γ-Pyrone Compounds. IV: Synthesis and Antiplatelet Effects of Mono- and Dioxygenated Xanthones and Xanthonoxypropanolamine

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Abstract □ Xanthodilol, mono- and dioxygenated xanthones, and 1,3-, 2,3-, 3,4-, 3,5-, 1,6-, 2,6-, and 3,6-dioxygenated xanthones were synthesized from benzophenone precursors by Friedel–Crafts acylation and subsequent base-catalyzed cyclization to eliminate methanol. 3-Hydroxyxanthone, xanthodilol, 2,3-dihydroxyxanthone diacetate, and 3,4-dihydroxyxanthone and its diacetate showed potent antiplatelet effects on arachidonate- and collagen-induced aggregation. 3,5-Dihydroxyxanthone and its diacetate, 1,6-dimethoxyxanthone, and 3,6-dihydroxyxanthone and its diacetate showed potent antiplatelet effects on arachidonate-induced aggregation.

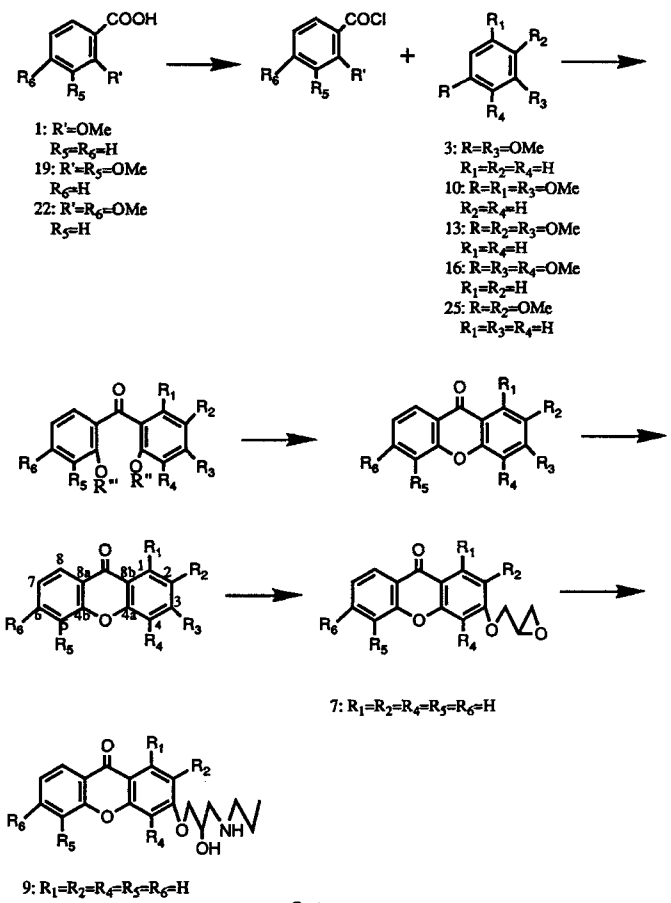
In a study of structure–activity relationships, we found that xanthone skeletons with 1,3,7-trioxygenated and 1,3,6,7-, 1,3,5,6-, 2,3,6,7-, and 3,4,6,7-tetraoxygenated xanthones possess antiplatelet effects and that the mechanism of action of 1,3,6,7-tetraoxygenated xanthones is due to both inhibition of thromboxane formation and phosphoinositide breakdown.[1–3] To study the structure–activity relationships of various xanthone derivatives and design of antithrombotic or/and antihypertensive agents, we synthesized 3-oxygenated xanthones, various dioxygenated xanthones, xanthonoxypropanolamines,[4] and xanthonoxyalkanolamines.[4,5]

Results and Discussion

Chemistry—3-Hydroxyxanthone, 1,3-, 2,3-, 3,4-, 3,5-, 1,6-, 2,6-, and 3,6-dihydroxyxanthones and their derivatives were synthesized (Scheme I) by a previously described method.[3] Synthesis of xanthodiol (**9**) or 3-[3-(propylamino)-2-hydroxypropoxy]xanthone (**9**; Scheme I) represents a typical example of the general synthesis of xanthonoxypropanolamines **9a**. 3-Hydroxyxanthone (**5H**) was allowed to react with 1 equivalent of sodium hydroxide in aqueous 2-propyl alcohol and an excess of epichlorohydrin (**6**) to yield the epoxide **7** as the major product. Ring-opening of the epoxide **7** with *n*-propylamine (**8**) in refluxing absolute ethanol afforded **9**.[4] The physical, spectral, and analytical data for the synthetic products and their derivatives are given in Tables I and II and the *Experimental Section*.

Pharmacology—The antiplatelet effects of **5M, 5H, 5A, 9, 12M, 12H, 12A, 15M, 15H, 15A, 18M, 18H, 18A, 21M, 21H, 21A, 24M, 24H, 24A, 27M, 27H, 27A, 29M, 29H,** and **29A** were studied on the aggregation of washed rabbit platelets induced by adenosine 5′-diphosphate (ADP; 20 μM), arachidonic acid (100 μM), platelet-activating factor (PAF; 2 ng/mL), and collagen (30 μM/mL). As shown in Table III, **5H** (300 μM/mL) showed significant antiplatelet effects on ADP-, arachidonic acid-, PAF-, and collagen-induced aggregation, but its acetate (**5A**, 300 μM/mL) and its *O*-methyl ether (**5M**, 300 μM/mL) did not enhance the antiplatelet effects. Although **12H** (300 μM/mL) only showed significant antiplatelet effects on collagen-induced aggregation and **15H** and **18H** only showed significant antiplatelet effects on arachidonate- and collagen-induced aggregation, the esterification of **12H, 15H,** and **18H** (to **12A, 15A,** and **18A**, respectively) at the same concentration very markedly enhanced the antiplatelet effects on arachidonate- and collagen-induced aggregation. The hydroxylated products of **5H**, with hydroxylation at C-2 and C-4 (**15H** and **18H**, respectively), did not enhance the antiplatelet effects, but **15H** and **18H** showed more specific antiplatelet effects because they inhibited aggregation induced only by arachidonic acid and collagen.

As shown in Table III, **21H** (<75 μM/mL), **21A** (300 μM/mL), **24M** (<75 μM/mL), **29H** (300 μM/mL), and **29A** (75 μM/mL) showed potent antiplatelet effects on arachidonate-induced aggregation. Esterification of **21H** and **29H** did not enhance the antiplatelet effects. From the antiplatelet effects



Scheme I

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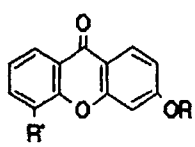
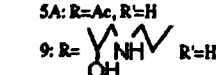
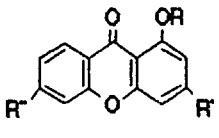
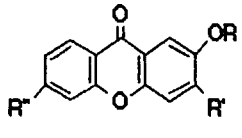
Table I—^{1}H NMR Data for Various Xanthone Derivatives



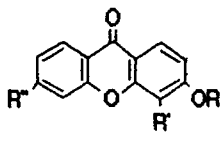
5: R=Me, R'=H
5H: R=H, R'=H
5A: R=Ac, R'=H
9: R=  R'=H
21H: R=H, R'=OH
21A: R=Ac, R'=OAc



12H: R=H, R'=OH, R"=H
12A: R=Ac, R'=OAc, R"=H
24M: R=Me, R'=H, R"=OMe
24H: R=R'=H, R"=OH
24A: R=Ac, R'=H, R"=OAc



15M: R=Me, R'=OMe, R"=H
15H: R=R"=H, R'=OH
15A: R=Ac, R'=OAC, R"=H
27H: R=R'=H, R"=OH
27A: R=Ac, R'=H, R"=OAc



18H: R=R"=H, R'=OH
18A: R=Ac, R'=OAc, R"=H
29H: R=R'=H, R"=OH
29A: R=Ac, R'=H, R"=OAc

Compound	H-1	H-2	H-3	H-4	H-5	H-6 H-7	H-8	OH(alls)	OMe(alls)	OAc(als)
5M	8.23(d)	6.92(dd)		6.85(d)	7.66(m)	7.35(m)	8.31(dd)		3.91	
5H	8.04(d)	6.91(dd)		6.87(d)	7.82(m)	7.43(m) 7.59(m)	8.16(dd)			
5A	8.36(d)	7.13(dd)		7.31(d)	7.72(m)	7.39(m) 7.48(m)	8.33(dd)			2.37
12M		6.29(d)		6.43(d)	7.60(m)	7.29(m)				
12H		6.19(d)		6.36(d)	7.81(m)	7.43–7.55(m)	8.08(dd)	12.79		
12A		6.84(d)		7.26(d)	7.67–7.72(m)	7.33–7.44(m)	8.25(dd)			2.35, 2.50
15H	7.46(s)			6.92(s)	7.31–7.36(m)	7.37–7.57(m)	8.13(dd)			
15A	8.11(s)			7.43(s)	7.69–7.75(m)	7.36–7.48(m)	8.30(dd)			2.33, 2.34
18M	8.09(d)	7.02(d)			7.69–7.74(m)	7.57(m) 7.34–7.40(m)	8.32(dd)		4.02, 4.04	
18H	7.57(d)	6.94(d)			7.80–7.86(m)	7.63(m) 7.41–7.46(m)	8.15(dd)			
18A	8.24(d)	7.23(d)			7.68–7.74(m)	7.36–7.47(m)	8.31(dd)			2.36, 2.46
21M	8.22(d)	6.92(dd)		6.98(d)		7.19(dd) 7.25(dd)	7.88(dd)		3.90, 4.02	
21H	8.03(d)	6.90(dd)		6.90(d)		7.27(dd) 7.22(dd)	7.56(dd)			
21A	8.28(d)	7.08(dd)		7.27(d)		7.43(dd) 7.30(dd)	8.15(dd)			2.29, 2.39
24M		6.74(dd)	7.50(t)	6.95(dd)	6.74(d)	6.85(dd)	8.16(d)		3.86, 3.97	
24H		6.77(dd)	7.66(t)	7.00(dd)	6.86(d)	6.93(dd)	8.02(d)	12.84		
24A		7.01(dd)	7.69(t)	7.40(dd)	7.28(d)	7.11(dd)	8.26(d)			2.36, 2.49
27M	7.66(d)		7.24(dd)	7.34(d)	6.80(d)	6.90(dd)	8.21(d)		3.89	
27H	7.44(d)		7.24(dd)	7.46(d)	6.83(d)	6.88(dd)	8.01(d)			
27A	8.01(d)		7.47(dd)	7.51(d)	7.32(d)	7.14(dd)	8.34(d)			2.35, 2.37
29M	8.23(d)	6.93(dd)			6.84(d)	6.93(dd)	8.23(d)		3.93	
29H	7.98(d)	6.86(dd)			6.82(d)	6.86(dd)	7.98(d)			
29A	8.36(d)	7.16(dd)			7.32(d)	7.16(dd)	8.36(d)			2.38

of **21H**, **21A**, **24M**, **29M**, and **29A**, it is clear that an additional oxygenated group substituted at C-5 or C-6 of 1- or 3-oxygenated xanthone markedly changes the quality of antiplatelet effects. The results shown in Table III and previous reports[1–3] indicate the oxygenated group of C-3 in the xanthone skeleton as the important moiety related to the antiplatelet effects.

Indomethacin was used in this study as a positive control. Indomethacin (20 μM) completely inhibited the platelet aggregation induced by arachidonic acid, slightly inhibited that induced by collagen, but did not affect that induced by ADP and PAF (Table III).

More experiments were performed to study the effects of mono- and dioxygenated xanthones on arachidonate- or collagen-induced platelet aggregation at various concentrations. In comparison with previously reported norathyriol tetraacetate (**30A**),[2] **15A** had almost the same potent antiplatelet effects but **18A** and **24M** had less potent antiplatelet effects when arachidonic acid (100 μM) was used as the aggregation agent (Figure 1). In collagen-induced platelet aggregation, **15A** was more potent, whereas **18A** and **24M** were less potent than **30A** (Figure 2). The antiplatelet action of **18H** is probably due to the inhibition of thromboxane synthetase to thromboxane A_2 formation.[5] However, based on the results with aggregation induced by various inducers, the above xanthones and xanthone derivatives may have different mechanisms and selectivities. Further experiments are required to elucidate the differences in the mechanism of action.

Flavonoxypropanolamines (**31**) and [2-(ω-aminoalkoxy)-phenyl]ethyl]benzenes (**32**) showed potent antihypertensive activity and antiplatelet effects on collagen-induced aggregation, respectively.[4,6] Given the above results, **9** was synthesized from **5H** and, at a concentration of 300 μM/mL, **9** exhibited slightly more potent antiplatelet effects than **5H** and almost the same antiplatelet effects as **18A** when collagen (10 μg/mL) was used as the aggregation agent (Table III, Figure 2).

Experimental Section

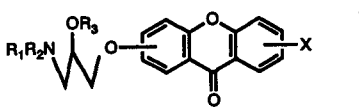
All mps were uncorrected. The IR spectra were recorded on a Hitachi model 260-30 IR spectrophotometer. The UV absorption spectra were measured on a Beckman model 34 spectrophotometer. The ^{1}H and ^{13}C NMR spectra [δ (ppm), J (Hz)] were determined with a VXR-300 MHz Fourier transform (FT)-NMR. Mass spectra were determined on a Jeol JMS-D-100 mass spectrometer. Elemental analyses were with ±0.4% of the theoretical value when indicated by symbols of the element, unless otherwise noted.

2-Hydroxy-4-methoxy-2'-methoxybenzophenone (4a) and 2,4-Dimethoxy-2'-hydroxybenzophenone (4b)—2-Methoxybenzoic acid (**1**, 2.0 g, 13.14 mmol) in dry C_6H_6 (60 mL) was treated with 5.0 mL of oxalyl chloride under an Ar atmosphere and thoroughly stirred at room temperature.[7] After 2 h, the solvent and the excess reagent were removed under reduced pressure. The residue, 2-methoxybenzoyl chloride (**2**), was dissolved in anhydrous Et_2O (80 mL) and 1,3-dimethoxybenzene (**3**, 1.8 g, 13.03 mmol) and $AlCl_3$ (5.0 g) were added.[7] After stirring for 8 h at room temperature, the mixture was

Table II—^{13}C NMR Data for Various Xanthone Derivatives[a]

Compound	C-1	C-2	C-3	C-4	C-4a	C-4b	C-5	C-6	C-7	C-8	C-8a	C-8b	C = O	OMe	OAc
5A	128.2	117.9	156.3	110.8	156.8	155.5	118.1	134.8	124.1	126.7	121.8	119.7	176.3		21.2, 168.4
12A	151.1	112.6	154.7	108.8	157.7	155.3	117.5	134.8	124.3	126.5	122.1	112.9	175.0		21.1, 167.9, 169.3
15M	105.4	152.4	155.4	99.6	146.7	156.0	117.6	133.9	123.7	126.5	121.5	114.9	176.0	56.3, 56.4	
15H	108.9	151.3	154.3	103.0	144.1	155.7	118.0	134.4	123.9	125.9	121.0	113.8	174.8		
15A	117.9	138.9	147.5	113.0	153.9	156.2	120.7	135.0	124.3	126.7	121.3	119.9	175.8		20.5, 20.7, 167.3, 168.1
18M	122.4	108.6	156.1	136.4	150.6	157.5	118.0	134.5	123.9	126.6	121.5	116.8	176.5	56.4, 61.5	
18H	116.8	113.4	151.8	132.9	146.6	155.8	118.2	135.0	124.2	126.1	121.1	115.0	175.6		
18A	117.9	124.5	147.5	131.2	149.4	155.7	118.6	135.0	124.3	126.7	121.5	120.6	175.9		20.2, 20.6, 167.2, 167.4
21M	128.0	113.8	165.0	100.2	157.8	146.4	148.4	117.6	123.3	115.0	122.8	115.6	176.1	55.8, 56.4	
21H	128.2	114.1	164.1	102.4	157.6	145.3	146.6	120.0	124.0	114.4	122.6	115.5	175.3		
21A	128.3	124.2	155.6	110.9	156.1	148.3	139.1	127.9	123.6	118.5	123.1	119.4	175.7		20.6, 21.1, 168.3, 168.4
24M	160.7	109.8	134.2	105.5	158.1	156.7	99.5	164.5	112.8	128.2	116.9	112.5	175.6	55.7, 56.3	
24H	161.3	110.4	136.9	107.2	158.1	156.0	102.3	165.2	114.7	127.7	112.7	108.1	180.9		
24A	150.1	118.3	134.6	110.4	157.4	155.9	116.1	155.5	118.4	128.1	115.0	120.0	175.0		21.2, 168.4, 169.7
27M	106.8	155.9	124.0	119.0	150.9	157.9	99.9	164.8	113.2	128.1	115.2	122.2	176.0	55.7, 55.8	
27H	109.0	154.0	123.8	119.3	149.4	157.8	102.1	164.0	114.1	128.1	113.7	122.0	175.0		
27A	118.6	146.7	128.9	119.2	153.7	156.7	110.8	155.6	118.4	128.2	119.1	122.3	175.7		21.0, 21.2, 168.4, 169.3
29M	128.1	112.8	164.6	100.2	158.0	158.0	100.2	164.6	112.8	128.1	115.8	115.8	175.5	55.7	
29H	128.0	113.9	163.6	102.3	157.7	157.7	102.3	163.6	113.9	128.0	114.2	114.2	174.2		
29A	128.2	118.4	155.5	110.8	156.8	156.8	110.8	155.5	118.4	128.2	119.5	119.5	175.5		21.1, 168.4

[a] References 8–11.



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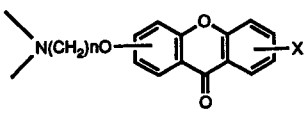

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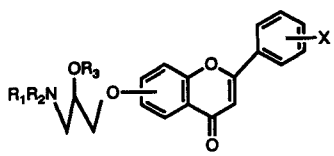

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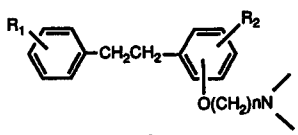

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hydrolyzed with ice-cold H_2O (500 mL) containing concentrated HCl (45 mL) and extracted with $CHCl_3$. Solvent removal gave a crude product that was purified by column chromatography (silica gel-$CHCl_3$) to yield 4 as a yellow oil (crystallized from MeOH; 2.20 g, 8.53 mmol, 65%); ^1H NMR ($CDCl_3$): δ 3.76, 3.82 (2s, 12H, 4OMe), 6.33 (dd, J = 8.5 and 2.4 Hz, 2H, H-5 of **4a** and **4b**), 6.47 (d, J = 2.4 Hz, 2H, H-3 of **4a** and **4b**), 7.01 (m, 4H, aromatic H), 7.24 (m, 4H, aromatic H), 7.42 (m, 2H, aromatic H), and 12.72 (s, 2H, 2OH of **4a** and **4b**, D_2O exchangeable).

3-Methoxyxanthone (5M)—Compound 4 (2.20 g, 8.53 mmol) was treated with pyridine (100 mL), H_2O (50 mL), and aqueous 10% tetramethylammonium hydroxide (45 mL). The mixture was refluxed for 36 h,[7] poured onto ice, acidified with HCl, and extracted with Et_2O. This procedure yielded an oil that, after purification by column chromatography (silica gel-$CHCl_3$) and crystallization from $CHCl_3$, yielded **5M** as a colorless powder (1.60 g, 7.08 mmol, 83%); mp 116–117 °C; MS: m/z (%) 226 (100) (M^+); IR (KBr): 1650 cm^{-1}; ^1H NMR ($CDCl_3$); see Tables I and II; ^{13}C NMR ($CDCl_3$): data identical to those reported in literature.[8]

Anal.—Calcd for $C_{14}H_{10}O_3$: C, H.

3-Hydroxyxanthone (5H)—A mixture of **5M** (1.60 g, 7.08 mmol), phenol (42 mL), and **HI** (35 mL) was refluxed at 160 °C for 8 h, and the reaction mixture was poured into aqueous $NaHSO_3$ solution. The resulting yellow precipitate was collected, purified by silica gel column chromatography ($CHCl_3$:MeOH, 4:1), and crystallized from MeOH to give **5H** as yellow needles (1.40 g, 6.60 mmol, 93%): mp 241–242 °C; MS: m/z (%) 212 (100) (M^+); UV: λ_{max} (MeOH) (log ϵ) 235 (4.06), 265 (sh) (3.39), and 330 (3.59) nm; λ_{max} (MeOH + NaOAc) 230, 265 (sh), and 335 nm; IR (KBr): 3115 and 1615 cm^{-1}; ^1H NMR [dimethyl sulfoxide (DMSO)-d_6]: see Tables I and II; ^{13}C NMR (DMSO-d_6): data identical to those reported in literature.[9]

Anal.—Calcd for $C_{13}H_8O_3$: C, H.

3-Hydroxyxanthone acetate (5A)—A solution of **5H** (0.2 g, 0.94 mmol) in 10 mL of anhydrous pyridine was treated with 10 mL of acetic anhydride in a water bath for 4 h. The reaction mixture was concentrated under reduced pressure to remove the excess solvent, and water was added to destroy the excess acetic anhydride. The residue was concentrated under reduced pressure to give crude **5a**. Purification by column chromatography (silica gel-$CHCl_3$) and crystallization from MeOH gave **5a** as colorless needles (0.22 g, 0.87 mmol, 92%); mp 148–149 °C; MS: m/z (%) 254 (30) (M^+), 212 (100); IR (KBr): 1755, 1665, and 1610 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{15}H_{10}O_4$: C, H.

3-(2,3-Epoxypropoxy)xanthone (7)—To a solution of 0.19 g (4.71 mmol) of sodium hydroxide in 1.3 mL of water were added 6.18 mL of 2-propyl alcohol and then 1.00 g (4.72 mmol) of **5H**. To the above mixture was then added 3.76 mL (46.86 mmol) of epichlorohydrin (**6**), and the mixture was heated at 70 °C for 2 h with stirring. The hot reaction mixture was filtered to remove a dimeric byproduct (a glycidyl ether[4]). The filtrate was concentrated under reduced pressure at 50–60 °C. The semisolid residue was treated with 10 mL of refluxing 2-propyl alcohol, and more of the dimer was filtered off from the hot mixture. The clear filtrate, on cooling, yielded a solid. This solid was collected, washed with 1.4 mL of 2-propyl alcohol and air dried to yield 945 mg (4.46 mmol, 74%) of a tan-colored product.[4] This product was purified by column chromatography (silica gel-CH_2Cl_2) and crystallized from CH_2Cl_2 to give **7** as a colorless powder; mp 157–158 °C; MS: m/z (%) 268 (100) (M^+); IR (KBr): 1645 and 1265 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.79–2.99 (m, CH_2 in the epoxide ring), 3.42 (m, 1H, CH in the epoxide ring), 4.05 (dd, J = 11 and 6.0 Hz, 1H, OC*H*H), 4.39 (dd, J = 11 and 3.0 Hz, 1H, OCH*H*), 6.91 (d, J = 2.4 Hz, 1H, H-4), 6.95 (dd, J = 9.0 and 2.4 Hz, 1H, H-2), 7.27–7.47 (m, 2H, H-6 and H-7), 7.65–7.70 (m, 1H, H-5), 8.26 (d, J = 9.0 Hz, 1H, H-1), and 8.32 (dd, J = 9.0 and 1.5 Hz, 1H, H-8)[4]; ^{13}C NMR ($CDCl_3$): δ 44.5 (CH_2 in the epoxide ring), 49.7 (CH in the epoxide ring), 69.2 (OCH_2), 101.1 (C-4), 113.4 (C-2), 116.2 (C-8b), 117.7 (C-5), 121.9 (C-8a), 123.9 (C-7), 126.6 (C-8), 128.4 (C-1), 134.3 (C-6), 156.2 (C-4b), 157.9 (C-4a), 163.7 (C-3), and 176.2 (CO).[8–10]

Anal.—Calcd for $C_{16}H_{12}O_4$: C, H.

3[3-(Propylamino)-2-hydroxypropoxy]xanthone (9)—To 20.0 mL (244 mmol) of *n*-propylamine (**8**) were added 900 mg (3.36 mmol) of **7** and 20 mL of absolute ethanol. The mixture was heated at 50–55 °C for 1.5 h with stirring. The reaction mixture was clarified by filtration, and the filtrate was concentrated under reduced pressure. The product was filtered, washed with absolute ethanol, purified by column chromatography (silica gel:$CHCl_3$:MeOH, 9:1) and crystallized from $CHCl_3$ to yield **9** as a pale yellow powder (0.60 g, 1.85 mmol, 55%); mp 109–110 °C; MS: m/z (%) 328 (3) ($M+1)^+$, 327 (3) (M^+) 298

Table III—Effect of Various Xanthone Derivatives on the Platelet Aggregation Induced by ADP, Arachidonic Acid, Collagen, and PAF[a]

Compound	Platelet Aggregation (% of control) Induced by:			
	ADP	Arachidonic Acid	Collagen	PAF
DMSO (control)	80.6 ± 1.08 (6)	86.4 ± 1.0 (6)	93.1 ± 2.1 (5)	94.3 ± 0.1 (6)
5M	—[b]	29.5 ± 9.9 (3)[c]	44.5 ± 5.0 (3)[c]	90.1 ± 2.2 (3)
5H	9.7 ± 4.9 (3)[c]	0.0 ± 0.0 (3)[c]	5.6 ± 3.0 (3)[c]	18.5 ± 5.1 (3)[c]
5A	—	74.2 ± 7.0 (3)	76.0 ± 3.0 (3)[d]	80.8 ± 5.6 (3)
9	30.7 ± 11.9 (3)[c]	0.0 ± 0.0 (3)[c]	2.8 ± 2.3 (3)[c]	33.5 ± 12.6[d]
12H	—	84.4 ± 3.7 (3)	63.5 ± 1.5 (3)[c]	90.9 ± 0.7
12A	71.8 ± 8.0	38.4 ± 19.2 (4)[e]	43.3 ± 10.0 (3)[c]	87.5 ± 2.7 (3)
15M	—	45.5 ± 11.4 (3)[c]	15.6 ± 1.7 (3)[c]	79.3 ± 7.1 (3)[e]
15H	—	43.0 ± 15.7 (5)[e]	16.2 ± 8.3 (3)[c]	92.0 ± 1.6 (3)
15A	—	0.0 ± 0.0 (3)[c]	2.6 ± 2.1 (3)[c]	87.4 ± 1.5 (3)
18H	—	2.7 ± 1.1 (3)[c]	8.8 ± 3.7 (3)[c]	90.6 ± 1.3 (3)
18A	73.2 ± 3.6 (3)	0.0 ± 0.0 (3)[c]	7.3 ± 2.7 (3)[c]	70.8 ± 2.3 (3)[c]
21H	—	7.0 ± 1.1 (3)[c]	85.6 ± 1.7 (3)[e]	88.6 ± 1.0 (3)
21A	—	1.3 ± 1.1 (3)[c]	88.9 ± 2.1 (3)	89.2 ± 2.4 (3)
24M	—	7.5 ± 6.1 (3)[c]	53.5 ± 3.8 (3)[c]	84.4 ± 2.7 (3)[e]
24H	—	83.7 ± 2.1 (3)	86.6 ± 0.3 (3)[c]	88.7 ± 3.0 (3)
24A	—	82.0 ± 2.4 (3)	77.0 ± 8.4 (3)[e]	85.2 ± 2.5 (3)
27H	—	79.2 ± 3.6 (3)	80.9 ± 6.3 (3)	83.2 ± 6.6 (3)
27A	—	83.2 ± 0.9 (3)	88.1 ± 0.5 (3)	88.2 ± 2.5 (3)
29H	—	0.0 ± 0.0 (3)[c]	83.6 ± 2.1 (3)[e]	90.8 ± 0.3 (3)
29A	—	1.3 ± 1.1 (3)[c]	84.7 ± 1.3 (3)[d]	87.4 ± 1.6 (3)
Indomethacin	69.5 ± 7.2 (3)	0.0 ± 0.0[c]	72.3 ± 6.0 (3)[e]	89.4 ± 0.4 (3)

[a] Platelets were preincubated with **5M** (300 μM/mL), **5H** (300 μM/mL), **5A** (300 μM/mL), **9** (300 μM/mL), **12H** (300 μM/mL), **12A** (300 μM/mL), **15M** (300 μM/mL), **15H** (300 μM/mL), **15A** (150 μM/mL), **18H** (300 μM/mL), **18A** (300 μM/mL), **21H** (<75 μM/mL), **21A** (300 μM/mL), **24M** (<75 μM/mL), **24H** (150 μM/mL), **24A** (300 μM/mL), **27H** (300 μM/mL), **27A** (75 μM/mL), **29H** (300 μM/mL), **29A** (75 μM/mL), Indomethacin (20 μM/mL) or DMSO (0.5%, control) at 37 °C for 3 min; then, ADP (20 μM), arachidonic acid (AA, 100 μM), collagen (10 μg/mL), or PAF (2 ng/mL) was added; percentages of aggregation are presented as means ± standard errors of the mean (n). [b] —, Not determined. [c] Significantly different compared with control ($p < 0.001$). [d] Significantly different compared with control ($p < 0.01$). [e] Significantly different compared with control ($p < 0.05$).

(10), 283 (19), 212 (44), 72 (100). IR (KBr): 3525, 3275, 1670, and 1660 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (t, J = 7.2 Hz, 3H, CH_3), 1.55 (qt, J = 7.2 Hz, 2H, CH_2CH_3), 2.64 (dt, J = 12.2 and 7.2 Hz, 1H, CH_2CHHNH), 2.65 (dt, J = 12.2 and 7.2 Hz, 1H, CH_2CHHNH), 2.78 (dd, J = 12.2 and 7.2 Hz, 1H, *H*CHCHOH), 2.90 (dd, J = 12.2 and 3.5 Hz, 1H, HC*H*CHOH), 4.11 (s, 3H, C*H*(OH) and CH_2O), 6.90 (d, J = 2.2 Hz, 1H, H-4), 6.95 (dd, J = 9.0 and 2.2 Hz, H-2), 7.32–7.46 (m, 2H, H-6 and H-7), 7.70 (m, 1H, H-5), 8.24 (d, J = 9.0 Hz, H-1), 8.31 (dd, J = 9.0 and 2.2 Hz, 1H, H-8)[4]; ^{13}C NMR ($CDCl_3$): δ 11.7 (CH_3), 23.2 (CH_2CH_3), 51.5 (CH_2CHOH), 51.7 (CH_2CH_2NH), 67.9 (OCH_2), 71.1 (CHOH), 100.9 (C-4), 113.5 (C-2), 115.9 (C-8b), 117.7 (C-5), 121.9 (C-8a), 123.9 (C-7), 126.6 (C-8), 128.3 (C-1), 134.3 (C-6), 156.2 (C-4b), 157.9 (C-4a), 164.1 (C-3), and 176.3 (CO).[8-10]

Anal.—Calcd for $C_{19}H_{21}O_4N \cdot H_2O$: C, H.

4,6-Dimethoxy-2-hydroxy-2′-methoxybenzophenone (11a) and 2,4,6-Trimethoxy-2′-hydroxybenzophenone (11b)—Compound **1** (2.00 g, 13.14 mmol) was treated as in **4a** and **4b** and reacted with 1,3,5-trimethoxybenzene (**10**; 2.19 g, 13.04 mmol) as in **4a** and **4b** to yield **11** as a pale yellow powder (crystallized from MeOH; 2.20 g, 7.75 mmol, 59%); ^1H NMR ($CDCl_3$); δ 3.64, 3.67, 3.77, 3.81, (4s, 18H, 6OMe), 5.81 (d, J = 2.4 Hz, 2H, H-5 of **11a** and **11b**), 6.09 (d, J = 2.4 Hz, 2H, H-3 of **11a** and **11b**), 6.36–6.72 (m, 8H, H-3′-H-6′ of **11a** and **11b**), and 13.48 (s, 2H, 2OH of **11a** and **11b**, D_2O exchangeable).

1,3-Dimethoxyxanthone (12M)—Compound **11** (2.20 g, 7.75 mmol) was treated as in **5M** to yield **12** as a colorless powder (crystallized from $CHCl_3$; 1.65 g, 6.45 mmol, 83%); mp 170–171 °C; MS: *m/z* (%) 256 (100) (M^+); IR (KBr): 1660 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): data identical to those reported in literature.[8]

Anal.—Calcd for $C_{15}H_{12}O_4 \cdot 1/3H_2O$: C, H.

1,3-Dihydroxyxanthone (12H)—Compound **12M** (1.65 g, 6.45 mmol) was treated as in **5H** to yield **12H** as a yellow powder (1.40 g, 6.14 mmol, 95%); mp 257–258 °C; MS: *m/z* (%) 228 (100) (M^+); UV: λ_{max} (MeOH) (log ε) 210 (4.00), 235 (4.21), 255 (sh) (4.05), 305 (3.85), and 345 (3.42) nm; λ_{max} (MeOH + $AlCl_3$) 218, 235 (sh) 265, 328, and 395 nm; λ_{max} (MeOH + NaOAc) 210, 235, 270 (sh), and 350 nm; IR (KBr): 3200 and 1620 cm^{-1}; ^1H NMR (DMSO-d_6); see Tables I and II; ^{13}C NMR (DMSO-d_6): data identical to those reported in literature.[9]

Anal.—Calcd for $C_{13}H_8O_4$: C, H.

1,3-Dihydroxyxanthone Diacetate (12A)—Compound **12H** (0.2 g, 0.88 mmol) was treated as in 7 to yield **12A** as colorless needles (0.22 g, 0.71 mmol, 80%); mp 116–118 °C; MS: *m/z* (%) 312 (6) (M^+); IR

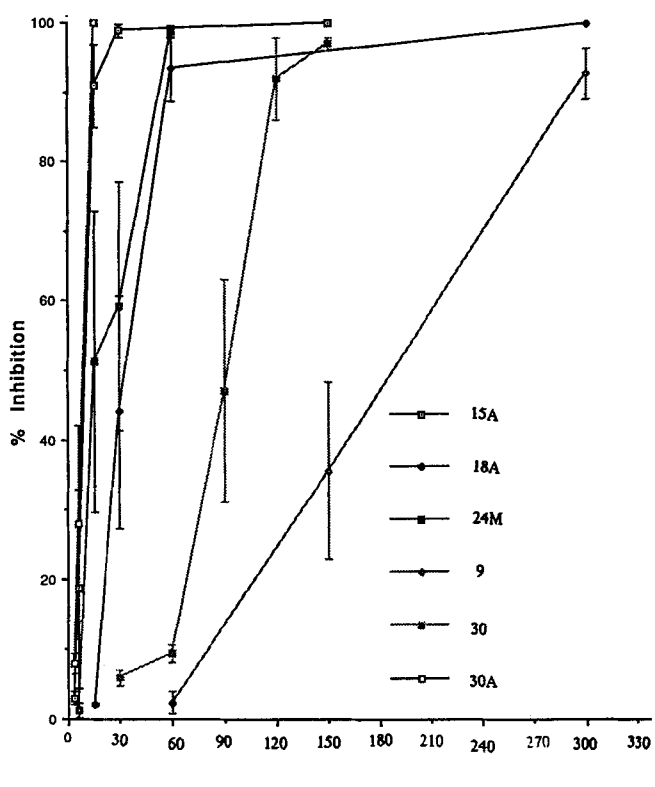

Figure 1—Effect of xanthone derivatives on the platelet aggregation induced by arachidonic acid. Washed rabbit platelets were incubated with various concentrations of **9**, **15A**, **18A**, and **24M**, then arachidonic acid (100 μM) was added to trigger the aggregation. Percent inhibitions are presented as means ± standard errors (n = 3–4).

(KBr): 1780 and 1670 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{17}H_{12}O_6$: C, H.

4,5-Dimethoxy-2-hydroxy-2′-methoxybenzophenone (14a) and 2,4,5-Trimethoxy-2′-hydroxybenzophenone (14b)—Compound **1** (2.00 g, 13.14 mmol) was treated as in **4a** and **4b** and reacted with 1,2,4-trimethoxybenzene (**13**; 2.19 g, 13.04 mmol) as in **4a** and **4b** to yield **14** as a yellow oil (2.10 g, 7.39 mmol, 56%); ^1H NMR ($CDCl_3$): δ 3.62, 3.74, 3.77, 3.83, 3.90 (5S, 18H, 6OMe), 6.50 (s, 2H, H-3 of **14a** and **14b**), 6.72–6.98 (m, 4H, aromatic H), 7.02, (s, 2H, H-6 of **14a** and **14b**), 7.24–7.43 (m, 4H, aromatic H), and 12.96 (s, 2H, 2OH of **14a** and **14b**, D_2O exchangeable).

2,3-Dimethoxyxanthone (15M)—Compound **14** (2.10 g, 7.39 mmol) was treated as in **5M** to yield **5M** as a colorless powder (crystallized from $CHCl_3$; 1.50 g, 5.86 mmol, 79%); mp 157–158 °C; MS: *m/z* (%) 256 (100) (M^+); IR (KBr): 1650 cm^{-1}; ^1H NMR ($CDCl_3$): data identical to those reported in literature[7]; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{15}H_{12}O_4$: C, H.

2,3-Dihydroxyxanthone (15H)—Compound **15M** (1.50 g, 5.86 mmol) was treated as in **5H** to yield **15H** as a pale yellow powder (crystallized from $CHCl_3$-MeOH; 1.25 g, 5.48 mmol, 94%); mp 293–295 °C; MS: *m/z* (%) 228 (100) (M^+); UV: λ_{max} (MeOH) (log ε) 205 (4.03), 220 (4.03), 240 (4.09), 270 (sh) (3.45), 310 (3.64), and 355 (3.53) nm; λ_{max} (MeOH + NaOAc) 230, 265 (sh), and 375 nm; λ_{max} (MeOH + NaOAc + H_3BO_3) 205, 225, 240 (sh), 327, and 370 nm; IR (KBr): 3200 and 1620 cm^{-1}; ^1H NMR (DMSO-d_6): see Tables I and II; ^{13}C NMR (DMSO-d_6): see Tables I and II.

Anal.—Calcd for $C_{13}H_8O_4 \cdot 1/2H_2O$: C, H.

2,3-Dihydroxyxanthone Diacetate (15A)—Compound **15H** (0.20 g, 0.88 mmol) was treated as in **5A** to yield **15A** as a colorless powder (crystallized from MeOH; 0.23 g, 0.74 mmol, 83%); mp 185–186 °C;

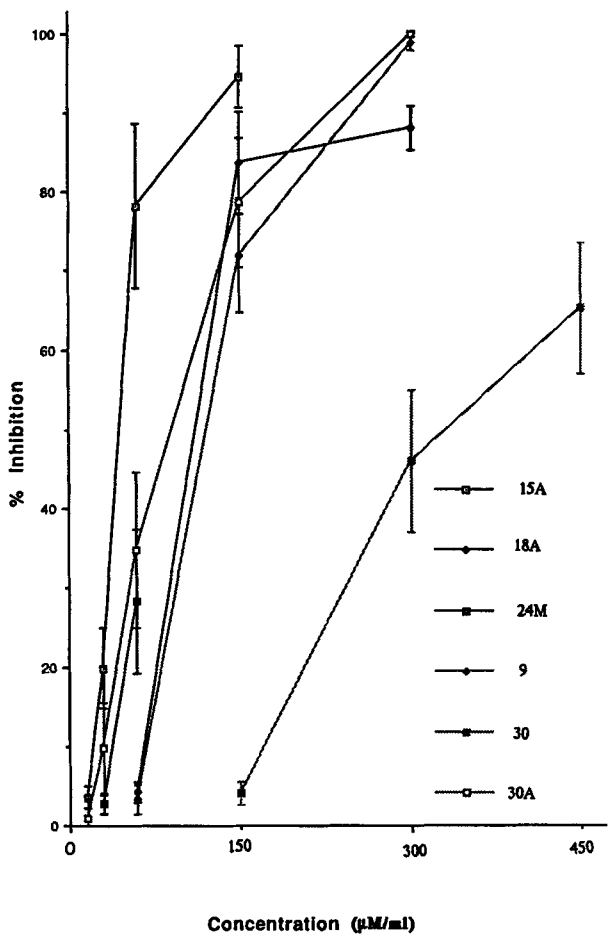

Figure 2—Effect of xanthone derivatives on the platelet aggregation induced by collagen. Washed rabbit platelets were incubated with various concentrations of **9**, **15A**, **18A**, and **24M**, then collagen (10 μg/mL) was added to trigger the aggregation. Percent inhibitions are presented as means ± standard errors (n = 3–4).

MS: *m/z* (%) 312 (7) (M^+); IR (KBr): 1770 and 1670 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd from $C_{17}H_{12}O_6$: C, H.

3,4-Dimethoxy-2-hydroxy-2′-methoxybenzophenone (17a) and 2,3,4-Trimethoxy-2′-hydroxybenzophenone (17b)—Compound **1** (2.00 g, 13.14 mmol) was treated as in **4a** and **4b** and treated with 1,2,3-trimethoxybenzene (**16**; 2.19 g, 13.04 mmol) as in **4a** and **4b** to yield **17** as a pale yellow oil (2.10 g, 7.39 mmol, 56%); ^1H NMR ($CDCl_3$: δ 3.77, 3.90, 3.92, 4.05 (4S, 18H, 6OMe), 6.40 (d, J = 9.0 Hz, 2H, H-5 of **17a** and **17b**), 6.99–7.07 (m, 2H, H-5′ of **17a** and **17b**), 7.10 (d, J = 9.0 Hz, 2H, H-6 of **17a** and **17b**), 7.24–7.29 (m, 2H, H-4′ of **17a** and **17b**), 7.43–7.49 (m, 2H, H-3′ of **17a** and **17b**), 8.15 (dd, J = 8.0 and 1.8 Hz, 2H, H-6′ of **17a** and **17b**), 12.52 (s, 2H, 2OH of **17a** and **17b**, D_2O exchangeable).

3,4-Dimethoxyxanthone (18M)—Compound **17** (2.10 g, 7.39 mmol) was treated as in **5M** to yield **18M** as a colorless powder (crystallized from $CHCl_3$; 1.60 g, 6.25 mmol, 84%); mp 141–143 °C; MS: *m/z* (%) 256 (100) (M^+); IR (KBr): 1665 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{15}H_{12}O_4$: C, H.

3,4-Dihydroxyxanthone (18H)—Compound **18M** (1.60 g, 6.25 mmol) was treated as in **5H** to yield **18H** as a pale yellow powder (crystallized from MeOH; 1.35 g, 5.92 mmol, 95%); mp 238–240 °C; MS: *m/z* (%) 228 (100) (M^+); UV: λ_{max} (MeOH) (log ε) 207 (3.80), 237 (4.18), 255 (4.08), 285 (sh) (3.49), and 315 (3.74) nm; λ_{max} (MeOH + NaOAc) 205, 235, 255 (sh), 288 (sh), and 320 nm; λ_{max} (MeOH + NaOAc + H_3BO_3) 208, 235, 265, 285 (sh), and 320 nm; IR (KBr): 3200 and 1640 cm^{-1}; ^1H NMR (DMSO-d_6): see Tables I and II; ^{13}C NMR (DMSO-d_6): see Tables I and II.

Anal.—Calcd for $C_{13}H_8O_4$: C, H.

3,4-Dihydroxyxanthone Diacetate (18A)—Compound **18H** (0.20 g, 0.88 mmol) was treated as in **7** to yield **18A** as a colorless powder (crystallized from MeOH; 0.21 g, 0.67 mmol, 76%); mp 157–159 °C; MS: *m/z* (%) 312 (36) (M^+); IR (KBr): 1805, 1780, and 1670 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{17}H_{12}O_6$: C, H.

2-Hydroxy-4-methoxy-2′,3′-dimethoxybenzophenone (20a) and 2,4-Dimethoxy-2′-hydroxy-3′-methoxybenzophenone (20b)—2,3-Dimethoxybenzoic acid (**19**; 3.00 g, 16.48 mmol) was treated as in **4a** and **4b** and reacted with **3** (2.27 g, 6.45 mmol) as in **4a** and **4b** to yield **20** as a pale yellow oil (2.50 g, 8.80 mmol, 54%); ^1H NMR ($CDCl_3$): 3.71, 3.72, 3.73, 3.83, 3.87, 3.88 (6S, 18H, 6OMe), 6.50 (m, 4H, H-3 and H-5 of **20a** and **20b**), 6.71 (m, 2H, aromatic H), 6.99 (m, 4H, aromatic H), 7.24 (d, J = 8.5 Hz, 2H, H-6 of **20a** and **20b**), and 12.50 (s, 2H, 2OH of **20a** and **20b**, D_2O exchangeable).

3,5-Dimethoxyxanthone (21M)—Compound **20** (2.50 g, 8.80 mmol) was treated as in **5M** to yield **21M** as a colorless powder (crystallized from $CHCl_3$); 1.95 g, 7.62 mmol, 86%); mp 177–178 °C; MS: *m/z* (%) 256 (100) (M^+); IR (KBr): 1660 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{15}H_{12}O_4$: C, H.

3,5-Dihydroxyxanthone (21H)—Compound **21M** (1.95 g, 7.62 mmol) was treated as in **5H** to yield **21H** as a pale yellow powder (crystallized from MeOH; 1.55 g, 6.80 mmol, 89%); mp >300 °C; MS: *m/z* (%) 228 (7) (M^+); UV: λ_{max} (MeOH) (log ε) 235 (4.04), 240 (sh) (4.03), 275 (3.71), 305 (3.64), 340 (sh), and (3.41) nm; λ_{max} (MeOH + NaOAc) 237, 270 (sh), 310 (sh), and 345 nm; IR (KBr): 3150 and 1650 cm^{-1}; ^1H NMR (DMSO-d_6): see Tables I and II; ^{13}C NMR (DMSO-d_6): see Tables I and II.

Anal.—Calcd for $C_{13}H_8O_4$: C, H.

3,5-Dihydroxyxanthone Diacetate (21A)—Compound **21H** (0.20 g, 0.88 mmol) was treated as in **5A** to yield **21A** as colorless needles (crystallized from MeOH; 0.20 g, 0.61 mmol, 69%); mp 138–140 °C; MS: *m/z* (%) 312 (11) (M^+); IR (KBr): 1770, 1670, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{17}H_{12}O_6$: C, H.

2-Hydroxy-6-methoxy-2′,4′-dimethoxybenzophenone (23a) and 2,6-Dimethoxy-2′-hydroxy-4′-methoxybenzophenone (23b)—2,4-Dimethoxybenzoic acid (**22**; 3.00 g, 16.48 mmol) was treated as in **4a** and **4b** and reacted with **3** (2.27 g, 16.45 mmol) as in **4a** and **4b** to yield **23** as a pale yellow oil (2.45 g, 8.63 mmol, 52%); ^1H NMR ($CDCl_3$): δ 3.74, 3.80 (2S, 18H, 6OMe), 6.35 (dd, J = 8.5 and 2.5 Hz, 2H, H-5′ of **23a** and **23b**), 6.49 (d, J = 2.5 Hz, 2H,H-3′ of **23a** and **23b**), 6.63 (d, J = 8.5 Hz, 4H, H-3 and H-5 of **23a** and **23b**), 7.19 (d, J = 8.5 Hz, 2H,

H-4 of **23a** and **23b**), 7.35 (d, J = 8.5 Hz, 1H, H-6′ of **23a** or **23b**), 7.38 (d, J = 8.5 Hz, 1H, H-6′ of **23a** or **23b**), 12.65 (s, 2H, 2OH of **23a** and **23b**, D_2O exchangeable).

1,6-Dimethoxyxanthone (24M)—Compound **23** (2.45 g, 8.63 mmol) was treated as in **5M** to yield **24M** as a colorless powder (crystallized from $CHCl_3$; 1.85 g, 7.23 mmol, 84%); mp 183–184 °C; MS: m/z (%) 256 (100) (M^+); IR (KBr): 1665 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{13}H_8O_4$: C, H.

1,6-Dihydroxyxanthone (24H)—Compound **24M** (1.85 g, 7.23 mmol) was treated as in **5H** to yield **24H** as a yellow powder (crystallized from MeOH; 1.50 g, 6.58 mmol, 91%); mp 242–243 °C; MS: m/z (%) 228 (100) (M^+); UV: λ_{max} (MeOH) (log ϵ) 228 (4.11), 245 (sh) (3.92), 305 (3.71), and 350 (3.50) nm; λ_{max} (MeOH + $AlCl_3$) 233, 255 (sh), 275, 330, and 405 nm; λ_{max} (MeOH + NaOAc) 205, 228, 255 (sh), 285 (sh), and 360 nm; IR (KBr): 3340 and 1640 cm^{-1}; ^1H NMR (DMSO-d_6): see Tables I and II; ^{13}C NMR (DMSO-d_6): see Tables I and II.

Anal.—Calcd for $C_{13}H_8O_4$: C, H.

1,6-Dihydroxyxanthone Diacetate (24A)—Compound **24H** (0.2 g, 0.88 mmol) was treated as in **5A** to yield **24A** as colorless needles (crystallization from MeOH; 0.21 g, 0.67 mmol, 76%); mp 151–153 °C; MS: m/z (%) 312 (8) (M^+); IR (KBr): 1770, 1670, and 1625 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{17}H_{12}O_6$: C, H.

2-Hydroxy-5-methoxy-2′,4′-dimethoxybenzophenone (26a) and 2,5-Dimethoxy-2′-hydroxy-4′-methoxybenzophenone (26b)—Compound **22** (3.00 g, 16.48 mmol) was treated as in **4a** and **4b** and reacted with 1,4-dimethoxybenzene (**25**; 2.27 g, 16.45 mmol) as in **4a** and **4b** to yield **26** as a pale yellow oil (2.50 g, 8.80 mmol, 54%); ^1H NMR ($CDCl_3$): δ 6.35 (dd, J = 8.5 and 2.5 Hz, 2H, H-5′ of **26a** and **26b**), 6.46 (d, J = 2.5 Hz, 2H, H-3′ of **26a** and **26b**), 6.83 (d, J = 3.0 Hz, 2H, H-6 of **26a** and **26b**), 6.92 (d, J = 8.5 Hz, 2H, H-3 of **26a** and **26b**), 6.96 (dd, J = 8.5 and 3.0 Hz, 2H, H-4 of **26a** and **26b**), 7.25 (d, J = 8.5 Hz, 2H, H-6′ of **26a** and **26b**), 12.64 (s, 2H, 2OH of **26a** and **26b**, D_2O exchangeable).

2,6-Dimethoxyxanthone (27M)—Compound **26** (2.50 g, 8.80 mmol) was treated as in **5M** to yield **27M** as a colorless powder (crystallized from $CHCl_3$; 1.90 g, 7.42 mmol, 84%); mp 143–144 °C; MS: m/z (%) 256 (100) (M^+); IR (KBr): 1660 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{15}H_{12}O_4$: C, H.

2,6-Dihydroxyxanthone (27H)—Compound **27M** (1.90 g, 7.42 mmol) was treated as in **5H** to yield **27H** as a pale yellow powder (crystallized from MeOH; 1.55 g, 6.8 mmol, 92%); mp >300 °C; MS: m/z (%) 228 (71) (M^+); UV: λ_{max} (MeOH) (log ϵ) 240 (4.24), 270 (sh) (3.64), 315 (3.93), and 350 (sh) (3.44) nm; λ_{max} (MeOH + NaOAc) 235, 315, and 350 nm; IR (KBr): 3300 and 1640 cm^{-1}; ^1H NMR (DMSO-d_6): see Tables I and II; ^{13}C NMR (DMSO-d_6): see Tables I and II.

Anal.—Calcd for $C_{13}H_8O_4$: C, H.

2,6-Dihydroxyxanthone Diacetate (27A)—Compound **27H** (0.20 g, 0.88 mmol) was treated as in **5A** to yield **27A** as a colorless powder (crystallized from MeOH; 0.22 g, 0.71 mmol, 80%); mp 167–168 °C; MS: m/z (%) 312 (28) (M^+); IR (KBr): 1765, 1670, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{17}H_{12}O_6$: C, H.

2-Hydroxy-4-methoxy-2′,4′-dimethoxybenzophenone (28a) and 2,4-Dimethoxy-2′-hydroxy-4′-methoxybenzophenone (28b)—Compound **22** (3.00 g, 16.48 mmol) was treated as in **4a** and **4b** and reacted with **3** (2.27 g, 16.45 mmol) as in **4a** and **4b** to yield **28** as a pale yellow oil (2.45 g, 8.63 mmol, 52%); ^1H NMR ($CDCl_3$): δ 3.67, 3.69, 3.73, 3.77 (4S, 18H, 6OMe), 6.31 (dd, J = 8.5 and 2.5 Hz, 2H, H-5 of **28a** and **28b**), 6.42 (d, J = 2.5 Hz, 2H, H-3 of **28a** and **28b**), 6.45 (dd, J = 8.5 and 1.8 Hz, 2H, H-5′ of **28a** and **28b**), 6.50 (d, J = 1.8 Hz, 2H, H-3′ of **28a** and **28b**), 7.21 (d, J = 8.5 Hz, 2H, H-6 of **28a** and H-6′ of **28b**), 7.28 (d, J = 8.5 Hz, 2H, H-6′ of **28a** and H-6 of **28b**).

3,6-Dimethoxyxanthone (29M)—Compound **28** (2.45 g, 8.63 mmol) was treated as in **5M** to yield **29M** as a colorless powder (crystallized from $CHCl_3$; 1.85 g, 7.23 mmol, 84%); mp 188–189 °C; MS: m/z (%) 256 (100) (M^+); IR (KBr): 1650 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{15}H_{12}O_4$: C, H.

3,6-Dihydroxyxanthone (29H)—Compound **29M** (1.85 g, 7.23 mmol) was treated as in **5H** to yield **29H** as a yellow powder (crystallized from MeOH; 1.50 g, 6.58 mmol, 91%); mp >300 °C; MS: m/z (%) 228 (100) (M^+); UV: λ_{max} (MeOH), (log ϵ) 207 (4.08), 237 (4.29), 267 (3.66), and 315 (4.05) nm; λ_{max} (MeOH + NaOAc) 208, 235, 265, 320, and 350 (sh) nm; IR (KBr): 3150 and 1640 cm^{-1}; ^1H NMR (DMSO-d_6): see Tables I and II; ^{13}C NMR (DMSO-d_6): see Tables I and II.

Anal.—Calcd for $C_{13}H_8O_4$: C, H.

3,6-Dihydroxyxanthone Diacetate (29A)—Compound **29H** (0.20 g, 0.88 mmol) was treated as in **5A** to yield **29A** as colorless needles (crystallized from MeOH; 0.21 g, 0.67 mmol, 76%); mp 198–201 °C; MS: m/z (%) 312 (14) (M^+); IR (KBr): 1770, 1670, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$): see Tables I and II; ^{13}C NMR ($CDCl_3$): see Tables I and II.

Anal.—Calcd for $C_{17}H_{12}O_6$: C, H.

Platelet Aggregation—Washed rabbit platelets were obtained from ethylenediaminetetraacetic acid (EDTA)-anticoagulated, platelet-rich plasma according to the washing procedures described previously.[12] Platelet numbers were counted with a Coulter counter (model ZM) and adjusted to 4.5×10^8 platelets/mL of Tyrode's 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 bovine serum albumin (0.35%). Aggregation was measured by the turbidimetric method,[13] and the absorbance of platelet suspension was assigned as 0% aggregation and the absorbance of platelet-free Tyrode's solution as 100% aggregation. The aggregation was measured with a Lumiaggregometer (Chrono-Log Company, Haverton, PA) connected to dual channel recorders. The platelet suspension was stirred at 1200 rpm. All the xanthone derivatives were dissolved in DMSO. To eliminate the effect of solvent on the aggregation, the final concentration of DMSO was fixed at 0.5%.

References and Notes

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Acknowledgments

We are indebted to the National Sciences Council of the Republic of China for financial support (NSC 80-0420-B037-04).