiplatelet effects in rabbit washed platelets and human platelet-rich plasma. The ethoxycarbonyl derivatives *3a* (20 μM) and *3b* (20 μM) strongly inhibited the aggregation of rabbit washed platelets induced by arachidonic acid and collagen. The compound *4b* showed the most potent inhibition of rabbit washed-platelet aggregation induced by arachidonic acid (IC50 = 8·3 μM). Of the compounds tested in human platelet-rich plasma, compound *4b* exhibited the most potent inhibition of primary and secondary aggregation induced by adrenaline (IC50 = 8·6 μM). We conclude that the antiplatelet effects of these four ethoxycarbonyl derivatives are mainly due to an inhibitory effect on thromboxane formation and interference in the adrenaline-receptor interaction.

In a study of structure-activity relationships of various natural and synthetic xanthones, we found that 2,3-dihydroxyxanthone (*1*) diacetate, and 3,4-dihydroxyxanthone (*2*) and its diacetate showed potent antiplatelet effects on arachidonate- and collagen-induced aggregation (Lin et al 1993) and the mechanism of action of 3,4-dihydroxyxanthone is due to inhibition of thromboxane formation (Lin et al 1991). In addition to the above evidence, benzodioxane derivatives of flavone bearing an ethoxycarbonyl side-chain exhibited potent inhibition of human washed-platelet aggregation induced by ADP, collagen, or thrombin (Ertan et al 1991). In the continued study of the structure-activity relationships of various xanthone derivatives and design of antithrombotic and antihypertensive agents, we further synthesized the benzodioxane derivatives of xanthone-bearing ethoxycarbonyl side-chain.

Materials and Methods

Platelet aggregation

Rabbit washed platelets were obtained from ethylenediaminetetraacetic acid (EDTA) anticoagulated platelet-rich plasma (PRP) according to the washing procedures described previously (Teng et al 1987). Human PRP was obtained from the supernatant after the centrifugation of blood mixed with 3·8% sodium citrate (1:9 to blood). Platelet numbers were counted by a Coulter Counter (model ZM) and adjusted to $4·5 \times 10^8$ platelets mL^{-1}. The platelet pellets were suspended in Tyrode solution containing (mM): NaCl 136·8, KCl 2·8, $NaHCO_3$ 11·9, $MgCl_2$ 2·1, NaH_2PO_4 0·33, $CaCl_2$ 1·0 and glucose 11·2 with 0·35% bovine serum albumin. All glassware was siliconized. Just 1 min before the addition of the aggregation inducer, PRP or the platelet suspension was stirred at 1200 rev min^{-1}. Aggregation was measured by a turbidimetric method (O'Brien 1962). The absorbance of PRP or the platelet suspension was taken as 0% aggregation and the absorbance of platelet-poor plasma or platelet-free Tyrode solution as 100% aggregation. The aggregation was measured by a Lumi-aggregometer (Chrono-Log Co., USA) connected to dual channel recorders. To eliminate the effect of the solvent on the aggregation, the final concentration of dimethylsulphoxide (DMSO) was fixed at 0·5%.

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Chemistry

Analytical methods

IR spectra were recorded on a Hitachi model 260-30 infrared spectrophotometer. ^1H and ^{13}C NMR spectra [δ(ppm), J(Hz)] were obtained on a VXR-300 MHz FT-NMR (reference TMS). Mass spectra were determined on a Jeol JMS-D-100 mass spectrometer. Optical rotation was measured on a Jasco model dip-181 digital polarimeter. Elemental analyses were within ±0·4% of the theoretical value when indicated by symbols of the element unless otherwise noted.

Preparation of 2,3-(1) *and 3,4-dihydroxyxanthone* (2)

The above compounds were synthesized and identified as previously (Lin et al 1993).

Preparation of 2,3-(3-ethoxycarbonyl-1,4-ethylenedioxy)xanthone (3a) *and 2,3-(2-ethoxycarbonyl-1,4-ethylenedioxy)xanthone* (3b)

To a solution of *1* (2·0 g, 8·77 mmol) in acetone (30 mL, dried on P_2O_5) was added anhydrous K_2CO_3 (1·2 g, 8·69 mmol) and the mixture was stirred under reflux and

Table 1. ^{1}H NMR data for aromatic protons of various xanthone derivatives*.

Compound	H-1	H-2	H-4	H-5	H-6	H-7	H-8
1	7·72(s)		6·91(s)		7·32–7·80(m)		8·49(dd)
2	8·09(d)	7·02(d)		7·69–7·74(m)	7·57(m)	7·34–7·40(m)	8·32(dd)
3a	7·80(s)		7·12(s)	7·69(m)	7·39(m)		8·30(dd)
3b	7·92(s)		6·97(s)	7·68(m)	7·38(m)		8·30(dd)
4a	7·89(d)	6·93(d)		7·72(m)	7·39(m)	7·60(m)	8·34(dd)
4b	7·92(d)	7·06(d)		7·72(m)	7·39(m)	7·56(m)	8·33(dd)

*2,3-Dimethoxyxanthone (*1*) and 3,4-dimethoxyxanthone (*2*) (Quillinan & Scheinmann 1973; Lin et al 1993).

2,3-dibromopropionic acid ethyl ester (1·7 g, 6·4 mmol) in 15 mL dry acetone was added dropwise over a 30-min period. Another 1·2 g of K_2CO_3 and 1·7 g of 2,3-dibromopropionic acid ethyl ester were added similarly. The mixture was stirred under reflux for 32 h. After addition of $CHCl_3$, the precipitate was removed by filtration and the filtrate was concentrated to give a brownish residue. The residue was chromatographed on silica gel. Elution with cyclohexane:CH_2Cl_2:EtOAc (2:1:0·2) yielded *3a* in the first fractions and *3b* in the later fractions. Compound *3a* recrystallized from CH_2Cl_2-cyclohexane to give colourless needles, 1·120 g (3·44 mmol, 39%), mp 179–180°C; MS, m/z: 326 (M^+); IR (KBr): 1740, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1·29 (3H, t, J = 7·1 Hz, CH_3), 4·29 (2H, q, J = 7·1 Hz OCH_2), 4·40 (1 H, dd, J = 2·9, 11·7 Hz, dioxane-H_A), 4·52 (1H, dd, J = 4·0, 11·7 Hz, dioxane-H_B), 4·96 (1H, dd, J = 2·9, 4·0 Hz, dioxane-H_X), other protons see Table 1; ^{13}C NMR ($CDCl_3$): see Table 2; anal. ($C_{18}H_{14}O_6$) C, H.

Compound *3b* recrystallized from CH_2Cl_2-cyclohexane to give colourless needles, 1·031 g (3·16 mmol, 36%) mp 171–172°C; MS, m/z: 326 (M^+); IR (KBr): 1760, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1·28 (3H, t, J = 7·1 Hz, CH_3), 4·28 (2H, q, J = 7·1 Hz, OCH_2), 4·47 (1H, dd, J = 3·1, 11·7 Hz, dioxane-H_A), 4·56 (1H, dd, J = 4·2, 11·7 Hz, dioxane-H_B), 4·90 (1H, dd, J = 3·1, 4·2 Hz, dioxane-H_X), other protons see Table 1; ^{13}C-NMR ($CDCl_3$): see Table 2; anal ($C_{18}H_{14}O_6$) C, H.

Table 2. ^{13}C NMR data for various xanthone derivatives*.

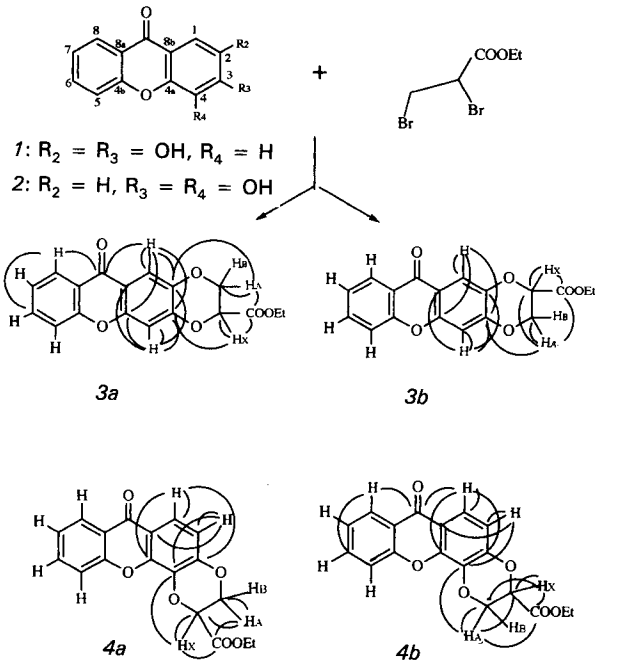
Carbon	*3a*	*3b*	*4a*	*4b*
C-1	113·0	113·5	118·9	119·3
C-2	140·4	139·8	113·7	113·8
C-3	148·6	149·1	146·5[a]	146·4[a]
C-4	105·1	105·2	130·7	131·4
C-4a	151·9	151·8	147·7[a]	147·1[a]
C-4b	156·1	156·2	156·0	155·9
C-5	117·6	117·7	118·1	117·9
C-6	134·3	134·3	134·4	134·5
C-7	123·6	123·7	124·1	124·2
C-8	126·2	126·6	126·6	126·7
C-8a	120·9	121·3	121·7	121·7
C-8b	116·2	116·9	117·1	116·9
C=O	176·3	176·1	176·2	176·2
Dioxane-CH_2	64·6	64·5	65·2	65·1
Dioxane-CH	72·2	71·5	71·8	72·2
$COOCH_2CH_3$	167·3	167·5	167·2	167·2
$COOCH_2CH_3$	62·2	62·2	62·3	62·4
$COOCH_2CH_3$	13·9	14·1	14·1	14·1

*The number of directly attached protons to each carbon was verified with the DEPT pulse sequence. [a]These signals may be interchangeable.

Preparation of 3,4-(3-ethoxycarbonyl-1,4-ethylenedioxyl)xanthone (4a) *and 3,4-(2-ethoxycarbonyl-1,4-ethylenedioxyl)xanthone* (4b)

To a solution of *2* (2·0 g, 8·77 mmol) in acetone (30 mL, dried on P_2O_5) was added anhydrous K_2CO_3 (1·2 g, 8·69 mmol) and the mixture was stirred under reflux and 2,3-dibromopropionic acid ethyl ester (1·7 g, 6·4 mmol) in 15 mL dry acetone was added and treated as for *3a* and *3b* to yield a brownish residue. The residue was chromatographed on silica gel. Elution with cyclohexane:CH_2Cl_2:EtOAc (1:1:0·2) yielded *4a* in the first fractions and *4b* in the later fractions.

Compound *4a* recrystallized from CH_2Cl_2-cyclohexane to give colourless needles, 0·274 g (0·84 mmol, 9·6%), mp 206°C; MS, m/z: 326 (M^+); IR(KBr): 1762, 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1·29 (3H, t, J = 7·1 Hz, CH_3), 4·30 (2H, m, OCH_2), 4·48 (1H, dd, J = 2·9, 11·7 Hz, dioxane-H_A), 4·63 (1H, dd, J = 3·8, 11·7 Hz, dioxane-H_B), 5·07 (1H, dd, J = 2·9, 3·7 Hz, dioxane-H_X), other protons see Table 1; ^{13}C NMR($CDCl_3$): see Table 2; anal. ($C_{18}H_{14}O_6$) C, H. Compound *4b* recrystallized from CH_2Cl_2-cyclohexane to give colourless needles, 1·773 g (5·44 mmol, 62%), mp 198°C; MS, m/z: 326 (M^+); IR (KBr): 1762, 1662 cm^{-1}; ^{1}H



SCHEME 1. ^{13}C–^{1}H long range COSY interactions of compounds *3a*, *3b*, *4a*, and *4b*.

Table 3. Effects of xanthone derivatives on the platelet aggregation induced by thrombin, arachidonic acid, collagen, and PAF in rabbit washed platelets.

Treatment	Aggregation (%)			
	Thrombin (0·1 units mL^{-1})	Arachidonic acid (100 μM)	Collagen (10 μg mL^{-1})	PAF (2 ng mL^{-1})
Control	90·0 ± 0·6	89·4 ± 1·6	87·3 ± 1·3	87·9 ± 2·0
3a 20 μM	[a]	0·0 ± 0·0**	7·6 ± 5·6**	–
3b 20 μM	–	0·0 ± 0·0**	0·0 ± 0·0**	–
4a 300 μM	83·6 ± 2·2*	78·4 ± 2·3*	75·7 ± 10·1	80·3 ± 4·1*
4b 300 μM	72·3 ± 3·1**	0·0 ± 0·0**	36·2 ± 2·2**	57·4 ± 7·5**
20 μM	–	0·0 ± 0·0**	–	–
10 μM	–	14·2 ± 5·9**	–	–
5 μM	–	73·1 ± 9·0	–	–
2 μM	–	90·3 ± 0·5	–	–
Aspirin 50 μM	–	0·0 ± 0·0**	85·4 ± 3·9	90·5 ± 1·2

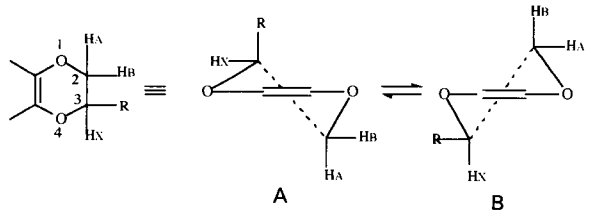
Platelets were preincubated with DMSO (0·5%, control) or xanthone derivatives (30 μM) or aspirin (50 μM) at 37°C for 3 min, and the inducer was then added. Values are presented as means ± s.e.m. (n = 3–4), [a], not determined. *$P < 0.01$, **$P < 0.001$ compared with the respective control.

NMR ($CDCl_3$): δ 1·30 (3H, t, J = 7·1 Hz, CH_3), 4·30 (2H, m, OCH_2), 4·53 (1H, dd, J = 2·9, 11·7 Hz, dioxane-H_A), 4·70 (1H, dd, J = 4·0, 11·7 Hz, dioxane-H_B), 5·00 (1H, dd, J = 2·9, 4·0 Hz, dioxane-H_X), other protons see Table 1; ^{13}C NMR ($CDCl_3$); see Table 2; Anal. ($C_{18}H_{14}O_6$) C, H.

Results and Discussion

Compounds *1* and *2* react with ethyl 2,3-dibromopropionic acid ethyl ester, to give two pairs of regioisomeric products *3a* (39%), *3b* (36%), and *4a* (9·6%), *4b* (62%) (Scheme 1) (Ertan et al 1987). Compounds *3a*, *3b*, *4a*, and *4b* were characterized by NMR spectrometry and the pair *3a*/*b* (and *4a*/*b*) are confirmed to be different compounds by mixed mp and mixed NMR spectra. The presence of an ethoxycarbonyl group at position 2 or 3 of the 1,4-dioxane ring in *3a* and *3b* induces a significant low-field shift of the nearest adjacent aromatic proton, H-1 or H-4, respectively (Table 1). This is in good agreement with those of benzodioxane derivatives of 3′,4′-dihydroxyflavone (Ertan et al 1987). The presence of an ethoxycarbonyl group at position 2 or 3 of the 1,4-dioxane ring in *4a* and *4b* did not induce a significant low-field shift of the nearest adjacent aromatic proton, H-2 (Table 1). Compounds *3a*, *3b*, *4a*, and *4b* were further characterized by ^{1}H-^{1}H, ^{13}C-^{1}H and ^{13}C-^{1}H long range COSY spectra. The ^{13}C NMR of these four compounds were assigned by DEPT pulse sequence, COSY spectra, and the chemical shift value compared with those for *1* or *2* (Table 2). The ^{13}C NMR spectrum also supported the structures elucidated as *3a*, *3b*, *4a* and *4b*. The coupling constants of the ABX spin systems of *3a*, *3b*, *4a*, and *4b* were determined directly from ABX signal patterns in the ^{1}H NMR spectra. As J_{AX} values of 2·9, 3·1, 2·9, and 2·9 Hz (Fig. 1) were found for the ABX spin systems in the ^{1}H NMR spectra of *3a*, *3b*, *4a*, and *4b*, respectively, the ethoxycarbonyl group can be assumed to occupy an axial position (Ertan et al 1987). This indicates that, of two possible half-chair conformations (Fig. 1), form A should predominate in the equilibrium at room temperature. This shows a good agreement with the results obtained for related benzodioxanes (Ertan et al 1987).

The antiplatelet effects of *3a*, *3b*, *4a*, and *4b* were studied on the aggregation of rabbit washed platelets induced by thrombin (0·1 units mL^{-1}), arachidonic acid (100 μM), collagen (10 μg mL^{-1}) and platelet-activating factor (PAF) (2 ng mL^{-1}) and the aggregation of human PRP induced by ADP (20 μM), collagen (10 μg mL^{-1}), and adrenaline (5 μM). As shown in Table 3, *3a* and *3b* (each 20 μM) showed potent antiplatelet effects on arachidonic acid- and collagen-induced aggregation. The antiplatelet effects of these two compounds were not studied at lower concentrations because the antiplatelet effects were decreased by prolonged incubation under



Compound	J_{AB}	J_{AX}	J_{BX}	Conformer
3a	11.7	2.9	4.0	A
3b	11.7	3.1	4.2	A
4a	11.7	2.9	3.8	A
4b	11.7	2.9	4.0	A

FIG. 1. Coupling constants (Hz) of ABX spin systems of *3a*, *3b*, *4a*, and *4b*.

Table 4. Effects of xanthone derivatives on the platelet aggregation induced by ADP, collagen, and adrenaline in human platelet – rich plasma (PRP).

Treatment	Aggregation		
	ADP (20 μM)	Collagen (10 μg mL^{-1})	Adrenaline (5 μM)
Control	88·8 ± 5·5	95·5 ± 0·5	91·0 ± 2·4
3a	84·5 ± 1·5	79·5 ± 5·2	44·7 ± 3·9***
3b	81·9 ± 1·9	95·5 ± 0·5	38·4 ± 6·8***
4a	69·0 ± 6·0	85·5 ± 2·4	21·2 ± 2·8***
4b	64·6 ± 4·8**	46·8 ± 12·7**	5·1 ± 3·0***
Aspirin	84·4 ± 1·2	74·0 ± 3·2	39·6 ± 15·4*

PRP was preincubated with DMSO (0·5%, control), xanthone derivatives (30 μM) or aspirin (50 μM) at 37°C for 3 min, and the inducer was then added. Values are presented as means ± s.e.m. (n = 3–6). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

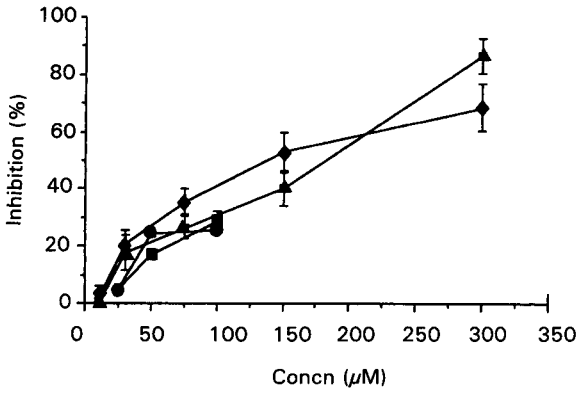


FIG. 2. Concentration-dependent inhibition of xanthone derivatives, *3a* (●), *3b* (■), *4a* (▲) and *4b* (◆) on the platelet aggregation induced by ADP of human platelet-rich plasma (PRP). PRP was incubated with various concentrations of xanthone derivatives or DMSO (0·5%) at 37°C for 3 min, and ADP (20 μM) was then added to trigger the aggregation. Values are presented as means ± s.e.m. (n = 3–6).

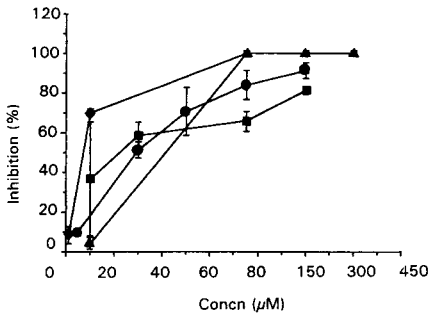


FIG. 4. Concentration-dependent inhibition of xanthone derivatives, *3a* (●), *3b* (■), *4a* (▲), and *4b* (◆) on the platelet aggregation induced by adrenaline in human platelet-rich plasma (PRP). PRP was incubated with various concentrations of xanthone derivatives or DMSO (0·5%) at 37°C for 3 min, and adrenaline (5 μM) was then added to trigger the aggregation. Values are presented as means ± s.e.m. (n = 3–6).

37°C. Although compound *4a* (300 μM) showed significant antiplatelet effects on thrombin-, arachidonic acid- and PAF-induced aggregation, the regioisomeric product, *4b*, in addition to showing significant antiplatelet effects on thrombin-, collagen-, and PAF-induced aggregation at high concentration (300 μM) indicated potent antiplatelet effect on arachidonic acid-induced aggregation at a lower concentration of 10 μM. This inhibition was concentration dependent (Table 3), and the IC50 value on aggregation of rabbit washed platelets was about 8·3 μM with a minimal effect at 5 μM and maximal effect at 20 μM. However, its inhibitory effect on arachidonic acid-induced aggregation was more marked above 10 μM but diminished rapidly below 10 μM. These results and a previous report (Lin et al 1993) indicated an ethoxycarbonyl-1,4-ethylenedioxyl moiety substituted at 3,4-dioxygenated xanthone enhanced the antiplatelet effect on arachidonic acid-induced aggregation. As can be seen from the data in Table 3, there are differences between the activity of isomers, *4a* and *4b*. Therefore *4a* and *4b* can be defined as specific antiplatelet agents.

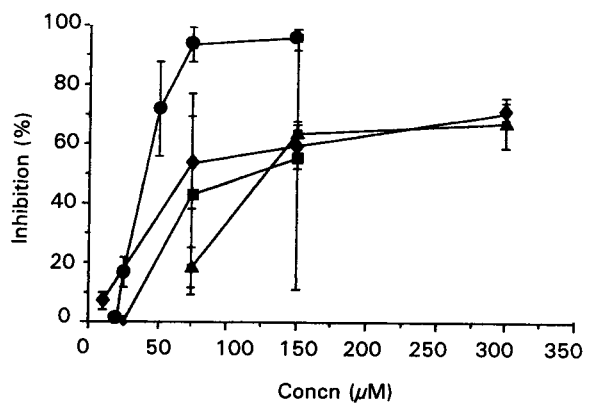


FIG. 3. Concentration-dependent inhibition of xanthone derivatives, *3a* (●), *3b* (■), *4a* (▲), and *4b* (◆) on the platelet aggregation induced by collagen in human platelet-rich plasma (PRP). PRP was incubated with various concentrations of xanthone derivatives or DMSO (0·5%) at 37°C for 3 min, and collagen (10 μg mL^{-1}) was then added to trigger the aggregation. Values are presented as means ± s.e.m. (n = 3–6).

Aspirin was used in this study as a positive control. It was found (Table 3) that aspirin (50 μM) inhibited completely the platelet aggregation induced by arachidonic acid but not that induced by collagen or PAF. The antiplatelet effects of *3a*, *3b*, *4a*, and *4b* were also studied on the aggregation of human PRP induced by ADP (20 μM), collagen (10 μg mL^{-1}), and adrenaline (5 μM). As shown in Table 4, although *4b* showed significant antiplatelet effects on ADP- and collagen-induced aggregation, *3a*, *3b*, *4a*, and *4b* (30 μM) all showed potent antiplatelet effects on adrenaline-induced aggregation. More experiments were performed to study the effects of *3a*, *3b*, *4a*, and *4b* on ADP-, collagen- and adrenaline-induced human platelet aggregation at various concentrations. These four compounds had almost the same potent antiplatelet effects (below 100 μM) when ADP was used as the aggregation agent (Fig. 2). In collagen-induced platelet aggregation, *3a* was more potent, whereas *3b*, *4a*, and *4b* had less potent antiplatelet effect (Fig. 3). In adrenaline-induced platelet aggregation, *4b* was more potent, but *3a*, *3b*, and *4a* had less potent antiplatelet effect (Fig. 4). Among the three inducers tested, adrenaline-induced aggregation was most easily inhibited by *4b* and the IC50 value was about 8·6 μM (Fig. 4). As shown in Figs 2–4 all four compounds had a nonspecific antiplatelet action when ADP was used as the aggregation agent; *3a* and *3b* had specific antiplatelet action when collagen was used as the aggregation agent; and *4a* and *4b* had a specific antiplatelet action when adrenaline was used as the aggregation agent.

In human PRP, all four compounds prevented secondary aggregation and suppressed the primary aggregation at higher concentrations induced by adrenaline (for example *4b* in Fig. 5). We conclude that their mechanism of action is chiefly due to the inhibition of thromboxane formation and interference in the adrenaline-receptor interaction (Mitchell & Sharp 1964; Macmillan 1966; Mustard et al 1975; Weiss 1983).

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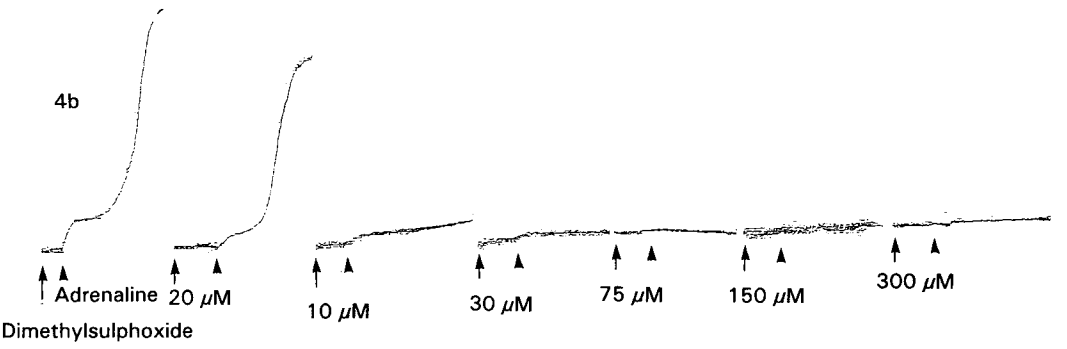

FIG. 5. Inhibitory effect of *4b* on the aggregation of human platelet-rich plasma (PRP) induced by adrenaline. PRP was incubated with DMSO (0·5%), various concentrations of *4b* for 3 min, then adrenaline (5 μM) was added to trigger the aggregation.

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