Table II. Physical Properties for the New Compounds of Table I

no.	mp, °C	formula	anal.
6	118–120	$C_{20}H_{21}N_3O \cdot 2HCl$	C, H, N, Cl
7	118–120	$C_{20}H_{21}N_3O \cdot 2HCl$	C, H, N, Cl
8	132–134	$C_{20}H_{21}N_3O \cdot HCl \cdot H_2O$	C, H, N
9	174–175	$C_{20}H_{21}N_3O \cdot HCl$	C, H, N, Cl
10	199–200	$C_{20}H_{21}N_3O \cdot 2HCl$	C, H, N, Cl

MeOH gave the desired 4-phenylquinoline-8-carboxylic acid (**17**) (31% yield), mp 161–161.5 °C. Anal. ($C_{16}H_{11}NO_2$) C, H, N.

5-Phenylquinoline-8-carboxylic Acid (20). A mixture of 3-amino-4-methylbiphenyl[28] (**18**) (11.5 g, 63 mmol), glycerol (21.5 g), anhydrous As_2O_5 (11 g), and concentrated H_2SO_4 (19.5 g) was stirred at 160–165 °C for 5 h, as described for the general Skraup synthesis of pyridylquinolines.[29] The cooled mixture was diluted with aqueous HCl, clarified with charcoal, filtered, and extracted with CH_2Cl_2. The residue of this extraction was then extracted with boiling petroleum ether to give 8-methyl-5-phenylquinoline (**19**) (8.8 g, 64%). A sample crystallized from aqueous MeOH as colorless prisms, mp 57.5–58 °C. Anal. ($C_{16}H_{13}N$) C, H, N.

SeO_2 oxidation of this compound by the above procedure gave 5-phenylquinoline-8-carboxylic acid (**20**). Crystallization from CH_2Cl_2/EtOH then EtOAc gave pure product (34% yield), mp 150–151 °C. Anal. ($C_{16}H_{11}NO_2$) C, H, N.

6-Phenylquinoline-8-carboxylic Acid (23). 3-Methyl-4-nitrobiphenyl[30] was reduced by Fe/HCl in DMF/EtOH/H_2O, and the resulting 4-amino-3-methylbiphenyl (**21**) was purified by crystallization of the hydrochloride salt from EtOAc/MeOH/HCl as prisms, mp 232–235 °C. Anal. ($C_{13}H_{13}N \cdot HCl$) C, H, N. This was used in the Skraup synthesis under identical conditions with those described above and provided 8-methyl-6-phenylquinoline (**22**) in 78% yield. A sample was crystallized from EtOAc/Me_2CO/HCl as the hydrochloride salt, mp 263–265 °C. Anal. ($C_{16}H_{13}N \cdot HCl$) C, H, N, Cl.

Oxidation with SeO_2 as described above, followed by crystallization of the product from EtOH and then EtOAc, gave 6-phenylquinoline-8-carboxylic acid (**23**) (31% yield), mp 170–171 °C. Anal. ($C_{16}H_{11}NO_2$) C, H, N.

Synthesis of Amides of Table I. General Example. 2-Phenylquinoline-8-carboxylic acid (1 equiv) was suspended in dry DMF (5 mL/g) and treated with 1,1′-carbonyldiimidazole[31] (1.5 equiv) at 20–50 °C for 30 min (until gas evolution ceased). The mixture was cooled to 20 °C and treated with *N*,*N*-dimethylethylenediamine (2.5 equiv). After 15 min, most of the solvent was removed under reduced pressure, and dilute aqueous Na_2CO_3 was added to precipitate the product. Extraction with CH_2Cl_2 gave the crude free base, which was crystallized from MeOH/EtOAc/HCl to give a 90% yield of *N*-[2-(dimethylamino)ethyl]-2-phenylquinoline-8-carboxamide dihydrochloride (compound **6** of Table I), mp 118–120 °C. Anal. (Table II). The other compounds of Table I were prepared similarly.

Acknowledgment. We thank Margaret Smith for supervision of the animal testing and Margaret Snow for preparation of the manuscript. This work was supported by the Auckland Division of the Cancer Society of New Zealand and the Medical Research Council of New Zealand.

Registry No. **2**, 89459-25-6; **5**, 112022-03-4; **6**, 107027-12-3; **6**·2HCl, 107026-86-8; **7**, 113431-33-7; **7**·2HCl, 113431-34-8; **8**, 113431-35-9; **8**·HCl, 113431-36-0; **9**, 113431-37-1; **9**·HCl, 113431-38-2; **10**, 113431-39-3; **10**·2HCl, 113431-40-6; **11**, 113431-41-7; **12**, 113431-42-8; **12**·HCl, 113431-43-9; **13**, 113431-44-0; **14**, 70453-86-0; **15**, 113431-45-1; **16**, 113431-46-2; **17**, 113431-47-3; **18**, 80938-67-6; **19**, 113431-48-4; **20**, 113431-49-5; **21**, 63019-98-7; **21**·HCl, 3419-49-6; **22**, 113431-50-8; **22**·HCl, 113431-51-9; **23**, 113431-52-0; $PhCH_2COCO_2H$, 156-06-9; *o*-$MeC_6H_4NH_2$, 95-53-4; $PhCOCH_2CO_2Et$, 94-02-0; 8-methyl-2-phenylquinoline, 5353-90-2; 2-phenyl-8-quinolinecarboxylic acid, 5093-81-2; 7-methylisatin, 1127-59-9; glycerol, 56-81-5; 3-methyl-4-nitrobiphenyl, 69314-47-2; *N*,*N*-dimethylethylenediamine, 110-70-3.

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(Acyloxy)benzophenones and (Acyloxy)-4-pyrones. A New Class of Inhibitors of Human Neutrophil Elastase

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A series of 4-(acyloxy)- and 4,4′-bis(acyloxy)benzophenones were synthesized. Some of them, pivalates (trimethylacetates) and isobutyrates in particular, were found to be potent and selective inhibitors of human neutrophil (leukocyte) elastase. A series of 2-[(acyloxy)methyl]-5-(acyloxy)-4-pyrones were synthesized regioselectively from kojic acid. The 4-pyrones bearing a long chain acyl group at the 2-position and either pivaloyloxy or isobutyryloxy at the 5-position were potent and selective inhibitors of the human elastase. A number of analogues and derivatives in both series were synthesized in order to study the structure–activity relationship as summarized in Tables I–VI and in Tables IX and X. The inhibition was selective to human neutrophil elastase. No inhibition of porcine pancreatic elastase or bovine pancreatic chymotrypsin (Tables VII and XI) was observed. The most likely mechanism of inhibition is discussed. The implication of these findings for the treatment of rheumatoid arthritis and emphysema is outlined.

Elastin is a connective tissue component that provides elasticity to lung connective tissue, yellow tendon, and cartilage of joints. Elastin turnover and remodelling is controlled by neutrophil and tissue elastases. The metabolic turnover of mature elastin is slow under normal circumstances where elastase activity is suppressed by α_1-antitrypsin and α_2-macroglobulin. However, the rate of elastin (and collagen) degradation is greatly enhanced under a variety of clinical conditions,[1] particularly in pulmonary emphysema,[2,3] and rheumatoid arthritis,[4–7]

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eventually destroying the connective tissue of the lung and joints. Neutrophil elastase is believed to participate in this process. Elastase may also accelerate inflammation indirectly by cleaving complement component, C'5, to C'5a, a potent chemoattractant for neutrophils. Moreover, elastase may contribute to the pathology of rheumatoid arthritis by stimulating the synthesis of rheumatoid factor.[8-10] Other disease states in which elastase can be implicated are gingivitis[10] and cancer metastasis.[11a-c]

There is reasonable expectation, therefore, that a selective inhibitor of human neutrophil elastase might be useful for the treatment of emphysema, rheumatoid arthritis, and other diseases.

Several classes of inhibitors[12] of human leukocyte elastase (HLE)[13] have been reported. They are *N*-arylbenzisothiazolinone 1,1-dioxides,[14] fatty acids,[15] sulfonyl fluorides,[16] the microbial product, elasnin,[17] 2-[(perfluoroacyl)amino]benzenesulfonyl fluorides,[18] 4*H*-3,1-benzoxazin-4-one,[19] 4-chloroquinazolines,[19] isatoic anhydride derivatives,[20] and azapeptide *p*-nitrophenyl esters.[21]

During random screening for elastase inhibitors, we discovered that several steroidal enol pivalates were potent, selective, and competitive inhibitors of HLE. The mechanism of the inhibition was presumably due to transfer of the pivaloyl group from the steroid to the serine residue located at the active site of elastase. In this context, the inhibitor acts as a suicidal substrate, the mechanism somewhat similar to the inhibition by α_1-antitrypsin.

The steroidal pivalates, SC-22260 being the most potent representative, were unstable and hydrolyzed to the parent unsaturated ketones in DMSO–aqueous buffers at 25 °C. We set out to find another lipophilic enol moiety that would provide chemically more stable pivalates with no endocrine side effect inherent to many steroid molecules.

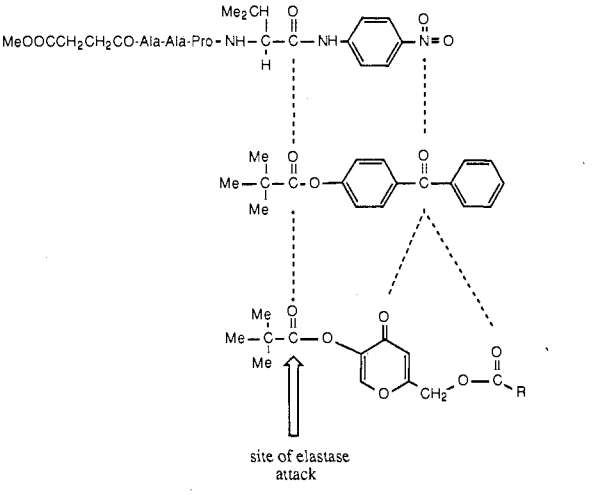
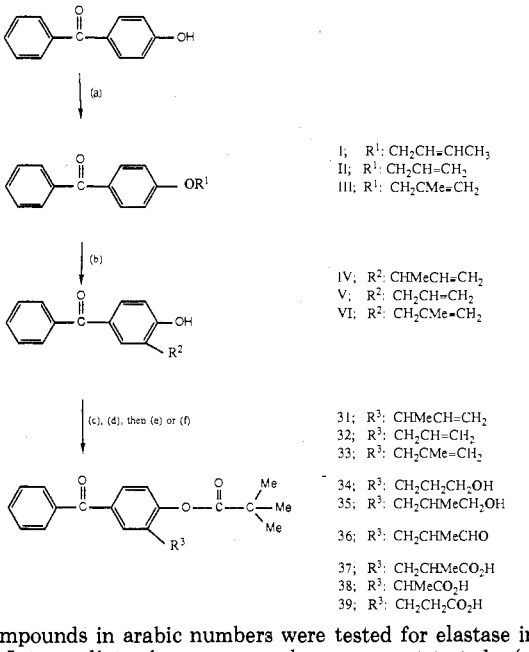
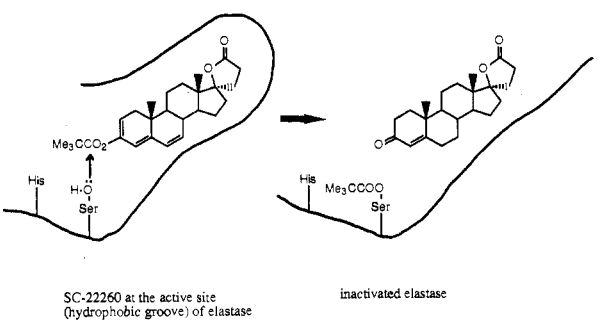


Figure 1. Topological relationship of new inhibitors and a substrate.

Scheme I[a]



[a] Compounds in arabic numbers were tested for elastase inhibition. Intermediates in roman numbers were not tested. (a) An allylic halide, NaI, K_2CO_3, acetone, reflux 1–4 days (general procedure C). (b) Diethylaniline, 205–210 °C for 3–4 h (general procedure D). (c) Pivaloyl chloride, pyridine, 0–50 °C (general procedure A). (d) 9-BBN, THF, 0–50 °C; then H_2O_2, NaOH, H_2O, 25 °C (general procedure E). (e) Swern oxidation for **36**. (f) NH_2SO_3H, $NaClO_2$, H_2O, 25 °C for **37**, **38**, **39**.



It was found that 2-[(acyloxy)methyl]-5-(pivaloyloxy)-4-pyrones, kojic acid derivatives, were potent, selective (no inhibition of porcine pancreatic elastase or bovine

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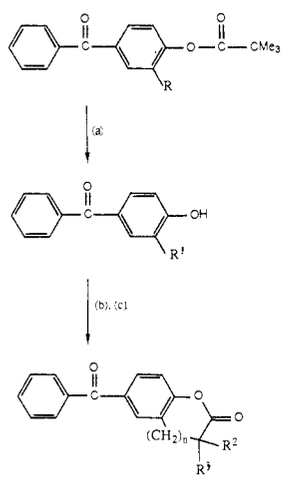
Scheme II[a]



[a] (a) NaOH, H_2O, MeOH, 50 °C (general procedure F). (b) Heat 190–210 °C, 6 min. (c) LDA, THF, −70 °C; MeI, −70 °C (general procedure G).

pancreatic chymotrypsin), and competitive inhibitors of HLE. It was also found that pivalates of hydroxybenzophenones were excellent inhibitors of HLE. Some of these compounds are among the most potent and selective inhibitors of HLE yet described.

The topological relationship of these new inhibitors and a substrate[22] for HLE is shown in Figure 1.

Chemistry

Most (acyloxy)benzophenones were prepared by treating a proper phenolic starting material with pivaloyl chloride in pyridine (general procedure A).

3-Substituted 4-(pivaloyloxy)benzophenones listed in Table VI were synthesized (Scheme I) by Claisen rearrangement of 4-(allyloxy)benzophenones (I–III) to 3-allyl-4-hydroxybenzophenones (IV–VI) followed by acylation (**31–33**) and further modifications for the 3-substituents. Thus, **31–33** were converted, through the hydroxy derivatives (**34**, **35**) or aldehyde (**36**), to 3-(ω-carboxyalkyl)-4-(pivaloyloxy)benzophenones (**37–39**).

The lactones listed in Table VIII were prepared (Scheme II) from **37–39** by removal of the pivaloyl group (VII–IX) followed by cyclization and α-methylation (**40–44**).

Kojic acid derivatives were synthesized in two different manners. As shown in Scheme III, the primary alcohol of kojic acid (X) was protected with the tetrahydropyranyl group (XI), and then the enol group was acylated with pivaloyl chloride (or with another acyl chloride) to give **61**. The acid hydrolysis of **61** produced kojic acid 5-*O*-pivalate (**59**) selectively. The second acyl group could be introduced easily into **59** to form various analogues (**45–47**, etc.). Alternatively, the primary alcohol group was first acylated by heating a mixture of kojic acid and a fatty acid in the presence of zinc chloride to 160 °C, and then the enol group was acylated with an acyl chloride (Scheme IV).

Results and Discussion in the Benzophenone Series

The structure–activity relationship (SAR) in 4-(acyloxy)benzophenones is summarized in Table I. Whereas 4-(acetyloxy)benzophenone (**4**, a known compound) and 4-(propionyloxy)benzophenone (**3**) exhibited marginal elastase inhibitory activities, 4-(isobutyryloxy)- and 4-(pivaloyloxy)benzophenones (**2**, **1**) were potent inhibitors.

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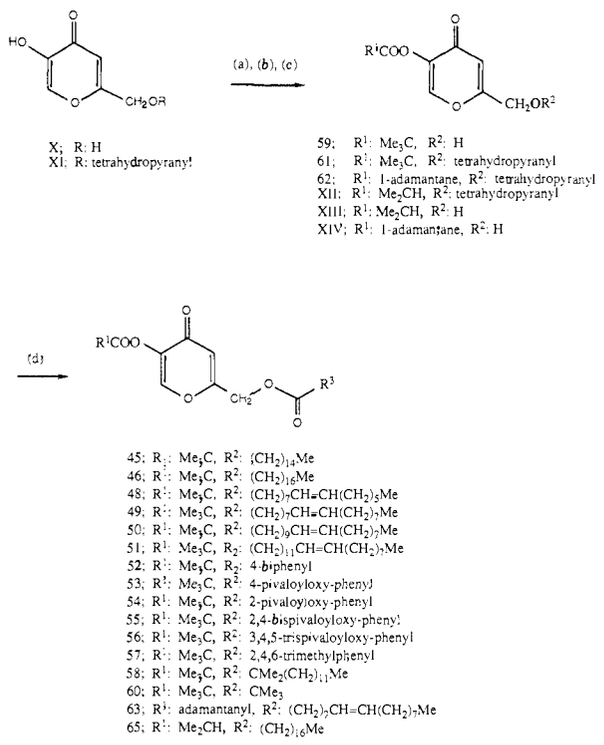
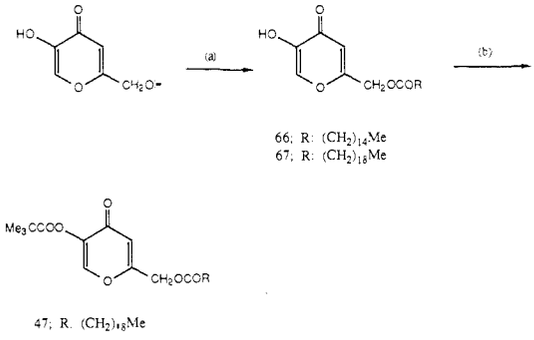
Scheme III[a]



[a] Compounds in arabic numbers were tested for elastase inhibition whereas intermediates in roman numbers were not tested. (a) Dihydropyran, TosOH. (b) R^1COCl, pyridine (general procedure H). (c) MeOH, HCl, H_2O (general procedure J). (d) R^3COCl, pyridine, heat (general procedure K).

Scheme IV



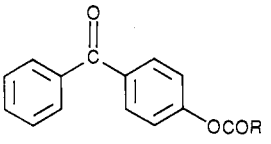
[a] (a) RCOOH, $ZnCl_2$, 160 °C (general procedure L). (b) Me_3CCOCl, pyridine (general procedure L). (b) Me_3CCOCl, pyridine (general procedure A).

Isobutyric and pivalic acids appear to fit exceptionally well. Minor structural modifications, for instance, from isobutyryl to methacroyl (**6**), cyclopropylcarbonyl (**7**), or cyclohexanoyl (**5**), resulted in significant loss of inhibitory activity. Incorporation of a polar group in the acyl moiety resulted in substantial decrease of potency (**8**, **9**).

As summarized in Table II, 4,4′-bis(acyloxy)benzophenones were more potent than the corresponding 4-(acyloxy)benzophenones. Hydrolysis of one of the acyloxy groups results in loss of more than 90% of the activity (**21** and **23**, Table IV). It is interesting that a carbonate ester, 4,4′-bis[[(*tert*-butyloxy)carbonyl]oxy]benzophenone (**14**), showed good potency.

The SAR of 4,4′-bis(acyloxy)benzophenone analogues upon modification of their central carbonyl group are summarized in Table III. Electron-withdrawing groups at this position enhance the potency (**12**, **17**, **18**). Incorporation of a hydrophilic group into this location results in significant loss of potency (**19**, **20**).

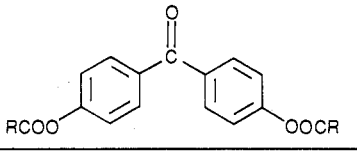
Table I. SAR on Modification of Acyl Group



no.	R	inhibn of elastase:[a] IC_{50}, M	method of prep	mp, °C (crystd from)	(formula) elements anal.
1	CMe_3	6.2×10^{-7}	A[b]	100–102 (EtOH)	($C_{18}H_{18}O_3$) C, H;[1]H NMR[d]
2	$CHMe_2$	2.5×10^{-7}	A	69–69.5 (EtOH)	($C_{17}H_{16}O_3$) C, H
3	CH_2Me	6.2×10^{-6}	A	53.5–54.5 (EtOH)	($C_{16}H_{14}O_3$) C, H
4	Me	1.6×10^{-5}	A(old)	82–83.5 (EtOH)	
5	cyclohexyl	2×10^{-5}	A	111–112 (EtOAc/EtOH/water)	($C_{20}H_{20}O_3$) C, H; ^{1}H NMR
6	$CMe{=}CH_2$	1.9×10^{-6}	A	69.5–70.5 (EtOAc/EtOH/water)	($C_{17}H_{14}O_3$) C, H
7	cyclopropyl	1.4×10^{-6}	A	81–81.5 (EtOAc/EtOH/water)	($C_{17}H_{14}O_3$) C, H; ^{1}H NMR
8	CMe_2NHAc	1.9×10^{-5}	B[c]	137–138 (EtOAc)	($C_{19}H_{19}NO_4$) C, H, N
9	CMe_2CO_2H	6×10^{-6}	B[c]	147–150 (EtOAc)	($C_{18}H_{16}O_5$) C, H; ^{1}H NMR[f]
10	CMe_2CO_2Me	1.0×10^{-6}	B[c]	121–122 (EtOH)	($C_{19}H_{18}O_5$) C, H; ^{1}H NMR[g]

[a] Human leukocyte elastase. [b] See general procedure A in the Experimental Section. [c] See the Experimental Section. [d] ($CDCl_3$, 80 MHz) 1.35 (s, 9 H), 7.05–7.90 (m, 9 H) ppm. [e] ($CDCl_3$, 60 MHz) 1.64 (s, 6 H, *gem*-Me_2), 1.96 (s, 3 H, acetyl), 6.65 (s, 1 H, NH) ppm. [f] (DMSO-d_6, 60 MHz) 1.54 (s, 6 H, *gem*-Me_2) ppm. [g] ($CDCl_3$, 60 MHz) 1.55 (s, 6 H, *gem*-Me_2), 3.70 (s, 3 H, CO_2Me) ppm.

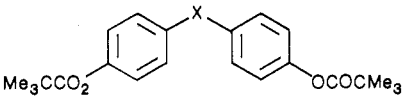
Table II. SAR on Modification of Acyl Groups



no.	R	inhibn of elastase:[a] IC_{50}, M	method of prep	mp, °C (crystd from)	(formula) elements anal.
11	$CHMe_2$	1.5×10^{-7}	A[b]	143.5–144.5 (EtOH)	($C_{21}H_{22}O_5$) C, H[d,e]
12	CMe_3	1.2×10^{-7} ($K_i = 7.1 \times 10^{-8}$)	A	166–167 (chromatograph)	($C_{23}H_{26}O_5$) C, H[e,f]
13	$CMe_2CH_2CH_2Me$	6.7×10^{-7}	A	59–60 (EtOH)	($C_{27}H_{34}O_5$) C, H[g]
14	$OCMe_3$	9.0×10^{-7}	B[c]	141–143 (EtOH)	($C_{23}H_{26}O_7$) C, H[h,i]

[a] Human leukocyte elastase. [b] See general procedure A in the Experimental Section. [c] See the Experimental Section. [d] ($CDCl_3$, 80 MHz) 1.34 (d, J = 5 Hz, 12 H, *i*-Pr), 2.82 (m, J = 5 Hz, 2H, *i*-Pr) ppm. [e] IR ($CHCl_3$) 1760 (ester), 1660 (ketone) cm^{-1}. [f] ($CDCl_3$, 60 MHz) 1.40 (s, 18 H), 7.20 (d, J = 8.5 Hz, 4 H), 7.87 (d, J = 8.5 Hz, 4 H) ppm. [g] ($CDCl_3$, 60 MHz) 1.34 (s, 12 H) ppm. [h] ($CDCl_3$, 60 MHz) 1.58 (s, 18 H) ppm. [i] IR ($CHCl_3$) 1765 (ester), 1665 (ketone) cm^{-1}.

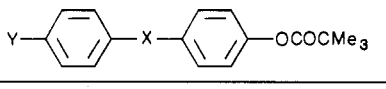
Table III. SAR upon Replacing Carbonyl Group



no.	X	inhibn of elastase:[a] IC_{50}, M	method of prep	mp, °C (crystd from)	(formula) elements anal.
12	C=O	1.2×10^{-7}	A[b]	166–167 (chromatograph)	($C_{23}H_{26}O_5$) C, H
15	CH_2	4.6×10^{-7}	A	130–133 (EtOH)	($C_{23}H_{28}O_4$) C, H; ^{1}H NMR[d]
16	O	4.5×10^{-7}	A	126–127 (EtOH)	($C_{22}H_{26}O_5$) C, H; ^{1}H NMR[e]
17	N=N	1.3×10^{-7}	A	185–188 (EtOH)	($C_{22}H_{26}N_2O_4$) C, H, N; ^{1}H NMR[f]
18	SO_2	8.3×10^{-8} ($K_i = 2 \times 10^{-7}$ M)	A	190–192 (chromatograph)	($C_{22}H_{26}O_6S$) C, H, S; ^{1}H NMR, IR[g]
19	CHOH	1.5×10^{-6}	B[c]	148.5–152.5 (chromatograph)	($C_{23}H_{28}O_5$) C, H; ^{1}H NMR,[h] IR,[i] UV[j]
20	$CHOCOCH_2CH_2CO_2Na$	3×10^{-6}	B[c]	higher than 270	($C_{27}H_{31}O_8Na$) C, H, Na

[a] Human leukocyte elastase. [b] See general procedure A in the Experimental Section. [c] See the Experimental Section. [d] ($CDCl_3$, 60 MHz) 1.32 (s, 18 H), 3.94 (s, 2 H, CH_2), 6.8–7.28 (m, 8 H) ppm. [e] ($CDCl_3$, 60 MHz) 1.34 (s, 18 H), 7.04 (s, 8 H) ppm. [f] ($CDCl_3$, 60 MHz) 1.38 (s, 18 H) ppm. [g] IR ($CHCl_3$) 1763 (ester), 1593, 1492, 1482 cm^{-1}. [h] ($CDCl_3$, 80 MHz) 1.33 (s, 18 H), 5.74 (s, 1 H, CHO). [i] IR ($CHCl_3$) 3590, 1740, 1597, 1500, 1475 cm^{-1}. [j] UV (MeOH) 224 nm (ϵ 17 300).

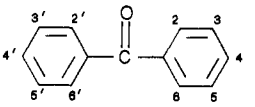
Table IV. Effect of OH and Cl



no.	X	Y	inhibn of elastase:[a] IC_{50}, M	method of prep	mp, °C (crystd from)	(formula) elements anal.
21	C=O	OH	2.7×10^{-6}	A[b]	172.5–175 (chromatograph)	($C_{18}H_{18}O_4$) C, H; ^{1}H NMR, IR
22	C=O	Cl	1.4×10^{-7}	A	113–114 (EtOH)	($C_{18}H_{17}O_3Cl$) C, H, Cl
23	SO_2	OH	1.8×10^{-6}	A	139–142.5 (chromatograph)	($C_{17}H_{18}O_5S$) C, H, S

[a] Human leukocyte elastase. [b] See general procedure A in the Experimental Section.

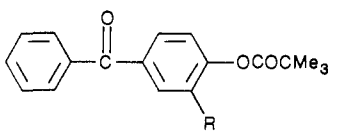
Table V. SAR on Various Substitution Patterns



no.	substituent	inhibn of elastase:[a] IC_{50}, M	method of prep	mp, °C (crystd from)	(formula) elements anal.
24	2,4,4′-tris(pivaloyloxy)	5.5×10^{-8}	A[b]	94–96 (EtOH)	($C_{28}H_{34}O_7$) C, H; ^{1}H NMR
25	2,4,2′,4′-tetrakis(pivaloyloxy)	2.7×10^{-8} ($K_i = 6.8 \times 10^{-8}$)	A	154–156 (EtOH)	($C_{33}H_{40}O_9$) C, H; ^{1}H NMR, IR
26	2,4,2′,4′-tetrakis[(3-methylpentanoyl)oxy]	1.5×10^{-6}	A	oil	($C_{37}H_{50}O_9$) C, H; ^{1}H NMR
27	2,3,4,3′,4′,5′-hexakis(pivaloyloxy)	3.6×10^{-7}	A	oil	($C_{43}H_{58}O_{13}$) C, H; ^{1}H NMR, IR
28	2-pivaloyloxy	1.0×10^{-5}	A	oil	($C_{18}H_{18}O_3$) C, H; ^{1}H NMR,[c] IR[d]
29	2,2′-bis(pivaloyloxy)	8.0×10^{-6}	A	106–108 (EtOH)	($C_{23}H_{26}O_5$), C, H; ^{1}H NMR,[e] IR
30	2,4-bis(pivaloyloxy)	8.4×10^{-8}	A	oil	($C_{23}H_{26}O_5$) C, H; ^{1}H NMR[f]

[a] Human leukocyte elastase. [b] See general procedure A in the Experimental Section. [c] ($CDCl_3$, 60 MHz) 1.10 (s, 9 H) ppm. [d] IR ($CHCl_3$) 1750 (ester), 1670 (ketone) cm^{-1}. [e] ($CDCl_3$, 60 MHz) 1.18 (s, 18 H) ppm. [f] ($CDCl_3$, 60 MHz) 1.10 (s, 9 H, 2-pivaloyl), 1.40 (s, 9 H, 4-pivaloyl) ppm.

Table VI. Effect of 3-Substituents

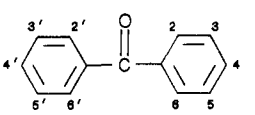


no.	R	inhibn of elastase:[a] IC_{50}, M	method of prep	mp, °C (crystd from)	(formula) elements anal.
31	$CHMeCH{=}CH_2$	3.2×10^{-7}	C, D, A[b]	oil	($C_{22}H_{24}O_3$) C, H; ^{1}H NMR,[e] IR, UV
32	$CH_2CH{=}CH_2$	8.0×10^{-7}	C, D, A	oil	($C_{21}H_{22}O_3$) C[n]; H; ^{1}H NMR,[g] UV
33	$CH_2CMe{=}CH_2$	8.5×10^{-7}	C, D, A	oil	($C_{22}H_{24}O_3$) C, H; ^{1}H NMR[h]
34	$(CH_2)_3OH$	3.5×10^{-7}	E[c]	oil	($C_{21}H_{24}O_4$) C, H; IR,[f] UV
35	$CH_2CHMeCH_2OH$	1.5×10^{-6}	E	oil	($C_{22}H_{26}O_4$) C, H; ^{1}H NMR[i]
36	$CH_2CHMeCHO$	8.0×10^{-7}	B[d]	oil	($C_{22}H_{24}O_4$) C, H; ^{1}H NMR[j]
37	$CH_2CHMeCO_2H$	2.2×10^{-6}	B[d]	119–120[m]	($C_{22}H_{24}O_5$) C, H
38	$CHMeCO_2H$	1.2×10^{-5}	B[d]	109–112.5[m]	($C_{21}H_{22}O_5$) C, H; ^{1}H NMR[k]
39	$CH_2CH_2CO_2H$	1.7×10^{-6}	B[d]	oil	($C_{21}H_{22}O_5$) C, H; ^{1}H NMR[l]

[a] Human leukocyte elastase. [b] See general procedurea A, C, and D in the Experimental Section. [c] General procedure E. [d] See the Experimental Section. [e] ($CDCl_3$, 80 MHz) ~1.38 (d, 3 H), 1.39 (s, 9 H), 3.70 (m, 1 H), ~5.0 (m, 2 H, $=CH_2$), ~5.95 (m, 1 H, CH=), 7.0–7.8 (m, 8 H) ppm. [f] IR ($CHCl_3$) 3625, 1750, 1655, 1600 cm^{-1}. [g] ($CDCl_3$, 80 MHz) 1.37 (s, 9 H), 3.32 (br d, J = 6.5, Hz, $CH_2C=$, 2 H), ~5 (m, 2 H, $=CH_2$), ~5.8 (m, 1 H, CH=), ~7.4 (m, 8 H) ppm. [h] ($CDCl_3$, 60 MHz) 1.38 (s, 9 H), 1.73 (s, 3 H), 3.33 (br s, 2 H), 4.65 (m, 1 H), 4.85 (m, 1 H) ppm. [i] ($CDCl_3$, 60 MHz) 0.92 (d, J = 7 Hz, 3 H), 1.40 (s. 9 H), 3.47 (d, J = 7 Hz, 2 H) ppm. [j] ($CDCl_3$, 60 MHz) 1.07 (d, J = 7 Hz, 3 H), 1.33 (s, 9 H), 9.71 (br s, 1 H, aldehyde) ppm. [k] ($CDCl_3$, 80 MHz) 1.36 (s, 9 H), 1.52 (d, J = 7 Hz, 3 H), 4.00 (q, J = 7 Hz, 1 H), 7.05–7.90 (m, 8 H) ppm. [l] ($CDCl_3$, 80 MHz) 1.39 (s, 9 H), 2.77 (m, 4 H, CCH_2CH_2C), 7.0–7.8 (m, 8 H) ppm. [m] Crystallized on workup. [n] C: calcd, 78.23; found, 78.88.

Unlike the steroidal enol pivalates, the (acyloxy)benzophenones and 2-[(acyloxy)methyl]-5-(acyloxy)-4-pyrones were chemically stable. They could be stored at 25 °C at least overnight. However, most of them were susceptible to hydrolysis (to be published elsewhere) by a hog pancreatic esterase preparation and also underwent extensive hydrolysis upon oral administration to a dog.[26] An alkenyl group was introduced into the ortho position of 4-(pivaloyloxy)benzophenone with the hope that a bulky 3-substituent might retard the hydrolysis by esterase without reducing elastase inhibitory activity. As summarized in Table VI, 3-alkenyl-4-(pivaloyloxy)benzophenones (**31–33**) were about as potent HLE inhibitors as their parent (**1**). Unfortunately, they too were hydrolyzed rapidly by esterases. The alkenyl groups were then converted to hydroxyalkyls (**34, 35**) or a formylalkyl (**36**) with little reduction of the HLE inhibitory activities. However, **34–36** were still susceptible to hydrolysis by the hog pancreatic esterase. A further oxidation of the 3-substituent to a carboxyalkyl resulted in a significant decrease of the HLE inhibitory activities (**37–39**).

Table VII. Selectivity of Benzophenone Analogues on Elastases



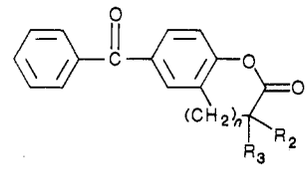
no.	substitution	IC_{50}, M: human leukocyte elastase	hog pancreatic elastase	bovine pancreatic elastase
1	4-pivaloyloxy	6.2×10^{-7}	inactive @ 1×10^{-5}	inactive @ 1×10^{-5}
12	4,4′-bis(pivaloyloxy)	1.2×10^{-7}	inactive[a] @ 1×10^{-5}	inactive @ 1×10^{-5}
25	2,4,2′,4′-tetrakis-(pivaloyloxy)	2.7×10^{-8}	inactive[a] @ 1×10^{-5}	inactive @ 1×10^{-5}

[a] Slightly stimulatory.

Both 4-(acyloxy)benzophenones and 2-[(acyloxy)-methyl]-5-(acyloxy)-4-pyrones were selective and competitive inhibitors of HLE. As shown in Table XII, the inhibitory activity of the pivalates declined gradually. The rate of decline was more remarkable when the initial concentrations of the inhibitor were low. This observation

(23) Nakajima, K.; Powers, J. C.; Ashe, B. M.; Zimmerman, M. *J. Biol. Chem.* **1979**, *254*, 4027.
(24) Visser, L.; Blout, E. R. *Biochem. Biophys. Acta* **1972**, *268*, 257.
(25) Bielefeld, D. R.; Senior, R. H.; Yu, S. Y. *Biochem. Biophys. Res. Commun.* **1975**, *67*, 1553.
(26) The bioavailability study was carried out by Dr. C. Cook of Metabolism Group, Searle Research & Development.

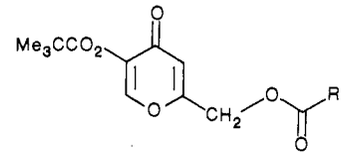
Table VIII. Benzophenone Lactones[a,b] as Stable "Pivaloate"



no.	n	R_2	R_3	mp, °C (crystd from)	(formula) elements anal.
40	1	H	H	128 (CH_2Cl_2/Et_2O)	($C_{16}H_{12}O_3$) C, H; ^{1}H NMR,[c] IR[d]
41	1	H	Me	141–142 (EtOAc/EtOH/water)	($C_{17}H_{14}O_3$) C, H
42	1	Me	Me	119–121 (EtOAc/EtOH/water)	($C_{18}H_{16}O_3$) C, H; ^{1}H NMR[e]
43	0	H	Me	116 (CH_2Cl_2/cyclohexane)	($C_{16}H_{12}O_3$) C, H; ^{1}H NMR,[f] IR[g]
44	0	Me	Me	114 (CH_2Cl_2/Et_2O)	($C_{17}H_{14}O_3$) C, H; ^{1}H NMR,[h] IR[i]

[a] None of them inhibited human leukocyte elastase at 1×10^{-2} M. [b] Prepared by general procedures F, G, and H as described in the Experimental Section. [c] ($CDCl_3$, 80 MHz) 2.82 (m, 2 H, right hand of A_2B_2 pattern), 3.07 (m, 2 H, left hand of A_2B_2) ppm. [d] IR ($CHCl_3$) 1782 (lactone), 1662 (ketone) cm^{-1}. [e] ($CDCl_3$, 60 MHz) 1.33 (s, 6 H), 2.97 (br s, 2 H) ppm. [f] ($CDCl_3$, 80 MHz) 1.60 (d, J = 8 Hz, 3 H), 3.79 (q, J = 8 Hz, 1 H) ppm. [g] IR ($CHCl_3$) 1820 (lactone), 1660 (ketone), 1620 cm^{-1}. [h] ($CDCl_3$, 80 MHz) 1.55 (s, 6 H). [i] IR ($CHCl_3$) 1815 (lactone), 1660 (ketone), 1615 cm^{-1}.

Table IX. SAR on Modification of R Group



no.[a]	R[b]	inhibn of elastase:[c] IC_{50}, M	method of prep	mp, °C (crystallized from)	(formula) elements analyzed
45	$(CH_2)_{14}Me$	1.1×10^{-7}	C	71–73 (MeOH)	($C_{27}H_{44}O_6$) C, H; ^{1}H NMR[d]
46	$(CH_2)_{16}Me$	1.0×10^{-7}	C	76–78 (EtOH)	($C_{29}H4_8O_6$) C, H; ^{1}H NMR
47	$(CH_2)_{18}Me$	1.3×10^{-7}	A	78–79 (MeOH)	($C_{31}H_{52}O_6$) C, H; ^{1}H NMR
48	$(CH_2)_7CH{=}CH(CH_2)_5Me$	1.3×10^{-7}	C	oil[e]	($C_{27}H_{42}O_6$) C, H; ^{1}H NMR[f]
49	$(CH_2)_7CH{=}CH(CH_2)_7Me$	3.0×10^{-7}	C	14–15	($C_{29}H_{46}O_6$) C, H; ^{1}H NMR
50	$(CH_2)_9CH{=}CH(CH_2)_7Me$	2.1×10^{-7}	C	oil[e]	($C_{31}H_{50}O_6$) C, H; ^{1}H NMR
51	$(CH_2)_{11}CH{=}CH(CH_2)_7Me$	1.6×10^{-7}	C	oil[e]	($C_{33}H_{54}O_6$) C, H; ^{1}H NMR
52	4-biphenyl	1.9×10^{-6}	C	113–114 (cyclohexane)	($C_{24}H_{22}O_6$) C, H; ^{1}H NMR, IR[g]
53	4-(pivaloyloxy)phenyl	2.0×10^{-7}	C	114–116 (EtOH)	($C_{23}H_{26}O_8$) C, H; ^{1}H NMR
54	2-(pivaloyloxy)phenyl	5.4×10^{-6}	C	127–128 (EtOH)	($C_{23}H_{26}O_8$) C, H; ^{1}H NMR
55	2,4-bis(pivaloyloxy)phenyl	2.7×10^{-8} ($K_i = 9 \times 10^{-8}$ M)	C	134–136 (EtOH)	($C_{28}H_{34}O_{10}$) C, H; ^{1}H NMR
56	3,4,5-tris(pivaloyloxy)phenyl	1.0×10^{-7}	C	176–179 (EtOH)	($C_{33}H_{42}O_{12}$) C, H; ^{1}H NMR, IR
57	2,4,6-trimethyl	8.4×10^{-6}	C	147–147.5 (EtOAc/hexane)	($C_{21}H_{24}O_6$) C, H; ^{1}H NMR,[h] IR[i]
58	$CMe_2(CH_2)_{11}Me$	6.0×10^{-7}	C	75–76 (chromatograph)	($C_{27}H_{44}O_6$) C, H; ^{1}H NMR,[j] IR[k]

[a] All compounds except **47** were prepared by acylation of **59** (general procedure C). Pivaloylation of **67** by general procedure A produced **47**. [b] All double bonds are *Z*. [c] Human leukocyte elastase. [d] ($CDCl_3$, 80 MHz) 1.35 (s, 9 H), 2.38 (t, J = 7 Hz, 2 H), 4.90 (s, 2 H) 6.42 (s, 1 H, H-3), 7.75 (s, 1 H, H-6) ppm. [e] Crystalline in a refrigerator. [f] ($CDCl_3$, 60 MHz) 1.36 (s, 9 H), 1.8–2.1 (m, 4 H, allyl H), 2.36 (t, J = 7 Hz, 2 H), 4.90 (s, 2 H), 5.34 (t, J = 4 Hz, olefinic H), 6.45 (s, 1 H), 7.83 (s, 1 H) ppm. [g] IR ($CHCl_3$) 1770 (pivaloyl), 1735 (phenylbenzoyl), 1675 (pyrone), 1650, 1615 cm^{-1}. [h] ($CDCl_3$, 80 MHz) 1.35 (s, 9 H, pivaloyl Me), 2.27 (s, 9 H, aromatic Me), 5.13 (s, 2 H), 6.50 (s, 1 H), 6.84 (s, 2 H, aromatic H), 7.82 (s, 1 H) ppm. [i] IR ($CHCl_3$) 1760 (pivaloyl), 1733, 1667 (pyrone), 1642, 1610 cm^{-1}. [j] ($CDCl_3$, 80 MHz) 1.19 (s, 6 H), 1.35 (s, 9 H), 4.88 (s, 2 H), 6.40 (s, 1 H), 7.78 (s, 1 H) ppm. [k] IR ($CHCl_3$) 1760 (pivaloyl), 1735, 1665 (pyrone), 1640, 1605 cm^{-1}.

is consistent with our view that the mechanism of inhibition was pivaloylation of the active serine residue with concomitant destruction of the inhibitor followed by a slow regeneration of the enzyme. None of the new inhibitors disclosed here inhibited hog pancreatic elastase or bovine pancreatic chymotrypsin (Table VII and XI).

Finally, benzophenone lactones (**40–44**, Table VIII), a special class of 4-(acyloxy)benzophenones, were prepared on the basis of the possibility that the lactone might be resistant to esterases and yet inhibit the elastase. None of these lactones inhibited HLE. This was surprising to us particularly in light of the reported potent HLE inhibition by several cyclic suicidal substrates: *N*-acylbenzisothiazoline 1,1-dioxides[14] and isatoic anhydride derivatives.[20,27]

Perhaps the biologically active conformation of **1** for the elastase inhibition resembles A rather than B (Figure 2). The lactone structure (C) represents an inactive conformation. The arrow in A indicates the trajectory of the

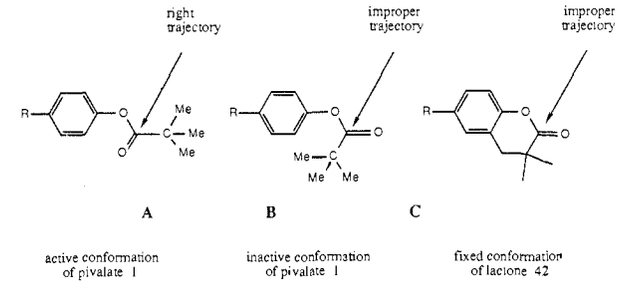


Figure 2. Direction of elastase approach.

approaching hydroxyl oxygen of the serine residue in the active site. A similar attack on B (lactone ring of **42**) from the same direction constitutes an improper trajectory.[28]

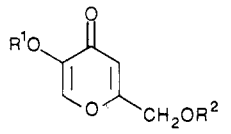
Results and Discussion in Kojic Acid Series

The SAR of 2-[(acyloxy)methyl]-5-(pivaloyloxy)-4-pyrones upon modification of the 2-acyl group are sum-

(27) Abeles, R. H. *Chem. Eng. News* **1983**, *Sept. 19*, 48.

(28) For review on the directionality of organic reactions, see: Menger, F. M. *Tetrahedron* **1983**, *39*, 1013.

Table X. SAR on Further Modifications



no.[a]	R^1	R^2	inhibn of elastase:[b] IC_{50}, M	method of prep[c]	mp, °C (crystd from)	(formula) elements anal.
59	Me_3CCO	H	inactive @ 1×10^{-4}	J	98 (EtOAc/cyclohexane)	($C_{11}H_{14}O_5$) C, H; ^1H NMR,[d] IR,[e] UV
60	Me_3CCO	$COCMe_3$	3.6×10^{-5}	K	102.5 (hexane)	($C_{16}H_{22}O_6$) C, H; ^1H NMR,[f] IR,[g] UV[h]
61	Me_3CCO	tetrahydropyranyl	4.3×10^{-5}	H	68.5 (ether/cyclohexane)	($C_{16}H_{22}O_6$) C, H; ^1H NMR,[i] IR, UV[j]
62	1-adamantanylcarbonyl	tetrahydropyranyl	33% inhibn @ 1×10^{-4}	H	105.5 (CH_2Cl_2/cyclohexane)	($C_{22}H_{28}O_6$) C, H; ^1H NMR, IR, UV
63	1-adamantanylcarbonyl	oleoyl	8.0×10^{-5}	K	oil	($C_{35}H_{52}O_6$) C, H; ^1H NMR
64	oleoyl	oleoyl	6.1×10^{-6}	A	gum	($C_{42}H_{70}O_6$) C,[o] H; ^1H NMR, IR, UV
65	Me_2CHCO	$CO(CH_2)_{16}Me$	7.2×10^{-8}	K	70–73	($C_{28}H_{46}O_6$) C, H; ^1H NMR[k]
66	H	$CO(CH_2)_{14}Me$	1×10^{-4}	L	94–97 (MeOH)	($C_{22}H_{36}O_5$) C, H
67	H	$CO(CH_2)_{18}Me$	9.0×10^{-6}	L	99–101 (MeOH)	($C_{26}H_{44}O_5$) C, H; ^1H NMR[l]
68	Me_3CCO	trityl	1.0×10^{-6}	B[n]	179–181 (EtOAc/cyclohexane)	($C_{30}H_{28}O_5$) C, H; ^1H NMR[m]

[a] All double bonds are *Z*. [b] Human leukocyte elastase. [c] General procedures A, H, J, K, L, respectively. [d] ($CDCl_3$, 80 MHz) 1.34 (s, 9 H), 4.42 (s, 2 H), 6.48 (s, 1 H), 7.82 (s, 1 H) ppm. [e] IR ($CHCl_3$) 3605, 3420, 1765, 1670, 1638 cm^{-1}. [f] ($CDCl_3$, 60 MHz) 1.24 (s, 9 H, pivaloyl on alcoholic OH), 1.35 (s, 9 H, pivaloyl on enolic OH), 4.95 (s, 2 H), 6.46 (s, 1 H), 7.88 (s, 1 H) ppm. [g] IR ($CHCl_3$) 1768 (pivaloyl on enolic OH), 1749 (pivaloyl on alcoholic OH), 1676 (pyrone), 1648 cm^{-1}. [h] UV (MeOH) 251 nm (10 800). [i] ($CDCl_3$, 60 MHz) 1.34 (s, 9 H), 1.70 (m, 6 H), 3.7 (m, 2 H), 4.43 (m 2 H), 4.73 (m, acetal H), 6.54 (s, 1 H), 7.85 (s, 1 H) ppm. [j] UV (MeOH) 211 nm (ϵ 8780), 249.5 (10 100). [k] ($CDCl_3$, 60 MHz) 1.26 (br s, 33 H, combination of CH_2 and isopropyl CH_3), 2.2–3.0 (m, 3 H, combination of $-COCH_2-$ and $OCOCHMe_2$), 4.91 (s, 2 H, CCH_2O) ppm. [l] ($CDCl_3$, 60 MHz) 1.25 (m, 32 H), 2.40 (m, 2 H), 4.91 (s, 2 H), 6.50 (s, 1 H), 7.84 (s, 1 H) ppm. [m] ($CDCl_3$, 60 MHz) 1.36 (s, 9 H), 4.00 (s, 2 H), 6.63 (s, 1 H), 7.2–7.5 (m, 15 H), 7.70 (s, 1 H). [n] See the Experimental Section. [o] C: calcd, 75.18; found, 73.82.

Table XI. Selectivity of Kojic Acid Analogues on Elastases

	IC_{50}, M		
no.	human leukocyte elastase	hog pancreatic elastase	bovine pancreatic elastase
46	1.5×10^{-7}	inactive @ 1×10^{-5}	inactive @ 1×10^{-5}
48	1.3×10^{-7}	inactive @ 1×10^{-5}	inactive @ 1×10^{-5}
53	2.0×10^{-7}	inactive @ 1×10^{-5}	inactive @ 1×10^{-5}
55	2.7×10^{-8}	inactive @ 1×10^{-5}	inactive @ 1×10^{-5}

marized in Tables IX and X. Long-chain fatty acids in this position provide more potent analogues (**45–51**) than the 2-arylacyl analogues (**52**, **57**). When additional pivaloyloxy groups are incorporated into the aromatic portion (**53**, **55**, **56**, for instance) the inhibitory potency is enhanced. That **61** exhibited only marginal activity (Table X) suggested that certain chain length is required for an efficient 2-acyl group.

The 5-pivaloyloxy group can be replaced with isobutyryloxy (**65**, Table X) with a small gain in biological potency. A long-chain acyl (**64**) or a bulky acyl (**63**) decreased the potency.

In conclusion, the structural requirement for a potent HLE inhibitor of this series is an α-branched acyl (typically pivaloyl) ester of a lipophilic enolic (phenolic included) compound. The lipophilic portion that fits into a large elongated lipophilic groove of HLE has to extend away from the ester function that comes in contact with the serine hydroxyl group at the catalytic site.

Experimental Section

Melting points were taken in a Thomas-Hoover Unimelt and were not corrected. ^1H NMR spectra were run on a Varian FT-80A or a 60AT spectrometer and the chemical shifts were given in ppm downfield from the internal TMS signal. The coupling constants are given in hertz.

Purified human leukocyte elastase was generously provided by Dr. Robert Senior, Washington University. Hog pancreatic elastase and bovine α-chymotrypsin were obtained from Cal Biochem. (Methoxysuccinyl)alanylalanylprolylvaline nitroanilide was kindly provided by Dr. J. C. Powers, Georgia Institute of Technology, or synthesized by us, and (*tert*-butoxycarbonyl)tyrosyl nitrophenyl ester was purchased from Bachem.

Enzyme Assays. Human leukocyte elastase (HLE) activity was quantitated by measuring the increase in absorption at 410 nm due to nitroanilide release from (methoxysuccinyl)alanylalanylprolylvalyl nitroanilide (10^{-4} M) with a Gilford recording spectrophotometer.[23] Incubations were carried out in 0.2 M Tris buffer, pH 8.0 at 30 °C. DMSO was utilized as solvent for the inhibitors and substrate and constituted 10% of the final incubation medium. Elastase was titrated to yield an increase of 0.12 optical density unit/min per 10 mm light path. K_i approximations for **12**, **18**, **25**, and **55** were via a standard Lineweaver-Burk plot.

Hog pancreatic elastase activity was assayed using the method of Visser and Blout.[24] Bovine α-chymotrypsin was assayed with (*tert*-butoxycarbonyl)tyrosylnitrophenol as substrate with the method described by Ashe and Zimmerman.[15] [^{14}C]Elastin hydrolysis by elastase was quantitated by the method of Bielefeld et al.[25]

4-(Pivaloyloxy)benzophenone (1). General Procedure A. A solution of 2.0 g (1 mmol) of 4-hydroxybenzophenone and 1.25 g (1.5 mmol) of trimethylacetyl chloride in 30 mL of pyridine was heated to 50 °C for 2 h. The reaction mixture was stripped of pyridine and then slurried into water. The crude product obtained by filtration was recrystallized from ethanol. The first crop (2.35 g, 79.9%, mp 100–102 °C) was used for analysis and biological evaluation.

4,4′-Bis(pivaloyloxy)diphenyl Sulfone (18) and 4-(Pivaloyloxy)-4′-hydroxydiphenyl Sulfone (23). General Procedure A. A solution of 15.0 g of 4,4′-sulfonyldiphenol in 60 mL of pyridine was treated with 60 mL of trimethylacetyl chloride initially at 0–25 °C and then under reflux for 4.5 h. The reaction mixture was stripped of pyridine under reduced pressure and then taken up with methylene chloride. The organic layer was washed with cold 2% hydrochloric acid, water, and finally 2% bicarbonate solution. The dried ($MgSO_4$) extract was concentrated (18.9 g) and chromatographed on a silica gel column with methylene chloride–ethanol to give the less polar product (**18**, 8.5 g, mp 190–192 °C) and the more polar product (**23**, 4.5 g, mp 139–142.5 °C).

4-[(α-Methyl-α-acetamidopropionyl)oxy]benzophenone (8). A solution of 2.06 g (10 mmol) of dicyclohexylcarbodiimide in 30

Table XII. Inhibition of [^{14}C]Elastin Hydrolysis by Selected Inhibitors

no.	concn, μM	% inhibition[a] 1 h	2 h	3 h
12	3	77	77	67
	2	62	42	46
	1	34	28	15
18	3	56	40	29
	2	39	29	8
	1	29	14	-
24	2	81	81	76
	1	45	63	47
	0.5	20	19	6
25	2	81	85	82
	1	62	72	59
	0.5	38	38	21
30	3	62	32	10
	2	36	12	9
	1	14	10	-
46	4	79	53	21
	3	67	39	13
	2	57	21	9
51	4	77	50	22
	3	74	46	32
	2	61	33	13
55	4	93	80	54
	2	36	16	1
	1	25	5	-1
56	3	71	67	31
	2	58	44	5
	1	39	15	3

[a] In these experiments, the substrate, [^{14}C]elastin, the inhibitors, and elastase were present throughout the experiment. Loss in inhibitory activity with time is apparent, especially at the lower inhibitor concentrations which we postulate to be the result of deacylation of pivaloylelastase. As support for this conclusion, we have incubated compounds **12** (0.3 μM) and **25** (0.1 μM) with elastase for 4 h. At 0, 0.5, 1, 2, and 4 h an aliquot of the incubation was taken, substrate, (methoxysuccinyl)alanylalanylpyrolylvalyl nitroaniline added and the enzyme activity determined. Inhibition of enzyme activity at these time intervals were 99%, 88%, 85%, 69%, and 24% for compound **12** and 66%, 66%, 51%, 14%, and 0% for compound **25**.

mL of methylene chloride was added to a slurry of *N*-acetyl-α,α-dimethylglycine (1.45 g, 10 mmol) in 20 mL of methylene chloride at −10 °C. The mixture was stirred for 0.5 h at −10 to 0 °C and then treated with a solution of 4-hydroxybenzophenone (2.0 g, 10 mmol) in 10 mL of methylene chloride at −10 to 0 °C for 2 h. The reaction mixture was allowed to stand at 25 °C overnight and then filtered by suction. The filtrate was stripped of the solvent, taken up with 1:1 ethyl acetate–ether, and filtered again. The final filtrate was concentrated and the residue was recrystallized from ethyl acetate to give 2.2 g (68%) of **8**.

4-[(2-Methyl-2-carboxypropionyl)oxy]benzophenone (9). To a solution of 2 g (12 mmol) of dimethylmalonyl chloride in 10 mL of methylene chloride a solution of 2 g (10 mmol) of 4-hydroxybenzophenone in 10 mL of pyridine was added over 15 min at −5 °C. The mixture was stirred at 0 °C for 0.5 h, allowed to warm to 25 °C over 1 h, then stripped of the solvent, and finally stirred with 1:1 ethyl acetate–water for 1.5 h at 25 °C. The organic phase was washed with cold 2% hydrochloric acid and then with water and finally extracted with 5% sodium bicarbonate solution. The aqueous extract was acidified to pH 3 and filtered to collect crude **9**. The pure **9** was obtained by recrystallization from EtOH–water, 0.325 g (10%).

4-[(2-Methyl-2-carbomethoxypropionyl)oxy]benzophenone (10). This compound was obtained by a routine treatment of **9** with diazomethane followed by a recrystallization from ethanol.

4,4′-Bis[[(*tert*-butyloxy)carbonyl]oxy]benzophenone (14). A solution of 2.14 g (10 mmol) of 4,4′-dihydroxybenzophenone and 4.4 g (20 mmol) of di-*tert*-butyl dicarbonate in 30 mL of pyridine was warmed to 50 °C until evolution of CO_2 ceased (2 h). Upon addition of water, crystalline **14** was obtained, which was then recrystallized from ethanol; yield 3.6 g (86%).

4,4′-Bis(pivaloyloxy)benzhydrol (19). An ethanolic solution (60 mL) of 1.0 g of **12** was treated with 67 mg of sodium borohydride initially at 0 °C, treated with acetic acid to remove excess borohydride, stripped of the solvent, and taken up with ether. A chromatographic separation on a silica gel column using toluene–ethyl acetate gave 0.47 g (47%) of **19**.

Sodium 3-[[[4,4′-Bis(pivaloyloxy)benzhydryl]oxy]carbonyl]propionate (20). A solution of 500 mg of **19**, 260 mg of succinic anhydride, and 160 mg of 4-(dimethylamino)pyridine in 2 mL of pyridine was allowed to stand for 2 days. The reaction mixture was stripped of the solvent, taken up with ethyl acetate washed with sodium bicarbonate solution, washed with brine, and dried on Na_2SO_4. Evaporation of the solvent left 319 mg (51%) of **20**, which did not melt up to 270 °C.

4-(Methallyloxy)benzophenone (III). General Procedure C. A mixture of 34 g of 4-hydroxybenzophenone, 1.0 g of sodium iodide, 18.7 mL of methallyl chloride, and 25 g of potassium carbonate in 350 mL of acetone was refluxed for 96 h. After cooling, the reaction mixture was filtered, concentrated, dissolved in methylene chloride, washed with sodium hydroxide solution, washed with water, dried over magnesium sulfate, and finally concentrated. The crystalline III thus obtained (41.6 g, mp 85–86.5 °C) was used for the Claisen rearrangement: ^{1}H NMR ($CDCl_3$, 60 MHz) 1.88 (br s, 2 H), 5.12 (m, 2 H) ppm.

3-Methallyl-4-hydroxybenzophenone (VI). General Procedure D. A mixture of 38.0 g of III and an equal amount of diethylaniline was heated to 207–218 °C for 3.5 h. The reaction mixture was taken up with methylene chloride, washed with 2 M sulfuric acid, washed successively with water, 5% potassium hydroxide, and water, dried ($MgSO_4$), and concentrated to give 27.8 g of VI (mp 131–133 °C): ^{1}H NMR ($CDCl_3$, 60 MHz) 1.79 (br s, 3 H), 3.48 (br s, 2 H), 4.95 (m, 2 H) ppm.

3-Methallyl-4-(pivaloyloxy)benzophenone (33). This substance (36 g) was prepared from VI (29 g) by general procedure A: ^{1}H NMR ($CDCl_3$, 60 MHz) 1.38 (s, 9 H), 1.73 (s, 3 H), 3.33 (br s, 2 H), 4.65 (m, 1 H), 4.85 (m, 1 H) ppm.

3-Allyl-4-(pivaloyloxy)benzophenone (32). 4-Hydroxybenzophenone (25 g) was converted to 4-(allyloxy)benzophenone (II, 29.2 g, yellow solid) by general procedure C. Claisen rearrangement (general procedure D) of II (29.2 g) gave only 13.5 g (47%) of V, the balance being recovered II. Finally acylation of V (5.9 g) according to general procedure A produced 6.9 g (86%) of oily **32**: ^{1}H NMR ($CDCl_3$, 80 MHz) 1.37 (s, 9 H), 3.32 (br d, J = 6.5 Hz, CH_2C=, 2 H), 5.0 (m, 2 H, =CH_2), 5.8 (m, 1 H, CH=), 7.4 (m, 8 H) ppm; UV (MeOH) 257 nm (ε 18 100).

3-(1-Methylallyl)-4-(pivaloyloxy)benzophenone (31). 4-(Crotyloxy)benzophenone(I) was prepared from 4-hydroxybenzophenone and technical grade crotyl bromide (Aldrich Chemical Co.) (general procedure C). The crude I was converted (general procedure D) into 3-(α-methylallyl)-4-hydroxybenzophenone(IV). The crude IV (10.1 g) was acylated (general procedure A) and purified by chromatography (40:60 hexane–methylene chloride on silica gel) to produce 12.25 g (91%) of **31**: ^{1}H NMR ($CDCl_3$, 80 MHz) 1.38 (d, 3 H), 1.39 (s, 9 H), 3.70 (m, 1 H), 5.0 (m, 2 H, =CH_2), 5.95 (m, 1 H, CH=), 7.0–7.8 (m, 8 H) ppm; IR ($CHCl_3$) 1750, 1657, 1580 cm^{-1}; UV (MeOH) 255.5 nm (ε 19 100).

3-(2-Methyl-3-hydroxypropyl)-4-(pivaloyloxy)benzophenone (35). General Procedure E. A solution of 15.0 g of **33** in 30 mL of THF was treated with 100 mL of 0.5 M solution of 9-BBN in THF at 0 °C. The mixture was stirred at 25 °C for 3 h and at 50 °C for 1 h. To the cooled reaction mixture were added 30 mL of ethanol, 9.5 mL of 6 N sodium hydroxide, and 18 mL of 30% hydrogen peroxide. After being stirred at 25 °C for 2 h, the oxidation mixture was treated with solid potassium carbonate followed by a small amount of water. The organic layer was separated and dried over $MgSO_4$. The crude product (22 g) was chromatographed on a silica gel column with toluene–ethyl acetate. Oily **35** (8.0 g) was obtained: ^{1}H NMR ($CDCl_3$, 60 MHz) 0.92 (d, 3 H, J = 7 Hz), 1.40 (s, 9 H), 3.47 (d, J = 7 Hz, 2 H) ppm.

3-(3-Hydroxypropyl)-4-(pivaloyloxy)benzophenone (34). According to general procedure E, 2.0 g of **32** was hydroborated to **34** (1.48 g after chromatography): IR ($CHCl_3$) 3625, 1750, 1655, 1600 cm^{-1}.

3-(2-Formylpropyl)-4-(pivaloyloxy)benzophenone (36). To a solution of 1.8 mL of oxalyl chloride in 43 mL of methylene chloride were added dropwise a solution of 3.0 mL of DMSO in 9 mL of methylene chloride at −60 °C and then a solution of 6.14

g of **35** in 17 mL of methylene chloride. The mixture was stirred at between −50 and −60 sC for 15 min and then treated with 12.1 mL of triethylamine. The reaction mixture was stirred at −50 °C for 5 min, warmed to 25 °C, and then treated with 85 mL of water. The organic layer was washed with dilute hydrochloric acid and then with brine, dried ($MgSO_4$), and concentrated to give 5.0 g of oily **36**: ^1H NMR ($CDCl_3$, 60 MHz) 1.07 (d, 3 H, J = 7 Hz), 1.33 (s, 9 H), 9.71 (br s, 1 H, aldehyde) ppm.

3-(2-Carboxypropyl)-4-(pivaloyloxy)benzophenone (37). To a stirred mixture of 0.59 g of **36** and 0.212 g of NH_2SO_3H in 55 mL of water was added 0.172 g of sodium chlorite. After 0.5 h the reaction mixture was extracted with ether. The ethereal extract (dried over Na_2SO_4) gave 0.52 g of **37**, mp 119–120 °C.

3-(2-Carboxyethyl)-4-(pivaloyloxy)benzophenone (39). A solution of 1.01 g of **34** in 40 mL of acetone was treated with 1.5 mL of 8 N Jones' reagent at 0 °C for 1 h. The reaction mixture was treated with 5 mL of 2-propanol and filtered to remove inorganic material. The filtrate was evaporated and the residue was taken up with toluene. The organic phase was extracted with 3% $KHCO_3$ solution and the aqueous extract was acidified to pH 2. The acidic product was extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated to give 0.784 mg (74%) of **39**: ^1H NMR ($CDCl_3$, 80 MHz) 1.39 (s, 9 H), 2.77 (m, 4 H, CCH_2CH_2C), 7.0–7.8 (m, 8 H) ppm.

3-(α-Carboxyethyl)-4-(pivaloyloxy)benzophenone (38). A solution of 5.05 g of **31** in 40 mL of ethanol was treated with 7.23 g of sodium periodate in 30 mL of water and 0.5 mg of osmium tetraoxide at 25 °C for 4 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was taken up with ether, washed with brine, dried ($MgSO_4$), and concentrated to give 5.1 g of crude aldehyde. Flash chromatography produced 2.98 g (59%) of pure aldehyde, which was dissolved in 20 mL of acetone and oxidized with 2.0 mL of 8 N Jones' reagent at 0 °C. Extractive workup afforded 1.57 g (50%) of **38** (mp 109–112.5 °C): ^1H NMR ($CDCl_3$, 80 MHz) 1.36 (s, 9 H), 1.52 (d, J = 7 Hz, 3 H), 4.00 (q, J = 7 Hz, 1 H), 7.05–7.90 (m, 8 H) ppm.

2-Oxo-3-methyl-6-benzoyl-2,3-dihydro-4*H*-1-benzopyran (41). General Procedure F. A solution of 2 g of **37** and 2 g of sodium hydroxide in 35 mL of methanol was heated to 50 °C for 3 h, cooled, and poured into iced water. The aqueous solution was acidified with hydrochloric acid to pH 4 and extracted with ether. The ethereal extract was dried over Na_2SO_4 and evaporated to give 3-(2-hydroxy-5-benzoylphenyl)-2-methylpropionic acid (VIII). VIII was heated neat to 205–210 °C for 6 min to give 1.4 g of **41**.

2-Oxo-6-benzoyl-2,3-dihydro-4*H*-1-benzopyran (40). According to general procedure F, **39** was hydrolyzed to give 3-(2-hydroxy-5-benzoylphenyl)propionic acid (VII) with mp 142 °C. VII was heated to 205–210 °C neat for 6 min to give **40**.

2-Oxo-3-methyl-5-benzoyl-2,3-dihydrobenzofuran (43). The pivaloate acid (**38**) was hydrolyzed (general procedure F) to IX (mp 191 °C) and then cyclized to **43** by heating at 191–202 °C for 10 min.

2-Oxo-3,3-dimethyl-6-benzoyl-2,3-dihydro-4*H*-1-benzopyran (42). General Procedure G. A solution of lithium diisopropylamide in 6 mL of THF, which had been prepared from 0.230 mL of diisopropylamine and 0.965 mL of 1.6 M *n*-butyllithium in hexane, was cooled to −70 °C. A solution of 0.400 g of **41** in 2.4 mL of THF was added. The mixture was stirred at −70 °C for 20 min and then treated with 0.32 mL of HMPA and 2.4 mL of methyl iodide at −70 °C for 1 h. The reaction mixture was taken up with ether, washed with 2% hydrochloric acid, washed with brine, dried, concentrated, and chromatographed on a silica gel column with toluene–ethyl acetate. Pure **42** (0.290 g, 69%) was obtained followed by recovered starting material (**41**, 0.073 g, 18%).

2-Oxo-3,3-dimethyl-5-benzoyl-2,3-dihydrobenzofuran (44). According to the general procedure F, **43** was methylated to give **44**.

5-Hydroxy-2-[(tetrahydropyranyloxy)methyl]-4-pyrone (XI). To a solution of 56.8 g of 5-hydroxy-2-(hydroxymethyl)-4-pyrone (kojic acid, X) and 39 g of dihydropyran in 2 L of methylene chloride was added 0.4 g of *p*-toluenesulfonic acid monohydrate, and the mixture was stirred for 1.5 h at 23 °C. The reaction mixture was extracted with 3% sodium hydroxide solution twice and then the combined aqueous phase was neutralized to pH 8 with 0.5 M sodium dihydrogen phosphate. An extractive workup (methylene chloride) followed by recrystallization afforded 67 g (75%) of XI: mp 94 °C; ^1H NMR ($CDCl_3$, 60 MHz) 4.32 (d, J = 14 Hz, 1 H, right hand of AB pattern), 4.61 (d, J = 14 Hz, left half of AB pattern), 4.73 (br s, 1 H, acetal H), 6.60 (s, 1 H, H-3), 7.86 (s, 1 H, H-5) ppm; IR ($CHCl_3$) 3430, 1640, 1600 cm^{-1}; UV (MeOH) 270 nm (ε 7400). Anal. ($C_{11}H_{14}O_5$) C, H.

2-[(Tetrahydropyranyloxy)methyl]-5-(pivaloyloxy)-4-pyrone (61). General Procedure H. To 67.0 g of XI in 600 mL of pyridine was added 54 g of pivaloyl chloride over 15 min. Heat was evolved. The mixture was stirred for 1.5 h without external heating, then poured into 3 L of ice water, and extracted with ether. The ethereal extract was washed with 1% sodium hydroxide, washed with water, dried over $MgSO_4$, concentrated, and finally recrystallized from ether–cyclohexane to give 68 g (73%) of **61**: mp 68.5 °C; ^1H NMR ($CDCl_3$, 60 MHz) 1.34 (s, H-3), 1.70 (m, 6 H), 3.7 (m, 2 H), 4.43 (m, 2 H), 4.73 (m, 1 H), 6.54 (s, H-3), 7.85 (m, H-5) ppm; IR ($CHCl_3$) 1770, 1675, 1645, 1612, 1485 cm^{-1}; UV (MeOH) 211 nm (ε 8780), 249.5 (10 100). Anal. ($C_{16}H_{22}O_6$) C, H.

2-[(Tetrahydropyranyloxy)methyl]-5-(isobutyryloxy)-4-pyrone (XII): prepared by general procedure H from isobutyryl chloride and XI. The crude product (oil) was used for the next step.

2-[(Tetrahydropyranyloxy)methyl]-5-[(1-adamantanylcarbonyl)oxy]-4-pyrone (62). Acylation of XI with 1-adamantanecarbonyl chloride according to general procedure H produced **62**: mp; 105.5 °C (recrystallized from CH_2Cl_2–cyclohexane).

2-(Hydroxymethyl)-5-(pivaloyloxy)-4-pyrone (59). General Procedure J. To a solution of 68 g of **61** in 1.3 L of methanol was added 20 mL of concentrated hydrochloric acid and the mixture was stirred at 25 °C for 1.5 h. The reaction mixture was treated with 20 g of sodium acetate and stripped of the solvent, and the residue was taken up with 1 L of hot toluene. The organic extract was dried on $MgSO_4$ while hot and blown down under nitrogen to 250 mL. Upon cooling, 37 g (74%) of crystalline **59** was obtained, which was used for subsequent reactions. Recrystallization from ethyl acetate–cyclohexane gave pure **59** for analysis: mp 98 °C.

2-(Hydroxymethyl)-5-(isobutyryloxy)-4-pyrone (XIII). Methanolysis of XII according to general procedure J produced XIII: mp 66–68 °C (recrystallized from ethyl acetate–cyclohexane); ^1H NMR ($CDCl_3$, 60 MHz) 1.30 (d, J = 7 Hz, 6 H), 2.4–3.0 (septet, J = 7 Hz, 1 H), 4.46 (s, 2 H), 6.50 (s, 1 H) ppm. Anal. ($C_{10}H_{12}O_5$) C, H.

2-(Hydroxymethyl)-5-[(1-adamantanylcarbonyl)oxy]-4-pyrone (XIV). Methanolysis of **62** according to general procedure J produced XIV: mp 182 °C (recrystallized from toluene); ^1H NMR ($CDCl_3$, 80 MHz) 1.24 (m), 2.04 (m), 4.45 (m, 2 H, hydroxymethyl), 6.47 (s, 1 H), 7.78 (s, 1 H) ppm; IR ($CHCl_3$) 3410, 1763, 1675, 1645 cm^{-1}. Anal. ($C_{17}H_{20}O_5$) C, H.

2-[(Octadecanoyloxy)methyl]-5-(pivaloyloxy)-4-pyrone (46). General Procedure K. A solution of 2.0 g of **59** and 2.75 g of stearoyl chloride in 100 mL of pyridine was heated to 80 °C for 3 h. After cooling, the reaction mixture was concentrated and treated with water. Crystals were collected by suction, air-dried, and recrystallized from ethanol to give 1.5 g of pure **46**: mp 76–78 °C.

2-[(Oleoyloxy)methyl]-5-(1-adamantanylcarboxy)-4-pyrone (63). Acylation of XIV with oleoyl chloride in pyridine according to general procedure K produced **63**.

2-(Eicosanoylmethyl)-5-hydroxy-4-pyrone (67). General Procedure L (Nencki Reaction). A mixture of 5.0 g of eicosanoic acid and 1.0 g of anhydrous zinc chloride was heated to 160 °C. To this hot homogeneous paste was added 1.0 g of kojic acid and the mixture was stirred at 160 °C for 1 h and then allowed to cool to 130 °C over 1 h. The reaction mixture was treated with toluene, ethyl acetate, and water. The organic layer was washed with water, dried (Na_2SO_4), concentrated, and chromatographed on Florisil with toluene–ethyl acetate. The crystalline product from 25% ethyl acetate–toluene was recrystallized from methanol to give pure **67**: mp 99–101 °C.

2-[(Oleoyloxy)methyl]-5-(oleoyloxy)-4-pyrone (64). Direct acylation of kojic acid with excess oleoyl chloride in pyridine

according to general procedure H followed by chromatography on silica gel with toluene–ethyl acetate produced gummy **64**.

2-[(Trityloxy)methyl]-5-(pivaloyloxy)-4-pyrone (68). A mixture of 0.188 g of **59** and 0.232 g of trityl chloride in 10 mL of pyridine was refluxed for 4 days. Most of pyridine was blown off under nitrogen stream and the residue was treated with water and toluene. The organic layer was dried ($MgSO_4$), absorbed on a Florisil column, and eluted with toluene. After a small amount of triphenylcarbinol, the desired **68** was eluted. Recrystallization from ethyl acetate–cyclohexane produced 0.170 g of **68**.

Book Reviews

Modern Biological Theories of Aging. Vol. 31 of Aging. Edited by Hobert R. Warner, Robert N. Butler, Richard L. Sprott, Edward L. Schneider. Raven, New York. 1987. xviii + 324 pp. 16 × 24 cm. ISBN 0-88167-310-2. $69.50.

Aging is inevitable; it starts the minute one is born. The first 30 years of life involve physiological development, the remainder covers decline. This slowing down of hundreds of functions may proceed fast or gradually. According to the best estimates, the upper life expectancy for humans is 115 years (including Methusaleh in whose days years were not clearly defined) and for laboratory mutant mice, less than 10 years. Medicinal chemists might be able to flatten the curve of aging to a more gradual slope and to make it end in a whisper rather than a tortuous terminal ordeal.

The book under discussion represents the results of a conference on aging by the National Institute on Aging. It lists advances in theories of such topics as senility, Alzheimer's disease, recognized changes in neuroendocrine substances, genetic materials, and components of "normal" organs, especially hepatic tissues. Twenty-seven contributors have labored to offer a comprehensive picture of the present stage of research on aging. There are six symposia: evolution of life span in placental mammals; developmentally programmed aging; free radical damage; error catastrophe; DNA damage and repair; and organ systems as pacemakers of aging. Each of these symposia is introduced with an overview of the discussions and summarized at the end.

The individual papers open up a pandora box of new vistas, new observations, and importantly, the shelving of some concepts which, only a decade ago, were regarded as gospel. The error catastrophe theory is one example of such changes in research emphasis. Medicinal scientists could dip into reservoirs of compounds left over from anti-irradiation drug research and submit them as free radical inhibitors in tests that bear on aging. This is at present the area most amenable to drug research, but there is a question whether it will remain pertinent to the problem of aging. Those of us in the upper brackets of statistical life expectancy who are struggling with restrictive diets and with exercise should program our souls to look down from the stratosphere, or up from the interior of earth's hot magma, and watch with interest where the next volumes in this series will take us.

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Pharmazeutische Wirkstoffe. Synthesen, Patente, Anwendungen. Supplementary Volume 1982–1987. A. Kleeman and J. Engel. Georg Thieme Verlag, Stuttgart and New York. 1987. viii + 288 pp. 17 × 24 cm. ISBN 3-13-701301-1. DM 178.

This is a catalog of new and old drugs. For each of them is listed a brief therapeutic application, similar to entries in the much more comprehensive *Merck Index*. Then follow extensive synthetic schemes with ample structures, formulas, and references. Proprietary names are given according to the countries where applicable, especially France, Germany, Italy, Britain, Japan, and U.S.A. There are indexes of all the drugs in the volume and their synthetic intermediates and indexes according to medicinal indications and trade names.

The most valuable feature of this register is the listing of synthetic methods leading to the drugs. There are strange bedfellows: besides many exotic agents with unfamiliar generic names, there are phenolphthalein, primaquin, proguanil, inositol, methylene blue, khellin, chlorthalidon, eucalyptol, benzyl alcohol, L-aspartic acid, and dozens of other old and even ancient standby's that have been known for decades. An instructive insight is gained from inspecting the proprietary names. It demonstrates how few of the world's medicinal agents have been approved in the U.S.A.

Users of the *Merck Index* who can read German will find this volume a welcome more international compilation of some drugs and their chemical accessibility.

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Stereoselective Synthesis. By Mihály Nógrádi. VCH, Weinheim, FRG, and New York, NY. 1987. xiv + 356 pp. 17 × 24 cm. ISBN 0-89573-494-X. $93.00.

This book, which uses the term "stereoselective" (rather than the more nebulous "asymmetric") synthesis in the title, deals with the subject in eight chapters comprising 1381 references, covering the literature through 1984. Most of the references postdate the previous comprehensive treatise of the subject by J. D. Morrison and H. S. Mosher (1971). Some of the material in the five major chapters—Stereoselective Catalytic Reduction, Stereoselective Non-Catalytic Reduction, Stereoselective Carbon–Carbon Bond Forming Reactions by Nucleophilic Addition to Carbonyl Groups, Stereoselective Carbon–Carbon Bond Forming Reactions, Stereoselective Carbon–Carbon Bond Formation by Pericyclic Reactions—has, however, been summarized elsewhere, notably in the five-volume treatise edited by J. D. Morrison (1983–1985).

There are a few surprising omissions of general references e.g. (in the introductory chapter on General Concepts of Stereoselective Synthesis) of the excellent review by J. Seeman, *Chem. Rev.* **1983**, *83*, 83 and of the review on prochirality (heterotopism) by E. L. Eliel, *Top. Curr. Chem.* **1982**, *105*, 1. Perusal of these reviews might have led to a less superficial treatment of the Curtin–Hammett principle and might have avoided two somewhat serious errors in dealing with prochirality, which is confused with heterotopicity on p 13; on the same page, the Prelog–Helmchen Re/Si nomenclature is mistakenly equated to the Hanson *pro-R*/*pro-S* designation.

The book is handsomely laid out, written in excellent and clear English, and relatively free of misprints except in a few names (Wittig's name is repeatedly misspelled in Chapter 7). There are, however, a number of errors in the diagrams; this reviewer has the misfortune that both the structure of the chiral auxiliary used in a stereoselective synthesis devised by him (structure **17** in Figure 5-5) and the table referring to the synthesis (Table 5-3, allyl instead of vinyl) are mistaken. Anyone using the information in this book should, as always, check the original source!

There is an adequate subject index and, interestingly, a table of the cost, on a molar basis, of 71 frequently used chiral auxiliaries relative to (+)-tartaric acid taken as unity.

Most of the examples in the book relate to enantioselective synthesis; diastereoselective reactions are, in general, dealt with only as they ultimately lead to optically active products for, according to the author (p 131) "the most important aspects of