Synthetic *aci*-Reductones: 3,4-Dihydroxy-2*H*-1-benzopyran-2-ones and Their *cis*- and *trans*-4a,5,6,7,8,8a-Hexahydro Diastereomers. Antiaggregatory, Antilipidemic, and Redox Properties Compared to Those of the 4-Substituted 2-Hydroxytetronic Acids[1]

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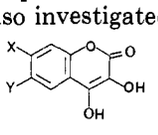
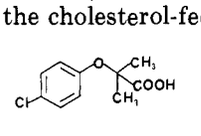
Synthetic procedures for the elaboration of *aci*-reductones belonging to the 6- or 7-mono- or bis-substituted-3,4-dihydroxy-2*H*-1-benzopyran-2-ones (**6–10**) and their *cis*- and *trans*-4a,5,6,7,8,8a-hexahydro diastereomers (**11**, **12**) are described. Hexahydrobenzopyranone *aci*-reductones were conveniently prepared by using Meldrum's synthon (2,2-dimethyl-1,3-dioxane-4,6-dione, **49**). Certain of these substances were evaluated for antilipidemic activity in the cholesterol-fed rat model, and all analogues were studied for their ability to inhibit aggregation of human platelets. Results are compared to *aci*-reductones belonging to the 4-aryl- and 4-spiroalkyl-2-hydroxytetronic acid systems (**4**, **5a,b**). Redox potentials for all *aci*-reductones were determined with cyclic voltammetry. It would appear that the 4-aryl-2-hydroxytetronic acids represent leads for further study as antiatherosclerotic drugs owing to their favorable antilipidemic and antiaggregatory properties whereas the benzopyranones are of most interest as probes for platelet antiaggregatory mechanism studies.

Previously, we reported synthetic methods for the preparation of *aci*-reductones[2,3] and the antiaggregatory activity of 6-chloro-3,4-dihydroxy-2*H*-1-benzopyran-2-one (CDBP, **1**) in human platelets.[2] This *aci*-reductone inhibited aggregatory and serotonin secretory responses to adenosine diphosphate (ADP) and arachidonic acid (AA) and is of interest since it was more potent than clofibric acid (**2**) or its cyclic 2,3-dihydrobenzofuran analogue **3** as an inhibitor of thrombin-induced [^{3}H]AA release or the blockade of the ADP- or AA-mediated pathway of platelet aggregation. We suggested[2] that CDBP and other redox analogues such as 2-hydroxytetronic acid (**4**)[4] or possibly spiro derivatives **5**[3] might function as antioxidants in membranes or interfere with free radical processes involved in the biosynthesis of prostaglandin endoperoxides and subsequently of thromboxane A_2 from AA.[5,6] Because of our interest in the antilipidemic and antiatherosclerotic properties of *aci*-reductones,[4,7] selected compounds were also investigated in the cholesterol-fed rat model.



1, X=H, Y=Cl
6, X=Y=H
7, X=H, Y=OH
8, X=H, Y=Ph
9, X,Y=OCH_2O
10, X=t-Bu, Y=OH



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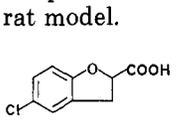

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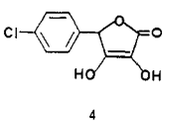

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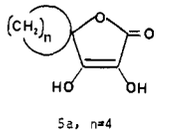
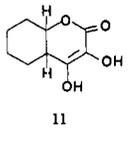


5a, n=4
b, n=5



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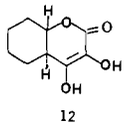

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Unlike *aci*-reductone **4**, the redox functionality in benzopyranones **1** and **6–10** is in conjugation with the benzannelated ring, and substituents X and Y may more effectively attenuate the redox potential and influence redox related biological properties. To further test this possibility, we constructed a limited series of benzopyranones (**6–10**) for biological comparison with the diastereomeric hexahydrobenzopyranones **11** (cis) and **12** (trans) and the 4-aryl- and 4-spiroalkyl-2-hydroxytetronic acids (**4** and **5**, respectively). Furthermore, *aci*-reductone **6**, a deschloro analogue of **1**, is less lipophilic than **1**, whereas **8** and **10** contain the very lipophilic phenyl and *t*-Bu groups, respectively. The methylenedioxy function in **9** places an additional oxygen in conjugation with the redox functionality. In this paper, we summarize synthetic chemistry leading to the preparation of compounds **6–12**, the redox potentials of *aci*-reductones **1** and **4–12** compared to that of ascorbic acid, and their relevant biological properties.

Chemistry. The method developed[2] for CDBP (**1**) employing a Claisen condensation was suitable for **7**. Thus, benzylation of bis(phenol) **13** afforded salicylate **14**, which condensed with ethyl (phenylmethoxy)acetate[8,9] with LDA in THF (–78 °C) to yield intermediate **15** (33%). Transfer hydrogenation (10% Pd/C, cyclohexene, ethanol, reflux)[10] of **15** followed by lactonization produced **7** (60%). This

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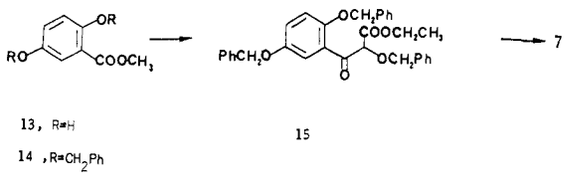
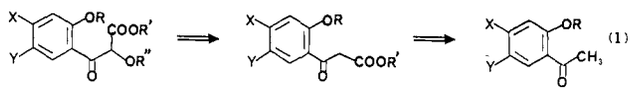


13, R=H

14, R=CH_2Ph

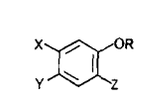
15

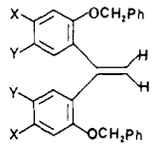
approach was, however, unsuccessful for the preparation of other substituted targets. For these reasons, an alternate approach summarized in retrosynthetic eq 1 was explored.



(1)

Benzylation of commercially available acetophenones **16** and **17** provided protected derivatives **18** (86%) and **19** (88%). Fries rearrangement product **20**[11] similarly served as precursor to **21** (95%). Acylation of sesamol (**22**) with Ac_2O/BF_3–Et_2O afforded methylenedioxy ketone **24** (75%). Alternatively, bromo derivatives **23**, **27**, and **29** were most useful precursors to the respective acetophenones. Reaction of the corresponding Grignard reagents with AcCl (THF; −78 °C) produced the respective O-benzylated intermediates **25** (72%), **28** (64%), and **30** (56%). Minor (5–7%) dimeric products, **31**–**33**, were separated by chromatography on silica gel. β-Keto esters **34**–**39** were obtained in 88–91% yield by reaction of the appropriate acetophenone precursor with $(MeO)_2CO$/NaH (70–75 °C).





16, X=Y=R=H, Z=$COCH_3$

17, X=R=H, Y=OH, Z=$COCH_3$

18, X=Y=H, Z=$COCH_3$, R=CH_2Ph

19, X=H, Y=OCH_2Ph, Z=$COCH_3$, R=CH_2Ph

20, X=R=H, Y=Cl, Z=$COCH_3$

21, X=H, Y=Cl, Z=$COCH_3$, R=CH_2Ph

22, X,Y=OCH_2O, Z, R=H

23, X,Y=OCH_2O, Z=Br, R=CH_2Ph

24, X,Y=OCH_2O, Z=$COCH_3$, R=H

25, X,Y=OCH_2O, Z=$COCH_3$, R=CH_2Ph

26, X=t-Bu, Y=OCH_2Ph, Z=H, R=CH_2Ph

27, X=t-Bu, Y=OCH_2Ph, Z=Br, R=CH_2Ph

28, X=t-Bu, Y=OCH_2Ph, Z=$COCH_3$, R=CH_2Ph

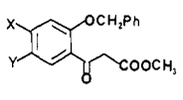
29, X=H, Y=Ph, Z=Br, R=CH_2Ph

30, X=H, Y=Ph, Z=$COCH_3$, R=CH_2Ph

31, X,Y=OCH_2O

32, X=t-Bu, Y=OCH_2Ph

33, X=H, Y=Ph



34, X=Y=H

35, X=H, Y=Cl

36, X=H, Y=OCH_2Ph

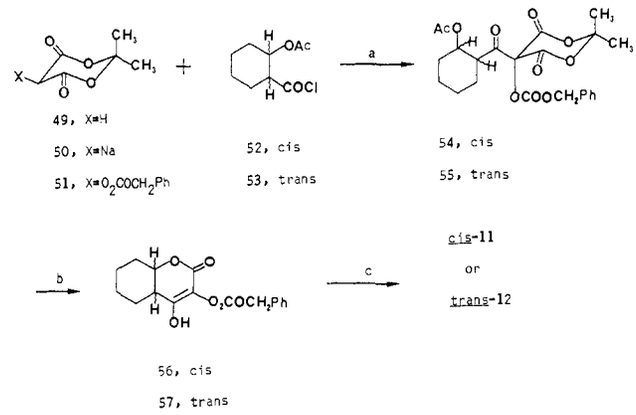
37, X=H, Y=Ph

38, X,Y=OCH_2O

39, X=t-Bu, Y=OCH_2Ph

Acetoxylation of **34** with lead tetraacetate[12] failed to provide **40**, but treatment with NaH and freshly crystallized benzoyl peroxide[13,14] in benzene afforded applicable oxygenated intermediate **41** (76%). Transfer hydrogenation (10% Pd/C, cyclohexene, EtOH, reflux) followed by acid-catalyzed lactonization produced **48** (73%). Hydrolysis (*p*-TsOH) in refluxing $EtOH/H_2O$ (4:1) yielded target *aci*-reductone **6** (37%). Alternatively, use of dibenzyl peroxydicarbonate[15] generated **42**–**47** (45–65%) from **34**–**39**, respectively. Minor bis(oxygenated) contaminants were removed by flash chromatography (silica gel). Transfer hydrogenation and lactonization (HCl/MeOH) yielded the respective targets **1** and **6**–**10** (65–80%).

Scheme I[a]



49, X=H

50, X=Na

51, X=O_2COCH_2Ph

52, cis

53, trans

54, cis

55, trans

cis-11

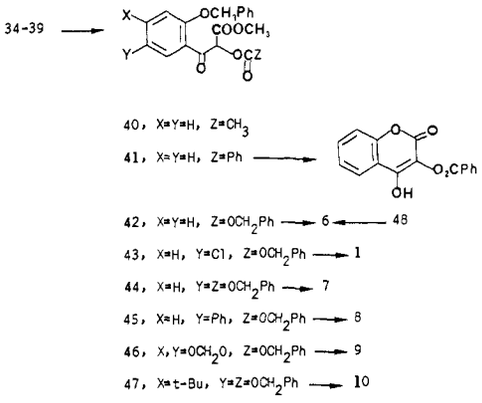
or

trans-12

56, cis

57, trans

[a] (a) Pyridine, CH_2Cl_2, argon, room temperature; (b) *p*-TsOH, MeOH, reflux; (c) 10% Pd/C, cyclohexene, EtOH, argon, reflux.



40, X=Y=H, Z=CH_3

41, X=Y=H, Z=Ph

42, X=Y=H, Z=OCH_2Ph → 6 ← 48

43, X=H, Y=Cl, Z=OCH_2Ph → 1

44, X=H, Y=Z=OCH_2Ph → 7

45, X=H, Y=Ph, Z=OCH_2Ph → 8

46, X,Y=OCH_2O, Z=OCH_2Ph → 9

47, X=t-Bu, Y=Z=OCH_2Ph → 10

Synthesis of hexahydrobenzopyranones *cis*-**11** and *trans*-**12** is complicated by the problem of epimerization that one may encounter during their preparation by methodologies employing either Claisen condensation or peroxide oxidation (as discussed above). To circumvent the epimerization problem we investigated the use of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione; **49**),[16-18] which serves as an excellent precursor for β-keto esters under extremely mild conditions (Scheme I).

Thus, Meldrum's acid (**49**) was first oxygenated at C-5 by reacting its sodium salt (**50**)[19] with dibenzyl peroxydicarbonate[15] to give **51** (81%). Condensation of synthon **51** with cis or trans acetoxy acyl chlorides **52** and **53**, respectively, in pyridine/dry CH_2Cl_2 followed by flash chromatographic purification [silica gel, petroleum ether/EtOAc (6:1)] afforded adducts **54** (53%) and **55** (64%). No epimerization of the cis diastereomer was detected. Hydrolysis (*p*-TsOH in refluxing MeOH) afforded the corresponding stereoisomeric bicyclic products **56** (62%)

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Table I. Redox Potentials[a] for Ascorbic Acid and Experimental *aci*-Reductones

compound	pH 1.0 E_1	pH 1.0 chemical reversibility[b]	pH 7.4 E_1	pH 7.4 chemical reversibility[b]
ascorbic acid	0.504	irreversible	0.162	irreversible
1	0.587	irreversible	0.202	irreversible
4	0.492	irreversible	0.112	irreversible
5b	0.497	irreversible	0.157	irreversible
6	0.562	irreversible	0.182	irreversible
7	0.562	reversible	0.177	reversible
8	0.572	irreversible	0.209[c]	irreversible
9	0.542	irreversible	0.172	reversible
10	0.547	reversible	0.182	reversible
11			0.070	irreversible
12	0.432	irreversible	0.027	irreversible

[a] E_1 were reproducible to ±10 mV. [b] As inferred from the presence of a reverse voltametric wave. [c] This value was incorrectly presently as 0.672 V in the *Proceedings of the French–Italian Joint Meeting on Medicinal Chemistry*; Pisa, Italy, Sept 22–26, 1987.[7]

and **57** (68%), respectively. Trace amounts of debenzylated targets **11** and **12** were also obtained under these conditions. Debenzylation (transfer hydrogenation) followed by immediate crystallization afforded targets[20] **11** (78%) and **12** (84%), respectively. The desired cis and trans acetoxy acyl chlorides **52** and **53** were prepared from corresponding known cis and trans carboxylic acids.[21]

Redox Potentials for Experimental *aci*-Reductones Compared to Those of Ascorbic Acid. All voltammetry was conducted in 0.1 M H_2SO_4 or pH 7.4, 0.1 M phosphate buffer, both degassed with argon before use. A Ag/AgCl (3 M NaCl) reference electrode was used (E_{ref} = +0.222 vs NHE), but all potentials reported here are relative to the normal hydrogen electrode, NHE. A 0.071-cm^2 planar glassy carbon working electrode (Bioanalytical Systems) was activated by three 21 MW/cm^2 Nd:YAG laser pulses, as described previously.[22] Voltammograms were obtained at 0.1 V/s with a Bioanalytical Systems CV-1B-voltammograph. Chemical reversibility of the first oxidation peak was assessed by observing the presence or absence of a reverse peak.

Table I shows the observed redox potentials[22] for ascorbic acid and 10 experimental *aci*-reductones (**1**, **4–12**). Several general observations deserve note. First, the redox potentials decrease with increasing pH due to loss of the hydroxyl protons upon oxidation. The slope of this decrease changes from 0.059 V/pH unit to 0.029 V/pH unit at the pK_a of the reduced material, 4.2 in the case of ascorbic acid.[23] Second, the *aci*-reductones differ in their chemical reversibility. The presence of a reverse wave for several compounds indicates the oxidized forms are more stable than oxidized ascorbic acid. Third, measurement of redox potentials at equilibrium will in general be more negative than voltammetric potentials from Table I owing to hydration of the oxidized form.[24] Furthermore, voltammetric potentials are indicative of general trends but are not necessarily equal to thermodynamic redox potentials.

The *aci*-reductones fall into two groups on the basis of their redox potentials at pH 7.4. The first group has potentials near that of ascorbate, ranging from 0.157 to 0.209 vs NHE at pH 7.4 (**1**, **5b**, **6–10**). The fused aromatic ring system in **1** and **6–10** increases E_1 relative to ascorbate with this group being harder to oxidize than ascorbate by about 10–50 mV at pH 7.4. Compound **5b** does not include the fused aromatic ring and has an E_1 at least 20 mV lower (easier to oxidize) than compounds **6–10**. The second general group of compounds (**4**, **11**, and **12**) have significantly lower E_1 values than ascorbate, by 40–130 mV. The 182-mV range of E_1 observed for the entire series of compounds at pH 7.4 implies a large variation (a factor of 10^6) in the ratio of oxidized to reduced form in the presence of a biological oxidant.

Pharmacological Results. Antiaggregatory Activity Studies in Human Platelets. Each of the experimental *aci*-reductones, like clofibric acid (**2**), was a concentration-dependent inhibitor of the secondary phase of ADP-induced platelet aggregation and serotonin secretion

Table II. Comparative Potencies of Chlofibric Acid (**2**), Benzopyranone *aci*-Reductone CDBP (**1**) and Related Analogues (**6–10**), the *cis*- and *trans*-Hexahydrobenzopyranones (**11**, **12**), and Spirotetronic Acids (**5a**, **5b**) as Inhibitors of Human Platelet Aggregation and Serotonin Secretion by Adenosine Diphosphate (ADP), Arachidonic Acid (AA), and U46619[a]

compound	IC_{50},[b] μM ADP	AA	U46619
	I. Aggregation Studies		
aspirin	59 ± 14 (3)	89 ± 21 (5)	
indomethacin	0.8 ± 0.1 (4)	1 ± 0.3 (5)	
1	498 ± 55 (10)	780 ± 58 (16)	1399 ± 85 (8)
2	1238 ± 234 (5)	>3200 (8)	>4000 (6)
4	1090 ± 186 (5)	>4000 (3)	>4000 (3)
5a	>4000 (3)	>4000 (3)	>4000 (3)
5b	>3300 (3)	>4000 (3)	>4000 (3)
6	531 ± 75 (3)	561 ± 200 (5)	3413 ± 442 (4)
7	1422 ± 268 (4)	3506 ± 596 (5)	>4000 (4)
8	522 ± 93 (5)	253 ± 83 (7)	422 ± 110 (3)
9	426 ± 65 (4)	3979 ± 522 (7)	1107 ± 293 (6)
10	1645 ± 174 (4)	>4000 (3)	>4000 (3)
11	447 ± 73 (8)	>4000 (3)	>4000 (4)
12	481 ± 52 (7)	>4000 (3)	3090 ± 382 (4)
	II. Serotonin Secretion Studies		
aspirin	50 ± 10 (3)	95 ± 22 (4)	
indomethacin	0.7 ± 0.1 (4)	1 ± 0.4 (4)	
1	513 ± 79 (4)	1132 ± 191 (13)	2378 ± 394 (3)
2	1228 ± 188 (5)	>3500 (6)	3079 ± 382 (5)
4	1211 ± 222 (5)	>4000 (3)	>4000 (3)
5a	>4000 (3)	>4000 (3)	>4000 (3)
5b	>3000 (3)	>4000 (3)	>4000 (3)
6	472 ± 96 (3)	925 ± 196 (5)	3978 ± 690 (4)
7	1516 ± 130 (3)	3412 ± 378 (5)	>4000 (3)
8	450 ± 14 (4)	407 ± 54 (7)	345 ± 108 (4)
9	389 ± 110 (4)	1554 ± 283 (7)	744 ± 94 (6)
10	2177 ± 363 (3)	>4000 (3)	>4000 (3)
11	406 ± 61 (6)	>4000 (3)	>4000 (4)
12	492 ± 91 (4)	>4000 (3)	c

[a] Inhibitors were incubated 1 min before the stimulation of platelets by ADP (1–5 μM), AA (0.2–1 mM), or U46619 (0.3–0.5 μM). ADP data is for inhibition of secondary aggregation only. [b] Data are expressed as the mean IC_{53} ± SEM (n = number of donors). Maximal drug concentrations used were between 4000 and 5000 μM. [c] No concentration-dependent response was seen with this compound.

(20) (a) The ring juncture stereochemistry in *aci*-reductones **11** and **12** is reflected in their ^1H NMR spectra (270 MHz). The H-8a resonance signal for *cis*-**11** was observed as a sharp multiplet centered at δ 4.54 with line width = 2.5 Hz, whereas *trans*-**12** provided the H-8a signal as a doublet (J = 4.0 Hz) of triplets (J = 11.6 Hz) centered at δ 4.02 (line width = 27 Hz). (b) Target *aci*-reductones **11** and **12** exist as a mixture of keto and enol forms in $CDCl_3$. ^1H NMR analysis shows that the keto:enol ratio for **11** is 1:7; for **12**, 1:6. In polar DMSO-d_6, however, only the enol forms of **11** and **12** were observed.

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(24) For a referenced discussion of the details of these phenomena, see addendum (microfilm edition).

(Table II). The rank orders of inhibiting potencies of these analogues against these ADP-induced responses were the same (**9** > **1** = **6** = **8** > **7** = **10**). In addition, *cis*-**11** and *trans*-**12** were also inhibitors nearly as active as **8**.

Like **2**, *aci*-reductones analogues **7** and **10–12** possessed little activity against AA-induced responses (Table II) indicating that they may block the release of AA from platelet membranes. The rank orders of inhibitory potencies of the remaining compounds against AA-mediated responses were the same (**8** > **6** > **1** > **9**).

The rank orders of inhibitory potencies against aggregation and secretion induced by U46619, a stable epoxymethano prostaglandin H_2 (PGH_2) analogue having thromboxane A_2 (TXA_2) agonist properties, were **8** > **9** > **1** > **6**. Analogues **7** and **10–12**, like **2** were ineffective against U46619.

No differences in activity were observed when comparing *cis*-**11** to *trans*-**12**. Moreover, these two compounds were the most selective against ADP-mediated platelet stimulation, and only clofibric acid (**2**) and benzopyranone **10** exhibited the same profile of inhibitory activity. In contrast, analogues **1**, **6**, **8**, and **9** had activity against each inducer. In particular, analogue **8** showed nearly equal inhibitory activities against the three inducers, and benzopyranone **6** was equipotent against ADP and AA.

Antilipidemic Activities. Selected benzopyranones **1**, **6**, **7**, and **9** and 4-spiroalkyl-2-hydroxytetronic acids (**5a,b**)[3] were produced in large quantities and studied in male Sprague–Dawley rats, prefed a high-cholesterol semisynthetic diet.[4] After one week on this regimen, blood was withdrawn from the orbital plexus of ether-anesthetized animals, and serum cholesterol concentrations were determined (see supplementary material). On the basis of these values, rats were distributed through stratification randomization in different drug treatment and control groups. Rats received 0.4 mmol/kg body weight twice daily of the respective drug through intragastric administration with 0.25% methylcellulose vehicle for 14 days. Control rats received the same amount of methylcellulose only.

All rats were fasted 16–18 h before blood collection. Blood was drawn from the orbital plexus under light ether anesthesia on the day before (day–1) and after 4 and 7 days (day+4 and day+7) of drug treatment. After 14 days (day+14) of drug treatment, blood was collected by exsanquination from the abdominal aorta. All blood samples were kept for 2–3 h at 4 °C, and after coagulation, serum was separated by centrifugation at 2000*g* for 10 min.

None of the benzopyranones (**1**, **6**, **7**, or **9**) or the 4-spiroalkyl-2-hydroxytetronic acids (**5a,b**) tested lowered either serum cholesterol or triglyceride concentrations measured relative to controls on day–1, day+4, day+7, or day+14. The Experimental Section and tables of results are available as supplementary material.

Discussion

Elevated lipid levels and enhanced platelet activity are risk factors in atherosclerosis and coronary artery disease. These phenomena, as well as the atherosclerotic process itself, involve a number of free-radical events, which may be subject to modulation by redox containing drugs.[2-4] *aci*-Reductone 4-(4-chlorophenyl)-2-hydroxytetronic acid (CHTA, **4**) previously was observed to exhibit superior and qualitatively different antilipidemic activities and lipoprotein modifying effects relative to clofibrate in the cholesterol-fed rat model.[4,25] Thus, the abnormal cholesterol-rich VLDL, IDL, and LDL produced by cholesterol feeding were significantly reduced in their cholesterol content by treatment with CHTA.[25] CHTA, but not clofibrate, significantly lowered serum total cholesterol and triglyceride concentrations and did not alter SDS-PAGE apoprotein concentrations within VLDL, IDL, or HDL when compared to the cholesterol-fed group.[25] Isoelectric focusing of IDL and HDL apoproteins revealed clofibrate reduces apo-C-II, apo-C-III-O, apo-C-III-3, and apo-E, but no apoproteins were decreased in CHTA-treated rats.[25] Thus, the mechanism of the antilipidemic action of CHTA, a vinylogous acid containing a redox functionality, appears to differ markedly from the prototype drug clofibrate.

In this study, various inducers of platelet aggregation were chosen so as to provide insights into the mechanism of antiplatelet action of each *aci*-reductone. Although the antiplatelet potency of compounds used in this study are relatively low compared to aspirin and indomethacin (Table II), they are within the range of clinical plasma titers found in patients receiving clofibrate.[26] ADP activation of specific platelet receptors leads to a primary wave of aggregation, and subsequent dense granule secretion concurrent with a second wave of aggregation. The latter two events of ADP action are mediated through PG synthesis. The first step of PG synthesis involves release of AA from membrane phospholipids by the enzyme phospholipase A_2, and this is followed by metabolism of AA. Inhibitors of platelet secretion and the second wave of aggregation induced by ADP may either block the release of AA, the metabolism of AA, or the stimulating effects of bioactive prostaglandins PGH_2 and TXA_2, which are AA metabolites. Inhibitors of AA-induced platelet activation may antagonize AA metabolism or PG action. Finally, inhibitors of the PGH_2 analogue U46619 act only after the formation of AA metabolites.

CHTA, unlike CDBP redox analogue **1**, presented a similar profile to clofibric acid (**2**), the serum hydrolysis product of clofibrate, when assessed for antiaggregatory and antisecretory effects with human platelets in vitro.[2] Thus, CHTA and **2** appear to have a primary effect on inhibition of AA release rather than on prostaglandin synthesis.[4] Both CDBP and clofibric acid analogue **3**[2] were about 4-fold more potent inhibitors of AA-induced aggregation than was **2**.[2] Unlike **2**, CDBP and **3** were concentration-dependent inhibitors of aggregation induced by U46619. Like acid **3**, *aci*-reductone CDBP may act as an inhibitor of AA metabolism since it is a more potent inhibitor of AA-mediated responses than of U46619.[2] Furthermore, CDBP is a more potent inhibitor of thrombin-induced AA release than either **3** or **2** (CBDP ≫ **3** = **2**), possibly a function of redox-related mechanisms in platelet membranes.[2]

All benzopyranones (CDBP, **6–10**) and the diastereomeric hexahydrobenzopyranones (**11**, **12**), but not the 4-spiroalkyl-2-hydroxytetronic acids (**5a,b**), affected the prostaglandin-mediated effects of ADP-induced platelet aggregation and secretion and all but the two phenolic benzopyranones [6-hydroxy (**7**) and 6-hydroxy-7-*tert*-butyl (**10**)] were more potent than clofibric acid (**2**). Hexahydrobenzopyranones, *cis*-**11** and *trans*-**12**, phenols **7** and **10**, and clofibric acid (**2**) were much less effective against stimulation by exogenously added AA, indicating that these agents primarily affect the release of AA from platelet phospholipids. Clofibric acid (**2**) and CHTA (**4**) have previously been shown to act by this mechanism. CDBP (**1**) and its deschloro analogue **6** also block AA-induced

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platelet activation, but they were even more effective against stimulation by ADP, suggesting inhibition at two or more sites in the prostaglandin-dependent pathway of platelet activation. How much of these activities may be attributed to the *aci*-reductone functionality is difficult to assess since benzopyrancarboxylic acid **3** has similar biological properties.

Both CDBP (**1**) and acid **3** blocked the action of U46619 at higher concentrations. Apparently, these compounds possess a third site of action: inhibition of platelet stimulation by mediators PGH_2 and TXA_2. Methylenedioxy analogue **9** blocked U46619 and ADP more effectively than AA, implying a mechanism of action involving inhibition of prostaglandin agonist activity and release of AA, but not blockade of AA metabolism. Lipophilic phenyl analogue **8** is exceptional in that it is nearly equipotent against all three inducers. Possibly this reflects a major blockade at the prostaglandin receptor site. Since **8** also did not inhibit the primary phase of ADP-induced aggregation, this analogue appears to be specific for the PGH_2/TXA_i-dependent pathway of platelet activation.

Correlation of antiaggregatory activity with redox potentials is complicated because the oxidized form of *aci*-reductones undergo hydration, and in addition, these compounds differ in chemical reversibility.[24] It is clear that substituent effects, apparently independent of redox potential, markedly affect site of action and potency, and this is to be expected; i.e. lipophilicity, steric effects, etc., as well as redox potential all likely contribute to the biological properties and the multiple sites of action. Previously, we reported[27] that the increased inhibitory potency of 6-substituted chroman-2-carboxylates at the level of cyclooxygenase correlated favorably with lipophilicity, and with such acids there are no biologically applicable redox potentials. Furthermore, as previously discussed, the redox chemistry is complex owing to hydration of the oxidized form. The potentials reported here as E_1 are the redox potentials for the simple conversion to the triketo form. However, the biological activity may better correlate with an E reflecting, among other parameters, hydration of the oxidized form.

Irrespective of the limited conclusions that can be drawn at this time, it is clear that 4-aryl-substituted 2-hydroxytetronic acids of the type **4** represent leads for further study in atherosclerotic models owing to their favorable properties as both antilipidemic[25] and antiaggregatory drugs (Table II) whereas the benzopyranones (**1**, **6–10**) are of primary interest as probes of platelet aggregation mechanisms. The inactivity of spirotetronic acids (**5a,b**) as antilipidemic or antiaggregatory agents stresses the importance of aryl functionalities in the tetronic acid series. Lack of significant diastereomeric stereostructure–activity relationships for the antiaggregatory hexahydrobenzopyranones coupled with their intrinsic instability also eliminates these compounds from further consideration at this time.

Experimental Section

General Procedures. Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded with a Beckman Model 4230 spectrophotometer. Nuclear magnetic resonance spectra were recorded with either a Bruker WP-80, HX-90E, 270-MHz instrument or a Nicolet 500-MHz spectrometer. TMS ($CDCl_3$, DMSO-d_6) was used as internal standard. Chemical shifts are reported on the δ scale with peak multiplicities: br, broad; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; q, quartet; t, triplet; d, doublet, s, singlet. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Synthetic Chemistry. 6-Chloro-3,4-dihydroxy-2*H*-1-benzopyran-2-one (1) was prepared from **43** according to procedures identical with those described for the preparation of **6** from **42**, affording 0.65 g (77%) of **1** as a white solid, mp (EtOAc/petroleum ether) 244–247 °C dec, identical in all respects to **1** synthesized by an alternative route.[2]

3,4-Dihydroxy-2*H*-1-benzopyran-2-one (6). Method I. A mixture of **42** (1.74 g, 0.004 mol) and 10% Pd/C (0.347 g, 20% by weight of **42**) in 20 mL of EtOH and 10 mL of cyclohexene was heated at reflux for 1 h (argon atmosphere). After cooling to room temperature, the catalyst was removed by filtration, and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (15 mL) containing concentrated HCl (1.0 mL) and heated at reflux under argon for 1 h. After the solvent was removed under reduced pressure, the resulting residue was partitioned between EtOAc (50 mL) and 10% aqueous $NaHCO_3$ solution (50 mL). Acidification of the aqueous layer (ice/HCl) and extraction with EtOAc provided an organic layer, which was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from HOAc, affording 0.52 g (73%) of **6** as a white solid, mp 235–236 °C [lit.[28] mp (benzene/EtOH) 226–228 °C dec, lit.[29] mp (HOAc) 234 °C].

Method II. To a solution of **48** (0.282 g, 0.001 mol) in EtOH (12 mL) and H_2O (3 mL) was added 0.1 g of *p*-TsOH. The resulting solution was heated at reflux for 72 h, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O, and the organic layer was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from HOAc, yielding 0.065 g (37%) of **6**, identical in all respects with the material prepared from **42**.

3,4,6-Trihydroxy-2*H*-1-benzopyran-2-one (7). Method I. Compound **7** was prepared from **15** according to transfer hydrogenation conditions identical with those described for the preparation of **1**,[2] affording 0.233 g (60%) of **7**, identical in all respects with the material prepared from **44**.

Method II. Compound **7** was prepared from **44** according to procedures identical with those described for the preparation of **6** from **42**, affording 0.53 g (68%) of **7** as a white solid: mp (THF/petroleum ether) >260 °C (slow discoloration >250 °C); IR (KBr) 3355 (OH), 3080 (br s, OH), 1668 (carbonyl), 1635 (carbonyl) cm^{-1}; NMR (DMSO-d_6, 90 MHz) δ 6.8–7.3 (m, 3 H, Ar H), 8.8–9.5 (br s, 1 H, OH), 9.6 (s, 1 H, OH), 10.5–11.4 (br s, 1 H, OH). Anal. ($C_9H_6O_5$) C, H.

3,4-Dihydroxy-6-phenyl-2*H*-1-benzopyran-2-one (8) was prepared from **45** according to procedures identical with those described for the preparation of **6** from **42**, affording 0.81 g (80%) of **8** as a white solid: mp ($CHCl_3$/petroleum ether) 228–230 °C; IR (KBr) 3335 (OH), 3280 (sh, OH), 1690 (carbonyl), 1645 (carbonyl) cm^{-1}; NMR (DMSO-d_6, 90 MHz) δ 7.2–8.1 (m, 8 H, Ar H), 8.8–9.9 (br s, 1 H, OH), 10.7–11.9 (br s, 1 H, OH). Anal. ($C_{15}H_{10}O_4$) C, H.

3,4-Dihydroxy-6,7-(methylenedioxy)-2*H*-1-benzopyran-2-one (9) was prepared from **46** according to procedures identical with those described for the preparation of **6** from **42**, affording 0.64 g (72%) of **9** as a white solid: mp (THF/petroleum ether) >260 °C; IR (KBr) 3446 (OH), 3301 (br s, OH), 1650 (carbonyl), 1630 (sh, carbonyl) cm^{-1}; NMR (DMSO-d_6, 90 MHz) δ 6.11 (s, 2 H, OCH_2O), 7.04 (s, 1 H, Ar H), 7.11 (s, 1 H, Ar H), 8.7–9.3 (br s, 1 H, OH), 10.1–11.5 (br s, 1 H, OH). Anal. ($C_{10}H_6O_6$) C, H.

7-(1,1-Dimethylethyl)-3,4,6-trihydroxy-2*H*-1-benzopyran-2-one (10) was prepared from **47** according to procedures identical with those described for the preparation of **6** from **42**, affording 0.65 g (65%) of **10** as a white solid: mp (EtOAc/petroleum ether) 187–188 °C; IR (KBr) 3400 (OH), 3365 (OH), 3160 (br s, OH), 1666 (carbonyl), 1640 (carbonyl) cm^{-1}; NMR (DMSO-d_6, 90 MHz) δ 1.37 [s, 9 H, $C(CH_3)_3$], 7.07 (s, 1 H, Ar H), 7.09 (s, 1 H, Ar H), 8.7–9.6 (br s, 1 H, OH), 9.65 (s, 1 H), 10.3–11.5 (s, 1 H, OH). Anal. ($C_{14}H_{18}O_3$) C, H.

***cis*-4a,5,6,7,8,8a-Hexahydro-3,4-dihydroxy-2*H*-1-benzopyran-2-one (11)** was prepared from **56** by using methodology

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identical with that employed for the preparation of trans *aci*-reductone **12** from **57**. Benzyl carbonate **56** (0.096 g, 0.0003 mol) afforded 0.043 g (78%) of **11** as a white solid, mp ($CHCl_3$/hexane) 125–127 °C. This *aci*-reductone slowly decomposed on standing at room temperature: IR (KBr) 3425 (OH), 1684 (sh), 1656 (sh), 1645 (carbonyl) cm^{-1}. The ^1H NMR spectra ($CDCl_3$) showed *cis*-**11** to be a mixture of keto and enol forms (1:7): NMR ($CDCl_3$, 270 MHz) δ 1.1–1.8 (m, 6 H, $3CH_2$), 2.1–2.2 (m, 2 H, CH_2), 2.35 (dt, 1 H, J = 3.9 and 11.7 Hz, H-4a), 4.5–4.6 (sharp m, H-8a of enol form), 5.0–5.1 (unresolved br m, H-8a of keto form), 5.19 (s, H-3 of keto form), 5.1–6.0 (br s, OH). In DMSO-d_6 only, the enol form was observed. Anal. ($C_9H_{12}O_4$) C, H.

***trans*-4a,5,6,7,8,8a-Hexahydro-3,4-dihydroxy-2*H*-1-benzopyran-2-one (12).** To a suspension of trans benzyl carbonate **57** (0.318 g, 0.001 mol) in EtOH (5 mL) were added 10% Pd/C (0.032 g) and cyclohexene (2.5 mL). The resulting mixture was heated under reflux for 10 min (argon atmosphere) and allowed to cool to room temperature. Filtration, solvent removal under reduced pressure, and immediate recrystallization ($CHCl_3$/hexane) of the residue afforded 0.154 g (84%) of trans *aci*-reductone **12** (mp 111–113 °C), which slowly decomposed on standing at room temperature: IR (KBr) 3310 (OH), 1707, 1682, and 1644 (carbonyl) cm^{-1}. The ^1H NMR ($CDCl_3$) spectra showed *trans*-**12** to be a mixture of keto and enol forms (1:6): NMR ($CDCl_3$, 270 MHz) δ 1.0–2.5 (m, 8 H, 4 CH_2), 2.61 (dt, 1 H, J = 3.8 and 11.7 Hz, H-4a), 4.02 (dt, J = 4.0 and 11.6 Hz, H-8a of enol form), 4.47 (dt, J = 4.3 and 10.8 Hz, H-8a of keto form), 5.11 (s, H-3 of keto form), 5.12–6.3 (br s, OH). In DMSO-d_6 only the enol form was observed. Anal. ($C_9H_{12}O_4$) C, H.

Methyl 2,5-Bis(phenylmethoxy)benzoate (14). To a solution of methyl 2,5-bis(hydroxy)benzoate[30] (**13**; 5.04 g, 0.03 mol) in 20 mL of dry Me_2CO were added to anhydrous K_2CO_3 (4.55 g, 0.03 mol) and benzyl bromide (5.64 g, 0.033 mol). The resulting solution was refluxed overnight, and the solvent was evaporated under reduced pressure. The residue was partitioned between Et_2O and H_2O. The Et_2O layer was washed with 10% aqueous NaOH solution and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure, affording 9.62 g (92%) of **14**: mp (EtOH) 69.5–70 °C; IR (KBr) 1721 (ester) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.89 (s, 3 H, CO_2CH_3), 5.03 (s, 2 H, CH_2Ph), 5.11 (s, 2 H, CH_2Ph), 6.9–7.6 (m, 13 H, Ar H). Anal. ($C_{22}H_{20}O_4$) C, H.

Ethyl β-oxo-α,2,5-tris(phenylmethoxy)benzenepropanoate (15) was prepared according to the method used to prepare the analogous precursor to chloro target **1**.[2] Thus, **14** produced 1.34 g (33%) of **15** [mp (EtOH) 72–73 °C] following flash chromatography (silica gel) with petroleum ether/EtOAc (10:1) as eluent: IR (KBr) 1735 (ester), 1668 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.14 (t, 3 H, OCH_2, CH_3), 4.11 (q, 2 H, OCH_2CH_3), 4.58 (s, 2 H, OCH_2Ph), 5.02 (s, 4H, 2 OCH_2Ph), 5.38 (s, 1 H, CHCOOEt), 6.85 (d, 1 H, Ar H, J_{ortho} = 9.2 Hz), 6.9–7.6 (m, 17 H, Ar H). Anal. ($C_{32}H_{30}O_6$) C, H.

1-[2-(Phenylmethoxy)phenyl]ethanone (18). To a solution of 2-hydroxyacetophenone (**16**; 6.8 g, 0.05 mol; Aldrich) in dry acetone (100 mL) were added anhydrous K_2CO_3 (7.6 g, 0.055 mol) and benzyl bromide (9.4 g, 0.055 mol), and the mixture was treated as in the conversion of **13** to **14**, affording 9.7 g (86%) of **18** (petroleum ether) as white needles, mp 39.5–40 °C (lit.[31] mp 40 °C).

1-[2,5-Bis(phenylmethoxy)phenyl]ethanone (19) was prepared from **17** similar to the preparation of **18**. After the mixture was heated at reflux for 24 h, **19** [14.6 g (88%)] was produced as white needles: mp (EtOH) 76–76.5 °C; IR (KBr) 1683 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.60 (s, 3 H, CH_3), 5.04 (s, 2 H, CH_2Ph), 5.11 (s, 2 H, CH_2Ph), 6.8–7.5 (m, 13 H, Ar H). Anal. ($C_{22}H_{20}O_3$) C, H.

1-[5-Chloro-2-(phenylmethoxy)phenyl]ethanone (21) was prepared from **20** [1-(5-Chloro-2-hydroxyphenyl)ethanone][11] similar to the preparation of **18**. After the mixture was heated at reflux for 5 h, **21** [12.3 g (95%)] was produced as white crystals: mp (EtOH) 64.5–65 °C; IR (KBr) 1671 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.59 (s, 3 H, CH_3), 5.15 (s, 2 H, CH_2Ph), 6.96 (d, 1 H, J_{ortho} = 8.9 Hz, Ar H), 7.3–7.5 (m, 6 H, Ar H), 7.71 (d, 1 H, J_{meta} = 2.5 Hz, Ar H). Anal. ($C_{15}H_{13}ClO_2$) C, H, Cl.

6-Bromo-5-(phenylmethoxy)-1,3-benzodioxole (23). To a solution of *N*-bromosuccinimide (10.7 g, 0.06 mol) in dry DMF (70 mL) was added dropwise and with stirring a solution of 5-(phenylmethoxy)-1,3-benzodioxole[32] (13.68 g, 0.06 mol) in dry DMF (80 mL). The resulting solution was stirred for 24 h at room temperature, poured into 300 mL of H_2O, and extracted with $CHCl_3$ (3 × 70 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was recrystallized from absolute EtOH, affording 17.4 g (95%) of **23** as white crystals: mp 61.5–62 °C; NMR ($CDCl_3$, 90 MHz) δ 5.04 (s, 2 H, CH_2Ph), 5.91 (s, 2 H, OCH_2O), 6.56 (s, 1 H, Ar H), 6.99 (s, 1 H, Ar H), 7.1–7.6 (m, 5 H, CH_2Ph). Anal. ($C_{14}H_{11}BrO_3$) C, H, Br.

1-[4,5-(Methylenedioxy)-2-hydroxyphenyl]ethanone (24). To a solution of sesamol (**22**; 2.76 g, 0.02 mol) in Ac_2O (10 mL) was added under argon 5 mL of BF_3–etherate at 0 °C. The resulting solution was heated to 80–90 °C for 1 h and poured into a saturated NaOAc solution (20 mL). After extracting with Et_2O, the Et_2O solution was washed with 10% aqueous $NaHCO_3$ solution and H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was recrystallized from EtOH, affording 2.70 g (75%) of **24**, mp 111–112 °C (lit.[33] mp 112–113 °C).

1-[4,5-(Methylenedioxy)-2-(phenylmethoxy)phenyl]ethanone (25). The method used to prepare **25** from **23** was identical with the method described for the preparation of **30** from **29**. Thus, **23** afforded 3.87 g (72%) of **25**, mp (EtOH) 116.5–117 °C (lit.[34] mp 117–118 °C), after purification by flash chromatography (silica gel) with petroleum ether/EtOAc (15:1) as eluent. Additionally, **25** [11.4 g (84%)] was prepared from **24** under conditions identical with those used to prepare **18** from **16**.

2-(1,1-Dimethylethyl)-1,4-bis(phenylmethoxy)benzene (26) was prepared from *tert*-butylhydroquinone (4.98 g, 0.03 mol; Aldrich) according to the preparation of **14** from **13**, affording, after the mixture was refluxed for 72 h, 8.5 g (82%) of **26** as white needles: mp (EtOH) 94–94.5 °C; NMR ($CDCl_3$, 90 MHz) δ 1.38 [s, 9 H, $C(CH_3)_3$], 4.99 (s, 2 H, CH_2Ph), 5.05 (s, 2 H, CH_2Ph), 6.6–7.6 (m, 13 H, Ar H). Anal. ($C_{24}H_{26}O_2$) C, H.

2-Bromo-5-(1,1-dimethylethyl)-1,4-bis(phenylmethoxy)benzene (27) was prepared by a method identical with the one used to prepare **23**. Thus, **26** (20.8 g, 0.06 mol) produced white crystalline **27** (24.3 g, 95%): mp (EtOH) 134–135 °C; NMR ($CDCl_3$, 90 MHz) δ 1.32 [s, 9 H, $C(CH_3)_3$], 5.02 (s, 2 H, CH_2Ph), 5.08 (s, 2 H, CH_2Ph), 6.92 (s, 1 H, Ar H), 7.11 (s, 1 H, Ar H), 7.3–7.5 (m, 10 H, 2 CH_2Ph). Anal. ($C_{24}H_{25}BrO_2$) C, H, Br.

1-[4-(1,1-Dimethylethyl)-2,5-bis(phenylmethoxy)phenyl]ethanone (28). The method used to prepare **28** from **27** was identical with the method described for the preparation of **30** from **29**. Thus, **27** afforded 4.99 g (64%) of **28**, mp (EtOH) 114–115 °C, after purification by flash chromatography (silica gel) with petroleum ether/$CHCl_3$ (2:1) as eluent: IR (KBr) 1665 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 80 MHz) δ 1.37 [s, 9 H, $C(CH_3)_3$], 2.60 (s, 3 H, CH_3), 5.10 (s, 2 H, CH_2Ph), 5.14 (s, 2 H, CH_2Ph), 7.01 (s, 1 H, Ar H), 7.1–7.6 (m, 11 H, Ar H). Anal. ($C_{26}H_{28}O_3$) C, H.

2-Bromo-1-(phenylmethoxy)-4-phenylbenzene (29) was prepared from 2-bromo-4-phenylphenol[35] (7.47 g, 0.03 mol) according to the preparation of **14** from **13**, affording, after the mixture was refluxed for 4 h, 9.8 g (96%) of **29** as white needles: mp (EtOH) 51–52 °C; NMR ($CDCl_3$, 90 MHz) δ 5.20 (s, 2 H, CH_2Ph), 7.00 (d, 1 H, J_{ortho} = 8.7 Hz, Ar H), 7.2–7.6 (m, 11 H, Ar H), 7.81 (d, 1 H, J_{meta} = 2.2 Hz, Ar H). Anal. ($C_{19}H_{15}BrO$) C, H, Br.

1-[5-Phenyl-2-(phenylmethoxy)phenyl]ethanone (30). In a flame-dried flask was added under argon Mg (0.58 g, 0.024 mol) a few crystals of I_2 and dry THF (10 mL). A solution of **29** (6.78 g, 0.02 mol) in dry THF (15 mL) was added dropwise under reflux. Heating was continued for 3 h. The Grignard reagent was added over 1.5 h to a solution of freshly distilled CH_3COCl (7 mL) in dry THF (20 mL) held at −78 °C. The stirred reaction mixture

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was allowed to warm to room temperature overnight, poured into 2 N NH_4Cl solution (100 mL), and extracted with $CHCl_3$ (3 × 50 mL). The organic layer was washed with 10% NaOH and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to flash chromatography (silica gel) with petroleum ether/$CHCl_3$ (2:1) as eluent, affording 3.36 g (56%) of **30**, mp (EtOH) 83.5–84 °C (lit.[36] mp 80–81 °C).

Methyl β-Oxo-2-(phenylmethoxy)benzenepropanoate (34). A mixture of **18** (4.52 g, 0.02 mol), NaH (1.6 g of 60% NaH, 0.04 mol), and Me_2CO_3 (18 g, 0.2 mol) was heated to 70–75 °C for 20 min. After the excess Me_2CO_3 was evaporated under reduced pressure, the residue was acidified with 10% HCl solution and extracted with Et_2O. The Et_2O solution was washed with H_2O, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was filtered through silica gel with $CHCl_3$ as eluent, affording 5.1 g (90%) of **34** as light yellow crystals: mp (EtOH) 64–64.5 °C; IR (KBr) 1736 (ester), 1677 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.61 (s, 3 H, CO_2CH_3), 3.99 (s, 2 H, $CH_2CO_2CH_3$), 5.17 (s, 2 H, CH_2Ph), 6.9–8.0 (m, 9 H, Ar H). Anal. ($C_{16}H_{14}O_4$) C, H.

β-Keto esters 35–39 were prepared from appropriate precursors by using a procedure identical with that employed for the synthesis of **34**. Physical and spectral properties for these compounds follow.

Methyl 5-chloro-β-oxo-2-(phenylmethoxy)benzenepropanoate (35) [5.62 g (88%)], mp (EtOH) 74–75 °C, was obtained from **21**: IR (KBr) 1730 (ester), 1673 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.61 (s, 3 H, CO_2CH_3), 3.96 (s, 2 H, $CH_2CO_2CH_3$) 5.16 (s, 2 H, CH_2Ph), 6.95 (d, 1 H, J_{ortho} = 8.9 Hz, Ar H), 7.3–7.5 (m, 6 H, Ar H), 7.83 (d, 1 H, J_{meta} = 2.5 Hz, Ar H). Anal. ($C_{17}H_{15}ClO_4$) C, H, Cl.

Methyl β-oxo-2,5-bis(phenylmethoxy)benzenepropanoate (36) [7.06 g (91%)], mp (EtOH) 64.5–65 °C, was obtained from **19**: IR (KBr) 1736 (ester), 1666 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.61 (s, 3 H, CO_2CH_3), 3.99 (s, 2 H, $CH_2CO_2CH_3$), 5.04 (s, 2 H, CH_2Ph), 5.12 (s, 2 H, CH_2Ph), 6.8–7.7 (m, 13 H, Ar H). Anal. ($C_{24}H_{22}O_5$) C, H.

Methyl β-oxo-4-(phenylmethoxy)[1,1′-biphenyl]-3-propanoate (37) [6.49 g (90%)], mp (EtOH) 81–82 °C, was obtained from **30**: IR (KBr) 1757 (ester), 1677 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.62 (s, 3 H, CO_2CH_3), 4.02 (s, 2 H, $CH_2CO_2CH_3$), 5.21 (s, 2 H, CH_2Ph), 7.08 (d, 1 H, J_{ortho} = 8.6 Hz, Ar H), 7.2–7.8 (m, 11 H, Ar H), 8.12 (d, 1 H, J_{meta} = 2.5 Hz, Ar H). Anal. ($C_{23}H_{20}O_4$) C, H.

Methyl 4,5-(methylenedioxy)-β-oxo-2-(phenylmethoxy)-benzenepropanoate (38) [5.99 g (91%)], mp (EtOH) 86–86.5 °C, was obtained from **25**: IR (KBr) 1750 (ester), 1652 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.61 (s, 3 H, CO_2CH_3), 3.92 (s, 2 H, $CH_2CO_2CH_3$) 5.11 (s, 2 H, CH_2Ph), 5.98 (s, 2 H, OCH_2O), 6.54 (s, 1 H, Ar H), 7.39 (s, 5 H, CH_2Ph), 7.41 (s, 1 H, Ar H). Anal. ($C_{18}H_{16}O_6$) C, H.

Methyl 4-(1,1-dimethylethyl)-β-oxo-2,5-bis(phenylmethoxy)benzenepropanoate (39) [8.13 g (91%)], mp (EtOH) 106–107 °C, was obtained from **28**: IR (KBr) 1740 (ester), 1670 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.36 [s, 9 H, $C(CH_3)_3$], 3.63 (s, 3 H, CO_2CH_3), 4.00 (s, 2 H, $CH_2CO_2CH_3$), 5.11 (s, 2 H, CH_2Ph), 5.16 (s, 2 H, CH_2Ph), 6.99 (s, 1 H, Ar H), 7.2–7.5 (m, 10 H, $2CH_2Ph$), 7.54 (s, 1 H, Ar H). Anal. ($C_{28}H_{30}O_5$) C, H.

Methyl β-Oxo-2-(phenylmethoxy)-2-(benzoyloxy)-benzenepropanoate (41). To a stirred suspension of NaH (0.24 g of 60% NaH, 0.006 mol) in 2 mL of dry benzene was added dropwise a solution of **34** (1.42 g, 0.005 mol) in 5 mL of dry benzene. After being stirred for 1 h at room temperature, the mixture was cooled to 5–10 °C, and a solution of benzoyl peroxide (1.21 g, 0.005 mol) in 10 mL of dry benzene was added dropwise. Stirring was continued for an additional 1.5 h at room temperature. The reaction mixture was poured into cold water, and the organic layer was separated. The aqueous layer was acidified with 10% HCl solution and extracted with $CHCl_3$. The combined organic layers were washed with 10% aqueous NaOH solution and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was recrystallized from petroleum ether and Et_2O, yielding 1.54 g (76%) of **41** as white crystals: mp 75–76 °C; IR (KBr) 1760 (ester), 1722 (ester), 1667 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.69 (s, 3 H, CO_2CH_3), 5.16 (s, 2 H, CH_2Ph), 6.58 (s, 1 H, $CHCO_2CH_3$), 6.8–8.1 (m, 14 H, Ar H). Anal. ($C_{24}H_{20}O_6$) C, H.

Methyl 2-(Phenylmethoxy)-β-oxo-α-[[(phenylmethoxy)-carbonyl]oxy]benzenepropanoate (42). To a stirred suspension of NaH (0.29 g of 60% NaH, 0.007 mol) in 5 mL of dry benzene was added dropwise a solution of **34** (2.05 g, 0.007 mol) in 10 mL of dry benzene. After being stirred for 1 h at room temperature, the mixture was cooled to 5–10 °C, and a solution of dibenzyl peroxydicarbonate (1.82 g, 0.006 mol) in 30 mL of dry benzene was added dropwise during 45 min. The stirring was continued for an additional 1 h at the same temperature. The reaction mixture was poured into cold H_2O, and the organic layer was separated. The aqueous layer was acidified with 10% aqueous HCl solution and extracted with $CHCl_3$. The combined organic layers were washed with 10% aqueous NaOH solution and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel) with petroleum ether/EtOAc (9:1) as eluent afforded 1.56 g (60%) of **42** as white crystals: mp (Et_2O) 88–89 °C; IR (KBr) 1756 (ester), 1743 (ester), 1682 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.64 (s, 3 H, CO_2CH_3), 5.14 (s, 2 H, CH_2Ph), 5.16 (s, 2 H, CH_2Ph), 6.29 (s, 1 H, $CHCO_2CH_3$), 6.8–7.9 (m, 14 H, Ar H). Anal. ($C_{25}H_{22}O_7$) C, H.

[(Phenylmethoxy)carbonyl]oxy intermediates 43–47 were prepared from corresponding β-keto esters (**35–39**, respectively) by using the method employed for the preparation of **42** from **34**. Solvent systems for chromatographic purification varied for individual compounds as indicated. Physical and spectral properties for these compounds follow.

Methyl 5-Chloro-β-oxo-2-(phenylmethoxy)-α-[[(phenylmethoxy)carbonyl]oxy]benzenepropanoate (43). Purification by flash chromatography (silica gel) with petroleum ether/EtOAc (6:1) as eluent afforded 1.84 g (65%) of **43**: mp (Et_2O) 119.5–120.5 °C; IR (KBr) 1755 and 1745 (ester), 1686 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.65 (s, 3 H, CO_2CH_3), 5.12 (s, 2 H, CH_2Ph), 5.17 (s, 2 H, CH_2Ph), 6.25 (s, 1 H, $CHCO_2CH_3$), 6.89 (d, 1 H, Ar H, J_{ortho} = 8.9 Hz), 7.2–7.5 (m, 11 H, Ar H), 7.81 (d, 1 H, Ar H, J_{meta} = 2.5 Hz). Anal. ($C_{25}H_{21}ClO_7$) C, H, Cl.

Methyl β-Oxo-2,5-bis(phenylmethoxy)-α-[[(phenylmethoxy)carbonyl]oxy]benzenepropanoate (44). Purification by flash chromatography (silica gel) with petroleum ether/EtOAc (7:1) as eluent afforded 1.8 g (56%) of **44**: mp (Et_2O) 65–68 °C; IR (KBr) 1745 (ester), 1674 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.63 (s, 3 H, CO_2CH_3), 5.02 (s, 2 H, CH_2Ph), 5.10 (s, 2 H, CH_2Ph), 5.17 (s, 2 H, CH_2Ph), 6.31 (s, 1 H, $CHCO_2CH_3$), 6.87 (d, 1 H, Ar H, J_{ortho} = 8.9 Hz), 7.0–7.7 (m, 17 H, Ar H). Anal. ($C_{32}H_{28}O_8$) C, H.

Methyl β-Oxo-4-(phenylmethoxy)-α-[[(phenylmethoxy)-carbonyl]oxy][1,1′-biphenyl]-3-propanoate (45). Purification by flash chromatography (silica gel) with petroleum ether/Me_2CO (6:1) as eluent afforded 1.95 g (64%) of **45**: mp (Et_2O) 83–85 °C; IR (KBr) 1740 (ester), 1677 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.65 (s, 3 H, CO_2CH_3), 5.17 (s, 2 H, CH_2Ph), 6.32 (s, 1 H, $CHCO_2CH_3$), 7.02 (d, 1 H, Ar H, J_{ortho} = 8.6 Hz), 7.1–7.8 (m, 16 H, Ar H), 8.09 (d, 1 H, Ar H, J_{meta} = 2.5 Hz). Anal. ($C_{31}H_{26}O_7$) C, H.

Methyl 4,5-(Methylenedioxy)-β-oxo-2-(phenylmethoxy)-α-[[(phenylmethoxy)carbonyl]oxy]benzenepropanoate (46). Purification by flash chromatography (silica gel) with petroleum ether/EtOAc (3:1) as eluent afforded 1.28 g (45%) of **46**: mp (Et_2O) 106–106.5 °C; IR (KBr) 1744 (ester), 1666 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 3.64 (s, 3 H, CO_2CH_3), 5.09 (s, 2 H, CH_2Ph), 5.16 (s, 2 H, CH_2Ph), 5.97 (s, 2 H, OCH_2O), 6.25 (s, 1 H, $CHCO_2CH_3$), 6.47 (s, 1 H, Ar H), 7.2–7.5 (m, 11 H, Ar H). Anal. ($C_{26}H_{22}O_9$) C, H.

Methyl 4-(1,1-Dimethylethyl)-β-oxo-2,5-bis(phenylmethoxy)-α-[[(phenylmethoxy)carbonyl]oxy]benzenepropanoate (47). Purification by flash chromatography (silica gel) with petroleum ether/Me_2CO (8:1) as eluent afforded 2.13 g (60%) of **47**: mp (Et_2O) 118–119 °C; IR (KBr) 1744 (ester), 1676 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.32 [s, 9 H, $C(CH_3)_3$], 3.65 (s, 3 H, CO_2CH_3), 5.08 (s, 2 H, $CHCO_2Ph$), 5.13 (s, 2 H, CH_2Ph), 5.18 (s, 2 H, CH_2Ph), 6.33 (s, 1 H, $CHCO_2CH_3$, 6.93 (s, 1 H, Ar H), 7.1–7.7 (m, 16 H, Ar H). Anal. ($C_{36}H_{36}O_8$) C, H.

3-(Benzoyloxy)-4-hydroxy-2*H*-1-benzopyran-2-one (48). To a solution of **41** (0.61 g, 0.0015 mol) in absolute EtOH (6 mL)

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were added 10% Pd/C (0.061 g) and cyclohexene (3 mL). The resulting solution was heated under reflux for 1 h (argon). The mixture was filtered, and the solvent was removed under reduced pressure. To a solution of the residue in 5 mL of MeOH was added 5 mL of concentrated HCl. The resulting solution was refluxed for 20 min, and the solvent was removed under reduced pressure. The residue was partioned between EtOAc and 10% aqueous $NaHCO_3$ solution. After acidification with a mixture of ice and concentrated HCl, the aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from MeOH and H_2O, yielding 0.31 g (73%) of **48** as a white solid: mp 225–227 °C; IR (KBr) 3060 (OH), 1745 (ester), 1675 (carbonyl), 1620 (carbonyl) cm^{-1}; NMR (DMSO-d_6, 90 MHz) δ 7.1–8.2 (m, 9 H, Ar H). Anal. ($C_{16}H_{10}O_5$) C, H.

2,2-Dimethyl-5-[[(phenylmethoxy)carbonyl]oxy]-1,3-dioxane-4,6-dione (51). To a solution of the sodium salt (**50**;[19] 16.6 g, 0.1 mol) of Meldrum's acid in 150 mL of dry DMF was added dropwise under argon and with stirring a solution of dibenzyl peroxydicarbonate[15] (30.2 g, 0.1 mol) in dry DMF (100 mL) at −10 °C. After the mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature, 5% HCl solution (200 mL) was added. The resulting mixture was extracted with EtOAc, and the organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was recrystallized from EtOAc and petroleum ether, yielding 23.7 g (81%) of **51** as a white solid: mp 153–154 °C; IR (KBr) 1817 and 1756 (ester) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.85 (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3), 5.29 (s, 2 H, CO_2CH_2Ph), 5.69 (s, 1 H, $CHOCO_2CH_2Ph$) 7.40 (s, 5 H, CO_2CH_2Ph). Anal. ($C_{14}H_{14}O_7$) C, H.

***cis*-2-(Acetyloxy)-1-cyclohexanecarbonyl chloride (52)** was prepared from *cis*-2-(acetyloxy)-1-cyclohexanecarboxylic acid[21] (1.86 g, 0.01 mol) according to a procedure identical with the one used for the preparation of trans acyl chloride **53**. Distillation of the residue following concentration under reduced pressure at 65–67 °C (0.25 mmHg) afforded 1.49 g (73%) of cis acyl chloride **52**: IR (neat) 1795 (carbonyl), 1737 (ester) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.1–2.4 (m, 8 H, 4 CH_2), 2.06 (s, 3 H, CH_3), 2.9–3.1 (m, 1 H, H-1), 5.4–5.6 (m, 1 H, H-2).

***trans*-2-(Acetyloxy)-1-cyclohexanecarbonyl Chloride (53).** To a cooled solution (0 °C) of *trans*-2-acetoxy-1-cyclohexanecarboxylic acid[21] (3.72 g, 0.02 mol) in dry CH_2Cl_2 (20 mL) under argon was added oxalyl chloride (3.8 g, 0.03 mol). Stirring was continued for 30 min at 0 °C and for 3 h at room temperature. The solvent was removed under reduced pressure, and the residue was distilled at 68–71 °C (0.3 mmHg), affording 3.5 g (86%) of trans acyl chloride **53**: IR (neat) 1795 (carbonyl), 1742 (ester) cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.9–2.4 (m, 8 H, 4 CH_2), 1.99 (s, 3 H, CH_3), 2.7–3.1 (m, 1 H, H-1), 4.8–5.1 (m, 1 H, H-2).

***cis*-5-[[2-(Acetyloxy)cyclohexyl]carbonyl]-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl phenylmethyl carbonate (54)** was prepared from **52** by using methodology identical with that employed for the preparation of trans **55** from **53**. The cis acyl chloride **52** (0.41 g, 0.002 mol) afforded 0.49 g (53%) of cis **54**: mp (THF/petroleum ether) 85–86 °C; IR (KBr) 1793 (sh), 1770 (sh), 1758, 1742 (sh) (carbonyl) cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 1.2–2.2 (m, 8 H, 4 CH_2), 1.88 (s, 3 H, CH_3), 1.90 (s, 3 H, CH_3), 1.98 (s, 3 H, CH_3), 3.5–3.7 (m, 1 H, H-1), 5.23 (d, 1 H, J_{AB} = 11.9 Hz, CH_2Ph), 5.24 (d, 1 H, J_{AB} = 11.9 Hz, CH_2Ph), 5.2–5.3 (m, 1 H, H-2), 7.3–7.5 (m, 5 H, CH_2Ph). Anal. ($C_{23}H_{26}O_{10}$) C, H.

***trans*-5-[[2-(Acetyloxy)cyclohexyl]carbonyl]-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl phenylmethyl Carbonate (55).** To a solution of **51** (1.47 g, 0.005 mol) in dry CH_2Cl_2 (25 mL) held at room temperature under argon was added freshly distilled pyridine (0.79 g, 0.01 mol). After being stirred for 30 min, the solution was cooled (0 °C), and a solution of trans acyl chloride **53** (1.02 g, 0.005 mol) in dry CH_2Cl_2 (5 mL) was added dropwise. Stirring was continued at 0 °C for 1 h and at room temperature overnight. The reaction mixture was diluted with H_2O (20 mL), and the organic layer was separated. The organic layer was washed with 10% $NaHCO_3$ solution, 10% HCl solution, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure affording a light yellow oil. Purification of the oil by flash chromatography [silica gel, petroleum ether/EtOAc (7:1)] afforded 1.49 g (64%) of **55**: mp (THF/petroleum ether) 79–79.5 °C; IR (KBr) 1799, 1757 and 1732 (carbonyl) cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 1.2–1.4 (m, 4 H, 2 CH_2), 1.7–1.9 (m, 2 H, CH_2), 1.86 (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3), 1.93 (s, 3 H, CH_3), 2.1–2.2 (m, 2 H, CH_2), 3.4–3.5 (m, 1 H, H-1), 4.92 (dt, 1 H, J = 4.4, and 10.5 Hz, H-2), 5.26 (d, 1 H, J_{AB} = 12.3 Hz, CH_2Ph), 5.26 (d, 1 H, J_{AB} = 12.3 Hz, CH_2Ph), 7.3–7.4 (m, 5 H, CH_2Ph). Anal. ($C_{23}H_{26}O_{10}$) C, H.

***cis*-4a,5,6,7,8,8a-Hexahydro-3-[[(phenylmethoxy)carbonyl]oxy]-4-hydroxy-2*H*-1-benzopyran-2-one (56)** was prepared from **54** according to a procedure identical with that employed for the preparation of trans **57** from **55**. Thus, cis **54** (0.187 g, 0.0004 mol) afforded 0.08 g (62%) of cis benzyl carbonate **56**: mp (MeOH/EtOAc) 173–173.5 °C; IR (KBr) 3145 (br s, OH), 1775 (ester), 1681 and 1627 (carbonyl) cm^{-1}; NMR (DMSO-d_6, 500 MHz) δ 1.1–1.7 (m, 6 H, 3 CH_2), 1.8–2.0 (m, 2 H, CH_2), 2.4–2.6 (m, 1 H, H-4a), 4.5–4.6 (sharp m, 1 H, H-8a), 5.20 (d, 1 H, J_{AB} = 12.3 Hz, CH_2Ph), 5.21 (d, 1 H, J_{AB} = 12.3 Hz, CH_2Ph), 7.3–7.5 (m, 5 H, CH_2Ph). Anal. ($C_{17}H_{18}O_6$) C, H.

***trans*-4a,5,6,7,8,8a-Hexahydro-3-[[(phenylmethoxy)carbonyl]oxy]-4-hydroxy-2*H*-1-benzopyran-2-one (57).** A solution of trans **55** (0.93 g, 0.002 mol) and *p*-TsOH (0.025 g) in MeOH (10 mL) was heated at reflux for 24 h. The solvent was removed under reduced pressure, affording a white solid, which was recrystallized from MeOH and EtOAc, yielding 0.43 g (68%) of trans benzyl carbonate **57** as a white solid: mp 181–181.5 °C; IR (KBr) 3145 (br s, OH), 1783 (ester), 1696 and 1630 (carbonyl) cm^{-1}; NMR (DMSO-d_6, 500 MHz) δ 1.0–1.6 (m, 4 H, 2 CH_2), 1.6–2.2 (m, 4 H, 2 CH_2), 2.67 (dt, 1 H, J = 3.7 and 11.8 Hz, H-4a), 4.05 (dt, 1 H, J = 4.1 and 11.5 Hz, H-8a), 5.20 (d, 1 H, J_{AB} = 12.3 Hz, CH_2Ph), 5.22 (d, 1 H, J_{AB} = 12.3 Hz, CH_2Ph), 7.3–7.5 (m, 5 H, CH_2Ph). Anal. ($C_{17}H_{18}O_6$) C, H.

Antiaggregatory Studies. ADP and AA were obtained from Sigma Chemical Co. (St. Louis, MO). [^{14}C]Serotonin (57 mCi/mmol) and [^{3}H]AA (210 Ci/mmol) were supplied by Amersham (Arlington Heights, IL). U46619 [15(*S*)-hydroxy-11,9-(epoxymethano)prosta-5(*Z*),13(*E*)-dienoic acid] was purchased from Upjohn Diagnostics (Kalamazoo, MI). Drugs were freshly prepared in 10 mM sodium phosphate buffer, pH 7.4, containing 0.9% NaCl, and deoxygenated by bubbling with N_2. Dimethyl sulfoxide (DMSO) was employed as the solvent for compound **8**. The final DMSO concentration in platelet suspensions was 0.14% (18 mM), which did not affect aggregation in the absence of the inhibitor. Concentration-dependent effects of compound **8** were measured in the presence of constant amounts of DMSO.

For antiaggregatory studies blood was collected from normal human volunteers who reported to be free of medication for at least 10 days prior to blood collection. Platelet-rich plasma was prepared as described previously[37] and used for all studies. Platelet aggregation studies were performed according to the turbidometric method of Born[38] in Payton Model 600 or Chrono-Log Model 560 dual-channel aggregometers interfaced to Apple microcomputers for analysis of platelet aggregation data.[39] All inducers were used at the minimum concentrations required to stimulate maximal aggregation. Inhibitors were added 1 min prior to induction of platelet activation, and inhibitory concentration-50 (IC_{50}) values for each inhibitor were determined from changes in the amplitude of light transmittance after 6 min for ADP and 4 min for AA and U46619. Secretion of the contents of platelet-dense granules was measured by monitoring the release of radioactivity from platelets prelabeled with [^{14}C]serotonin.[37]

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Registry No. **1**, 103620-90-2; **2**, 882-09-7; **4**, 79821-07-1; **5a**, 107986-51-6; **5b**, 78229-45-5; **6**, 77889-64-6; **7**, 114250-09-8; **8**, 114250-10-1; **9**, 114250-11-2; **10**, 114250-12-3; **11** (keto), 114250-13-4; **11** (enol), 114250-14-5; **12** (keto), 114250-41-8; **12** (enol), 114250-42-9; **13**, 2150-46-1; **14**, 106296-25-7; **15**, 114250-15-6; **16**,

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Supplementary Material Available: Discussion of the determination of redox potentials for ascorbic acid and experimental *aci*-reductones and antilipidemic methods and results and tables listing the influence of 1, **2**, **5a**,**b**–**7**, and **9** on the serum cholesterol concentrations in rats fed a high-cholesterol diet (13 pages). Ordering information is given on any current masthead page.

Predictive Structure–Activity Relationships in a Series of Pyranoquinoline Derivatives. A New Primate Model for the Identification of Antiallergic Activity

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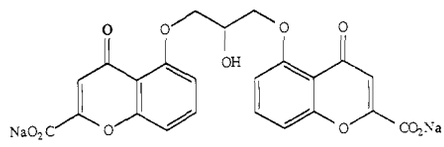
A new primate model has been developed for the evaluation of antiallergic agents. Compounds are tested for their ability to inhibit anti-IgE induced histamine release from the bronchoalveolar mast cells lavaged from the lungs of *Macaca arctoides* infected with the parasite *Ascaris suum*. A number of 6-substituted pyranoquinoline derivatives have been evaluated and the activities were subjected to Hansch analysis. A highly significant correlation with lipophilicity (π) and Hammett σ_p values was obtained. The relationship was used to predict further compounds for synthesis giving rise to new, potent analogues. Some apparently anomalous results could be explained by differences in the ionization of, or tautomerism in, the quinoline ring.

The difficulties associated with identifying prophylactic antiallergic drugs related to sodium cromoglycate (cromolyn sodium) (1) have been discussed in previous publications.[1,2] In our search for potent new analogues with topical activity (as opposed to orally effective agents) some of the problems have been obviated, but that of the poorly predictive nature of the pharmacological screens still remains. We have therefore developed an in vitro primate model using bronchoalveolar mast cells from *Macaca arctoides* monkeys infected with the nematode *Ascaris suum*.[1,3] This lumenal mast cell is particularly relevant to reversible obstructive airways disease as it is among the first to encounter both inhaled antigen and drug. The use of primate cells also minimized concern about interspecies variability. This paper describes the synthesis of a series of 6-substituted pyranoquinolines and their evaluation in the monkey lung lavage model. The biological results have been subjected to a Hansch analysis which has been used to predict new compounds for synthesis.



1

Chemistry

Thirty-one pyranoquinoline derivatives (**30**–**60**, Table I) were tested in the monkey bronchoalveolar lavage mast cell screen. The syntheses of some compounds have previously been described;[1] routes to all other analogues are summarized in Schemes I–V. Compounds for biological testing (except **48**) were prepared as their disodium salts (or trisodium salt in the case of **35**). With only two exceptions (**38** and **41**, see below) these were obtained from the corresponding diesters by hydrolysis with the theoretical quantity of sodium hydroxide in refluxing methanol.

Scheme I. Ethyl methyl 4,6-dioxo-10-propyl-*4H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (**2**)[1] was brominated with phosphoryl bromide in methylene chloride to give the 6-bromo compound **3**. This was converted into the perfluoroalkyl diesters **4**–**6** by a modification of the procedure of Kobayashi et al.,[4] using the appropriate perfluoroalkyl iodide in HMPA with an activated copper catalyst.

The pyranoquinolinone **2** was also converted to diethyl 6-amino-4-oxo-10-propyl-*4H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (**7**) with chlorosulfonyl isocyanate, by the procedure described by Wright.[5] This amine was converted to the 1-pyrrolyl **8** and phenylureido **9** diesters by standard methods.

Scheme II. The 6-methylpyranoquinoline derivative **10**[1] was condensed with benzaldehyde in acetic acid with tosic acid as catalyst to produce the styryl derivative **18**. Compound **10** was also used to prepare the key 6-formylpyranoquinoline derivative **11** by oxidation with selenium dioxide. The aldehyde **11** was converted to the difluoromethyl diester **12** with (diethylamido)sulfur trifluoride[6] in methylene chloride and was also used in the synthesis of the diesters of the benzoylhydrazone **13**,

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