(72%) of a tan solid: mp 320–322 °C dec; IR (KBr) no CN; ^{1}H NMR (Me_2SO-d_6–TFA-d) δ 2.30 (s, 6), 5.20 (s, 4), 7.20 (d, 4), 7.65 (d, 4), 7.80 (m, 4), 8.60 (m, 4).

3,3′-[9,10-Anthrylenebis(methylidenehydrazino)]dipropionitrile (37). Acrylonitrile (0.95 mL, 14.43 mmol) was added to hydrazine hydrate (755 mg, 12.98 mmol) while the temperature was kept below 35 °C with the aid of occasional cooling with an ice bath.[33] The mixture was stirred at room temperature for 2 h, and then any unreacted starting materials were removed by evaporating the solution at 40 °C (35 mmHg). A solution of the residue and **27** (975 mg, 4.17 mmol) in EtOH (25 mL) was stirred at room temperature for 3 h and then refluxed for 1 h. The mixture was cooled and filtered, and the solid was dried 2 h at 110 °C in vacuo to yield 1.35 g (88%) of yellow solid: mp 156–158 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.85 (t, 4), 3.60 (q, 4), 7.55 (m, 4), 7.85 (t, 2), 8.55 (m, 4), 8.80 (s, 2). Anal. ($C_{22}H_{20}N_6$) C, H, N.

Alkaline Elution Assays.[25] One million L-1210 cells in logarithmic growth, prelabeled with [^{14}C]thymidine (0.1 μCi/mL of 55 mCi/mmol activity), were exposed to drug for 1 h, then washed in fresh medium (RPMI 1640, Gibco N.Y.), and irradiated on ice with 6.5 or 30 cGy (Varian Linac 4 mEv) for SSB or DNA–protein cross-link assays, respectively. The cells were then loaded on 2.0 μm, 25 mm PVC filters (Millipore Corp, San Francisco, CA) and lysed with pH 10.0 solution of 0.2% *N*-laurolysarcosine. Proteinase K (0.5 mg/mL) (E. Merck Co, Darmstadt, Germany) was then pumped through the filters for 1 h (2.5 mL/h in SSB assays. DNA from the cells was then eluted over 16 h at 2.5 mL/h with a pH 12.1 solution of tetrapropylammonium hydroxide (Eastman Organic Chemicals, Rochester, NY) and 1% sodium dodecyl sulfate. Hourly fractions were collected and ^{14}C radioactivity was counted by scintillation in three volumes of scintillation fluid. The rapidly eluting fractions (DNA SSB's) were compared to the percent of radioactivity ([^{14}C]DNA) retained on the filter (nonsheared DNA).

Acknowledgment. This investigation was supported by grants CA 37798 (to W.A.R.) and CA 17094 (to D.S.A.) awarded by the National Cancer Institute, DHHS.

Registry No. **6**, 108365-87-3; **6**·2fumarate, 108366-14-9; **7**, 108365-88-4; **7**·2HCl, 108394-56-5; **8**, 108365-89-5; **9**, 108365-90-8; **9**·2HCl, 108366-10-5; **9**·2H_3C-*p*-$C_6H_4SO_3H$, 108366-26-3; **10**, 108365-91-9; **10**·2HCl, 108366-11-6; **11**, 108365-92-0; **11**·2HCl, 108366-12-7; **12**, 108365-93-1; **12**·2HCl, 108366-13-8; **13**, 78363-52-7; **14**, 108365-94-2; **14**·2fumarate, 108366-15-0; **15**, 106712-13-4; **15**·2fumarate, 108366-16-1; **16**, 108365-95-3; **16**·fumarate, 108394-57-6; **17**, 108365-96-4; **17**·fumarate, 108366-17-2; **18**, 108365-97-5; **18**·fumarate, 108366-18-3; **19**, 108365-98-6; **19**·fumarate, 108366-19-4; **20**, 108365-99-7; **20**·2fumarate, 108366-20-7; **21**, 108366-00-3; **21**·2citrate, 108366-21-8; **22**, 108366-01-4; **22**·fumarate, 108366-22-9; **23**, 108366-02-5; **23**·fumarate, 108366-23-0; **24**, 108366-03-6; **24**·fumarate, 108366-24-1; **25**, 108366-04-7; **25**·fumarate, 108366-25-2; **26**, 19926-09-1; **27**, 7044-91-9; **27** (ethyl acetate deriv.), 108366-28-5; **28**, 59214-44-7; **29**, 30216-51-4; **30**, 62806-30-8; **31**, 108366-05-8; **32**, 108366-06-9; **32** (imidate, 108366-27-4; **33**, 10387-13-0; **34**, 108365-86-2; **34**·2HCl, 108366-07-0; **35**, 108366-08-1; **36**, 6705-67-5; **37**, 108366-09-2; H_2NCH_2CN·HCl, 6011-14-9; H_2C=CHCN, 107-13-1; 4-$H_2N(CH_2)_2NHO_3SC_6H_4Me$, 14034-59-4; $NCCH_2P(O)(OPr\text{-}i)_2$, 58264-04-3; $H_2N(CH_2)_2NH_2$, 107-15-3; $BrCH_2CO_2Et$, 105-36-2; $H_2N(CH_2)_2NMe_2$, 108-00-9; $H_2N(CH_2)_2N(Pr\text{-}i)_2$, 121-05-1; $MeNH(CH_2)_2NMe_2$, 142-25-6; $MeNH(CH_2)_2NHMe$, 110-70-3; $HO(CH_2)_2NH(CH_2)_2NH_2$, 111-41-1; $H_2N(CH_2)_3NMe_2$, 30734-81-7; $H_2N(CH_2)_2O(CH_2)_2OH$, 929-06-6; $H_2N(CH_2)_4OH$, 13325-10-5; $H_2N(CH_2)_5OH$, 2508-29-4; 2-amino-imidazole, 7720-39-0; *N*-methyl-piperazine, 109-01-3; *N*-ethyl-3-aminopiperidine, 6789-94-2; *N*-(2-aminoethyl)morpholine, 2038-03-1; 2-aminoimidazole sulfate, 42383-61-9.

(33) Dorn, H.; Zubek, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 39.
(34) McKay, A. F.; Gilpin, J. R. *J. Am. Chem. Soc.* **1956**, *78*, 486.
(35) Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*, 1.
(36) Dorr, R. T.; Alberts, D. S.; Chen, H-S. G. *J. Pharmacol. Methods* **1980**, *4*, 237.

Antianaphylactic Benzophenones and Related Compounds

Delme Evans,† Mark E. Cracknell,† John C. Saunders,† Christine E. Smith,† W. R. Nigel Williamson,*† William Dawson,‡ and W. John F. Sweatman‡

Organic Chemistry Department and Pharmacology Department, Lilly Research Centre Limited, Eli Lilly & Company, Erl Wood Manor, Windlesham, Surrey GU20 6PH, England. *Received March 3, 1986*

The synthesis and biological properties of 85 benzophenones and related compounds are described. The majority of the compounds inhibit the release of leukotrienes (LT) C_4 and D_4 in vitro from sensitized guinea pig chopped lung. In addition, some of the compounds inhibited the release of LTs from passively sensitized human chopped lung and protected guinea pigs from the effects of anaphylaxis in a modified Herxheimer test.

To our knowledge, until the work described herein was undertaken, the possibility that 2-hydroxybenzophenones could be antiasthmatic agents had not been considered, despite the fact that compounds of this type contain structural features, namely, an oxygen atom ortho to an aromatic carbonyl group, that are found in the antiasthmatic agent disodium cromoglycate. Work in another field[1] made available a number of 2-hydroxybenzophenones and their oximes, which were submitted for screening in tests designed to reveal antianaphylactic activity.[2] This revealed that oxime **6a** and ketone **20** (Table I) possessed interesting antiallergic activity, and these two "lead" compounds formed the basis of the study reported here. Subsequent to the completion of this work, a paper[3] has appeared claiming *antiinflammatory* activity in a limited number of benzophenones, including 2-hydroxy derivatives.

Chemistry. The compounds were prepared by standard methods of organic chemistry. Further details are to be found in Tables I–III and the Experimental Section.

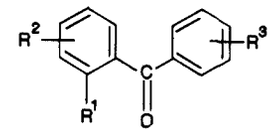
Antianaphylactic Activity. The following tests were used for the detection of antiallergic activity: (1) the guinea pig chopped lung test (in vitro) (GPCL),[4,5] (2) the

† Organic Chemistry Department.
‡ Pharmacology Department.

(1) Saunders, J. C.; Williamson, W. R. N, *J. Med. Chem.* **1979**, *22*, 1554.
(2) Ross, W. J.; Harrison, R. G.; Jolly, M. R. J.; Neville, M. C.; Todd, A.; Verge, J. P.; Dawson, W.; Sweatman, W. J. F. *J. Med. Chem.* **1979**, *22*, 412.
(3) Barton, H. *Pol. J. Pharmacol. Pharm.* **1979**, *31*, 169.
(4) Mongar, J. L.; Schild, H. O. *J. Physiol. (London)* **1956**, *131*, 207.

0022-2623/87/1830-1321$01.50/0

Table I.[a] Effect of Benzophenones and Oximes on Mediator Release from Sensitized Guinea Pig Chopped Lung upon Antigen Challenge



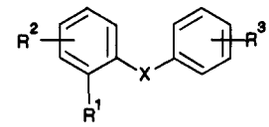
compd	R^1	R^2	R^3	yield, %	mp, °C, or bp, °C (mm)	method	formula[a] anal.	% inhibition[d] SRS-A	% inhibition[d] histamine
1	OH	H	H	purchsd	37–39[f]		$C_{13}H_{10}O_2$	0	nt[b]
2	OH	3-Me	H	23	114–117[c,g] (0.1)	13	$C_{14}H_{12}O_2$	0	nt
3	OH	3-Et	H	58	123–126[c,h] (0.14)	*n*	$C_{15}H_{14}O_2$	37*[q]	92**
4	OH	3-*n*-Pr	H	42	34–35	13	$C_{16}H_{16}O_2$	0	nt
5	OH	H	4-Cl	72	70–72[i]	13	$C_{13}H_9ClO_2$	0	nt
6	OH	3-Me	4-Cl	47	61–63[j]	*n*	$C_{14}H_{11}ClO_2$	36*	6
7	OH	3-Et	4-Cl	31	72–73[k]	*n*	$C_{15}H_{13}ClO_2$	2	nt
8	OH	3-Et	2,4-Cl_2	6	oil	1	$C_{15}H_{12}Cl_2O_2$	44*	8
9	OH	4-Me	4-Cl	22	80–81[l]	1	$C_{14}H_{11}ClO_2$	0	nt
10	OH	4-Et	4-Cl	83	52	*n*	$C_{15}H_{13}ClO_2$	8	nt
11	OH	4-Me	4-F	9	78	1	$C_{14}H_{11}FO_2$	10	nt
12	OH	4-Et	4-F	5	44–48	*n*	$C_{15}H_{13}FO_2$	5	nt
13	OH	4-Et	3-F	5	oil	1	$C_{15}H_{13}FO_2$	26	nt
14	OAc	4-Et	4-F	85	57–58	14	$C_{17}H_{15}FO_3$	9	nt
15	OH	5-Me	H	purchsd	81–84		$C_{14}H_{12}O_2$	39*	78**
16	OH	5-Et	H	60	69–72	1	$C_{15}H_{14}O_2$	22	nt
17	OH	5-Me	4-Cl	78	68	*n*	$C_{14}H_{11}ClO_2$	46*	0
18	OH	5-Et	2-Cl	60	138–140[c] (0.45)	1	$C_{15}H_{13}ClO_2$	14	nt
19	OH	5-Et	3-Cl	66	153–156[c] (0.25)	1	$C_{15}H_{13}ClO_2$	0	nt
20	OH	5-Et	4-Cl	72	41.5–43.5 150–160[c] (0.3)	1	$C_{15}H_{13}ClO_2$	51**	3
21	OCOPh	5-Et	4-Cl	90	79–81	5	$C_{22}H_{17}ClO_3$	71**	32*
22	OAc	5-Et	4-Cl	86	160–165[c] (0.35)	14	$C_{17}H_{15}ClO_3$	28	nt
23	OAc	5-Et	4-Me	64	142–146[c] (0.1)	14	$C_{18}H_{18}O_3$	49**	9
24	OH	5-Et	4-Br	45	186[c] (0.95)	1	$C_{15}H_{13}BrO_2$	10	nt
25	OH	5-Et	4-F	38	44–46	1	$C_{15}H_{13}FO_2$	1	nt
26	OH	5-Et	4-Me	38	49–51	1	$C_{16}H_{16}O_2$	76**	53**
27	OH	5-Et	4-NO_2	63	100–101.5	1	$C_{15}H_{13}NO_4$	5	nt
28	OMe	5-Et	4-NO_2	14	79–80	1	$C_{16}H_{15}NO_4$	0	nt
29	OH	5-Et	3-CN	27	77–80	6	$C_{16}H_{13}NO_2$	21	nt
30	OH	5-Et	2,4-Cl_2	34	44–46	1	$C_{15}H_{12}Cl_2O_2$	0	nt
31	OH	5-Et	3,4-Cl_2	30	175–177[c]	1	$C_{15}H_{12}Cl_2O_2$	0	nt
32	OH	3-*n*-Pr	4-Cl	35	68–70	13	$C_{16}H_{15}ClO_2$	0	nt
33	OH	5-*n*-Pr	4-Cl	27.5	151–153[c] (0.2)	1	$C_{16}H_{15}ClO_2$	0	nt
34	OH	5-*n*-Bu	4-Cl	54	174[c] (0.75)	1	$C_{17}H_{17}ClO_2$	0	nt
35	OH	5-Ac	4-Cl	7	127–130	7	$C_{15}H_{11}ClO_3$	42*	61**
36	OH	3,5-Et_2	4-Cl	53	188[c] (1.4)	1	$C_{17}H_{17}ClO_2$	38*	9
					Corresponding Oximes				
2a (*E*)[m]	OH	3-Me	H	31	164–166[p]	*n*	$C_{14}H_{13}NO_2$	0[o]	nt
3a (*E*)	OH	3-Et	H	100	146–148	*n*	$C_{15}H_{15}NO_2$	13	nt
6a (*E*)	OH	3-Me	4-Cl	68	178	*n*	$C_{14}H_{12}ClNO_2$	52**	52**
9a (*E*)	OH	4-Me	4-Cl	36.6	168–169	*n*	$C_{14}H_{12}ClNO_2$	0	nt
10a (*E*)	OH	4-Et	4-Cl	59	159–161	*n*	$C_{15}H_{14}ClNO_2$	0	nt
11a (*E*)	OH	4-Et	4-F	48	130–132	*n*	$C_{15}H_{14}FNO_2$	33*	46**
17a (*E*)	OH	5-Me	4-Cl	63	157–160	*n*	$C_{14}H_{12}ClNO_2$	40*	59**
17b (*Z*)				1	145–147	*n*	$C_{14}H_{12}ClNO_2$	32*	25
20a (*E*)	OH	5-Et	4-Cl	64	117	*n*	$C_{15}H_{14}ClNO_2$	51**	28
30a (*E*)	OH	5-Et	2,4-Cl_2	36	155–158	*n*	$C_{15}H_{13}Cl_2NO_2$	0	nt
31a (*E*)	OH	5-Et	3,4-Cl_2	42	132–134	*n*	$C_{15}H_{13}Cl_2NO_2$	2	nt
33a (*E*)	OH	5-*n*-Pr	4-Cl	41	104–105	*n*	$C_{16}H_{16}ClNO_2$	8	nt
KHF[e]								38**	37**

[a] Benzophenone numbering is retained for all compounds in the table, for ease of comparison. All compounds were analyzed for C, H, N, and halogen, where appropriate. [b] Not tested. [c] Boiling point (mmHg). [d] Of release from guinea pig chopped lung at 10 μg/mL. [e] Ketotifen hydrogen maleate. [f] Reference 13 quotes mp 39–40 °C for this compound. [g] Reference 14 gives bp 152–155 °C (2 mm) for this compound. [h] Reference 15 give bp 165–167 °C (3 mm) for this compound. [i] Reference 16 gives mp 74–75 °C for this compound. [j] Reference 17 quotes mp 61.5–62 °C for this compound. [k] Reference 1 gives mp 72–73 °C for this compound. [l] Reference 18 gives mp 81.5 °C for this compound. [m] The designation **2a** indicates that the oxime is the derivative of the benzophenone **2**, and a similar type of numbering system is used for the other oximes. [n] Method of preparation as given in ref 1. For structures of oximes **17a** and **17b**, see ref 1. [o] Oximes dosed at 1 μg/mL, except **30a** and **31a**, which were tested at 10 μg/mL. [p] Reference 14 gives mp 164–165 °C. [q] Significance of differences: (*) $p < 0.05$, (**) $p < 0.01$.

human chopped lung test,[6] and (3) the modified Herxheimer test.[7] The tests are designed to monitor slow reacting substance of anaphylaxis (SRS-A). The three main constituents of SRS-A have been shown in the case of human and guinea pig lung to be leukotrienes C_4, D_4, and E_4.[8-11] Although several other mediators have been

(5) Brocklehurst, W. E. *J. Physiol. (London)* **1960**, *151*, 416.
(6) Sheard, P.; Killingback, P. G.; Blair, A. M. J. N. *Nature (London)* **1967**, *216*, 283.
(7) Herxheimer, H. *J. Physiol. (London)* **1952**, *117*, 251.

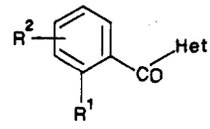
Table II.[a] Effect of Benzophenones and Related Compounds on Mediator Release from Sensitized Guinea Pig Chopped Lung upon Antigen Challenge



compd	R^1	R^2	X	R^3	yield, %	mp, °C or bp, °C (mm)	method	formula[a] anal.	% inhibition[d] SRS-A	% inhibition[d] histamine
37	OH	5-Et	CH_2	H	57	128 (0.65)[c]	18	$C_{15}H_{16}O$	36*[g]	0
38	OH	5-Et	CH_2	4-Me	62	44–47	18	$C_{16}H_{18}O$	0	nt[b]
39	OH	5-Et	CH_2	4-Cl	71	40–42	18	$C_{15}H_{15}ClO$	39*	17
40	OH	4-Et	CH_2	4-F	40	137–142 (0.3)[c]	18	$C_{15}H_{15}FO$	34*	33*
41	OH	5-Et	CHOH	H	50	oil[f]	15	$C_{15}H_{16}O_2$	37*	7
42	OH	5-Et	CHOH	4-Cl	93	69–71	15	$C_{15}H_{15}ClO_2$	5	nt
43	OMe	5-Et	CHOH	4-Cl	28	71–73	15	$C_{16}H_{17}ClO_2$	14	nt
44	OH	4-Et	CHOH	4-F	29	94–95	15	$C_{15}H_{15}FO_2$	34*	5
45	OMe	5-Et	CHOMe	4-Cl	22	48.5–50.5	16	$C_{17}H_{19}ClO_2$	32**	22
46	OH	5-Et	CHOH	4-NO_2	37	107–108	15	$C_{15}H_{15}NO_4$	33*	0
47	OMe	5-Et	CHOH	4-Me	41	57–58	15	$C_{17}H_{20}O_2$	28	nt
48	OH	5-Et	CCH_2	H	60	151 (0.9)[c]	19	$C_{16}H_{16}O$	24	nt
49	OH	4-Et	CCH_2	4-F	67	120–122 (0.05)[c]	19	$C_{16}H_{15}FO$	32	0
50	OH	5-Et	CCH_2	4-Me	73	121–124 (0.08)[c]	19	$C_{17}H_{18}O$	0	nt
51	OH	5-Et	CCH_2	4-Cl	85	136–138 (0.04)[c]	19	$C_{16}H_{15}ClO$	3	nt
52	SMe	5-Et	CO	4-Cl	38	176–182 (0.5)[c]	2	$C_{16}H_{15}ClOS$	29*	nt
53	SMe	5-Et	CO	4-Me	30	152–154 (0.01)[c]	2	$C_{17}H_{18}OS$	32*	0
54	SMe	5-Et	CO	H	47	140 (0.08)[c]	2	$C_{16}H_{16}OS$	52**	19
55	SOMe	5-Et	CO	4-Me	35	74–75	8	$C_{17}H_{18}O_2S$	40**	3
56	SOMe	5-Et	CO	4-Cl	36	90–92	8	$C_{16}H_{15}ClO_2S$	36*	1
57	SO_2Me	5-Et	CO	4-Cl	46.5	124–127	9	$C_{16}H_{15}ClO_3S$	17	nt
58	SO_2Me	5-Et	CO	H	73	114–116	9	$C_{16}H_{16}O_3S$	35**	13
59	SOMe	5-Et	CO	4-F	27.5	79–80	8	$C_{16}H_{15}FO_2S$	42**	9
60	SO_2Me	5-Et	CO	4-F	33	145–147	9	$C_{16}H_{15}FO_3S$	27*	nt
61	OH	4-Cl-5-Et	SO	4-Me	31	171	17	$C_{15}H_{15}ClO_2S$	5	nt
62	CO_2H	4 or 5-Et	CO	4-Cl	66	116–122	3	$C_{16}H_{13}ClO_3$	20	nt
63	SO_2Me	5-Et	CO	4-Me	46	92–95	9	$C_{17}H_{18}O_3S$	11	nt
64	SMe	5-Et	CO	4-F	75	154–156 (0.3)[c]	1	$C_{16}H_{15}FOS$	31**	14
65	SMe	5-Et	CHOH	4-Cl	99	83	15	$C_{16}H_{17}ClOS$	11	nt
66	OH	5-Et	S	H	27	n^{23}_D 1.613	4	$C_{14}H_{14}OS$	0	nt
67	OH	5-Et	S	4-Cl	9	n^{23}_D 1.62	4	$C_{14}H_{13}ClOS$	31*	31
68	OH	5-Et	SO	H	69	145	10	$C_{14}H_{14}O_2S$	36*	36*
69	OH	5-Et	SO	4-Cl	50	137	10	$C_{14}H_{13}ClO_2S$	48**	26
70	OH	5-Et	SO_2	H	67	103	11	$C_{14}H_{14}O_3S$	0	nt
71	OH	5-Et	SO_2	4-Cl	42	89	11	$C_{14}H_{13}ClO_3S$	19	nt
KHF[e]									38**	37**

[a] Benzophenone numbering is retained for all the compounds in the table, for ease of comparison. All compounds were analyzed for C, H, N. [b] Not tested. [c] Boiling point (mmHg). [d] Of release from guinea pig chopped lung at 10 μg/mL. [e] Ketotifen hydrogen maleate. [f] Purified by chromatography. [g] Significance of differences: (*) $p < 0.05$, (**) $p < 0.01$.

Table III. Effect of Heteroyl Phenyl Ketones on Mediator Release from Guinea Pig Chopped Lung upon Antigen Challenge



compd	R^1	R^2	Het	yield, %	mp, °C or bp, °C (mm)	method	formula[a] anal.	% inhibition[d] SRS-A	% inhibition[d] histamine
72	OH	5-Et	2-pyridyl	65	138 (0.2)[c]	21	$C_{14}H_{13}NO_2$	30*[g]	5
73	OH	5-Et	4-pyridyl	62	208–211[f]	21	$C_{14}H_{13}NO_2$·HBr	0	nt[b]
74	OMe	5-Et	2-pyridyl	43	149–151 (0.5)[c]	20	$C_{15}H_{15}NO_2$	0	nt
75	OMe	5-Et	4-pyridyl	48	154–156 (0.3)[c]	20	$C_{15}H_{15}NO_2$	0	nt
76	OMe	5-Et	4-pyridyl *N*-oxide	40	208 (0.3)[c]	22	$C_{15}H_{15}NO_3$	0	nt
77	OH	5-Et	3-pyridyl	62	57–59	21	$C_{14}H_{13}NO_2$	27	nt
78	OH	5-Et	1-naphthyl	69	147 (0.08)[c]	1	$C_{19}H_{16}O_2$	0	nt
79	OH	5-Et	2-naphthyl	45.5	62–63	1	$C_{19}H_{16}O_2$	2	nt
80	OH	5-Et	2-furyl	19.5	110 (0.3)[c]	12	$C_{13}H_{12}O_3$	32**	0
81	OH	5-Et	2-thienyl	3	118–122 (0.07)[c]	13	$C_{13}H_{12}O_2S$	59**	0
82	OH	5-Et	5-Cl-2-thienyl	4.5	136–138 (0.14)[c]	13	$C_{13}H_{11}ClO_2S$	21	nt
83	OH	5-Et	5-Me-2-thienyl	49	133–136 (0.1)[c]	13	$C_{14}H_{14}O_2S$	28	nt
84	OH	5-Et	3-thienyl	82.5	131–133 (0.4)[c]	12	$C_{13}H_{12}O_2S$	26	37*
85	OH	5-Et	1-Me-2-pyrryl	5.6	n^{23}_D 1.623	13	$C_{14}H_{15}NO_2$	0	nt
KHF[e]								38**	37**

[a] All compounds were analyzed for C, H, N. [b] Not tested. [c] Boiling point (mmHg). [d] Of release from guinea pig chopped lung at 10 μg/mL. [e] Ketotifen hydrogen maleate. [f] Hydrobromide. [g] Significance of differences: (*) $p < 0.05$, (**) $p < 0.01$.

Table IV. Effect of Compounds on Bronchospasm in Conscious Sensitized Guinea Pigs (4–5 Animals for Each Compound) upon Antigen Challenge (Herxheimer)

compd	dose, mg/kg po	time of dosing of compd before antigen challenge, h	D^a	$M + D^b$
12	100	2	1.2	2.3
	50	4	1.3	2.8
16	50	2	2.5	1.2
20	100	2	1.4	1.8
	25	4	0.8	2.7
28	50	2	0.8	2.1
37	50	2	3.0	1.6
43	25	2	0.8	2.7
50	50	2	1.0	3.5
52	50	2	0.6	2.3
69	50	2	1.0	1.7
	25	4	1.3	1.7
81	50	2	0.7	1.6
84	50	2	0.8	2.3
85	50	2	1.2	2.3
KHF[c]	2	2	4.2	3.1

[a] Mean collapse time after pretreatment with compound divided by mean collapse time of untreated control animals. [b] Mean collapse time after pretreatment with compound and mepyramine divided by mean collapse time of mepyramine-dosed control animals. [c] Ketotifen hydrogen maleate.

Table V. Effect of Compounds on Mediator Release from Passively Sensitized Human Lung upon Antigen Challenge

compd	% inhibition[a] SRS-A	% inhibition[a] histamine	dose, μg/mL
2a	62**[b]	15	10
	39*	8	1
6	100***	0	10
	100***	0	1
8	100***	60*	10
	85**	20	1
20	100***	0	10
	74**	0	1
20a	91***	0	10
	93**	0	1
50	84***	0	10
	46*	0	1
55	100***	0	10
	75**	0	1
69	99***	31	10
	69*	0	1
81	67**	0	10
	55*	0	1
KHF[c]	100***	23	10
	51*	0	1

[a] Of release from human lung at stated dose. [b] Significance of differences: (***) $p < 0.001$, (**) $p < 0.01$, (*) $p < 0.1$. [c] Ketotifen hydrogen maleate.

implicated in guinea pig anaphylaxis, e.g., platelet activating factor (PAF-acether) and thromboxanes, their contribution to the non-histamine biological activity in the bioassay systems used in the present study was found to be less than 5% of that attributable to SRS-A.

The oxime **6a** and the ketone **20** showed good activity in the GPCL test, and the other compounds in Tables I–III were prepared and tested in an attempt to improve on the original activities of these compounds. Table I shows the structure–activity results obtained when various substituents were moved around the hydroxylated benzophenone ring and when a variety of substituents were present in the other benzene ring. The substituents in the hydroxylated ring ranged from Me to *n*-Bu, with Me and Et tried in three of the four possible positions. This showed the 5-Et substitution to be the most favorable. With regard to substitution in the other benzene ring, the 4-Cl compound was the most active monochloro compound. Substitution with more than one chlorine atom was not advantageous. Of the other six types of substituents (H, Br, F, Me, NO_2, and CN) that were examined, only the Me compounds were as active as the Cl derivatives. A few other compounds, not within the above category, e.g., **21**, **23**, **26**, and **35**, which were very active in the GPCL, did not perform well on testing in the modified Herxheimer or human chopped lung tests. In general, the activities of oximes were correlated well with the activities of the corresponding ketones, but only **2a** and **20a** maintained activity on subsequent screening and only in the human lung test. Consequent upon the above results and particularly the good activity of **20**, subsequent analogues were based primarily on the 2-hydroxy-5-ethyl orientation. As seen in Tables II and III, variations in the group linking the benzene rings, in the group ortho to the linkage, and in the type of ring linked (via a group) to the 2-hydroxy-5-ethylbenzene were prepared. Of the compounds listed in Tables II and III, only five, **54**, **55**, **59**, **69**, and **81**, showed percentage inhibitions above 40%. Table IV lists activities in the modified Herxheimer test and Table V activities in the human chopped lung test. Only compounds **20**, **69**, and **81** had activities in all three of the above tests, with **20** and **81** showing greater than 50% inhibition of SRS-A release in GPCL, and **20** and **69** greater than 90% inhibition on the human lung test at 10 μg/mL. In the Herxheimer test, the majority of compounds tested were inactive at 4 h and are thus not recorded on Table IV. However, compounds **12**, **20**, and **69** were noteworthy in giving protection against the non-histamine component at 4 h. Compound **12** was also active at 4 h at a dose of 50 mg/kg orally, but was inactive on GPCL.

While we have seen only partial correlation of activities of the compounds in the three tests used, we feel nevertheless that this work has identified a new class of chemical structures that possesses antianaphylactic activity in experimental animals.

Experimental Section

Melting points are uncorrected. Microanalyses were carried out by G. Maciak and colleagues, Eli Lilly and Co., Indianapolis, IN, and microanalytical results were within 0.4% of the theoretical values. IR (Perkin-Elmer 457 spectrophotometer) and NMR (Varian A-60A spectrometer) spectra were obtained for all the compounds and were consistent with the given structures. Typical examples of the various methods are given below. Further details of the compounds are noted in Tables I–III.

Method 1. 2-Hydroxy-5-ethyl-4′-chlorobenzophenone (20) and 2-Hydroxy-3-methyl-4′-chlorobenzophenone Oxime (6a). As for compound II(2) and compound III(5), respectively, ref 1.

Method 2. 2-(Methylthio)-5-ethyl-4′-chlorobenzophenone (52). Aluminum chloride (2.66 g, 0.01 mol) was added in portions to a stirred solution of 4-ethylthioanisole (3.04 g, 0.02 mol) and 4-chlorobenzoyl chloride (3.85 g, 0.022 mol) in 1,1,2,2-tetrachloroethane (20 mL). The reaction mixture was ice-cooled. After 0.5 h at room temperature, the mixture was poured into ice and HCl, and this mixture was extracted with $CHCl_3$, which was washed (10% Na_2CO_3), dried ($MgSO_4$), evaporated, and distilled to give the product.

Method 3. 2-Carboxy-4(or 5)-ethyl-4′-chlorobenzophenone (62). Aluminum chloride (2.66 g, 0.02 mol) was added to a stirred solution of 4-ethylphthalic anhydride (1.76 g, 0.01 mol) in PhCl

(8) Samuelsson, B.; Hammarström, S. *Prostaglandins* **1980**, *19*, 645.
(9) Lewis, R. A.; Austen, K. F.; Drazen, J. M.; Clark, D. A.; Marfat A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77* 3710
(10) Morris, H. R.; Taylor, G. W.; Piper P. J.; Tippins, J. R. *Agents Actions Suppl.* **1979**, *9*, 27.
(11) Morris, H. R.; Taylor, G. W.; Piper, P. J.; Tippins, J. R. *Nature (London)* **1980**, *285*, 104.

(15 mL). The mixture became hot and was cooled in an ice bath. After 18 h at room temperature, the mixture was processed as in method 2 and the product was precipitated by acidification of the Na_2CO_3 solution and recrystallized from MeOH.

Method 4. 2-(Phenylthio)-4-ethylphenol (66). Cl_2 was passed into a stirred, ice-cooled solution of 4-ethylphenol (30 g, 0.25 mol) and thiophenol (22 g, 20.5 mL, 0.25 mol) in CH_2Cl_2 (100 mL) for 3 h. After standing at room temperature overnight, the solvent was evaporated to give an oil, which distilled at bp 170–180 °C (0.5 mm) (27.1 g). This was dissolved in hexane, treated with charcoal, filtered, and evaporated. The product was chromatographed on SiO_2, by using elution with hexane containing increasing amounts of $CHCl_3$ to give three fractions. The third fraction contained the required material (12.5 g).

Method 5. *O*-Benzoyl-2-hydroxy-5-ethyl-4′-chlorobenzophenone (21). Compound **20** (5 g, 0.019 mol) was stirred in 2.5 N NaOH solution (75 mL) with PhCOCl (12.12 g, 0.086 mol) for 1.5 h and extracted with Et_2O. The Et_2O was washed with saturated NaCl, dried (Na_2SO_4), filtered, and evaporated to give the product, which was recrystallized from hexane.

Method 6. 2-Hydroxy-5-ethyl-3′-cyanobenzophenone (29). 4-Ethylphenyl 3-cyanobenzoate, anal. ($C_{16}H_{13}NO_2$) C, H, N (5 g, 0.019 mol) (prepared by reaction of 4-ethylphenol with 3-cyanobenzoyl chloride), in ethanol (200 mL) was stirred and irradiated with UV light from a Hanovia 125-W lamp for 7 days. Evaporation of the EtOH gave the product, which was recrystallized from petroleum ether (bp 40–60 °C).

Method 7. 2-Hydroxy-5-acetyl-4′-chlorobenzophenone (35). The acid chloride (3.47 g, 0.03 mol) of 5-acetylsalicylic acid in PhCl (20 mL) with $AlCl_3$ (5.6 g, 0.045 mol) was stirred and heated at 100 °C for 24 h. Processing in the usual way gave the product.

Method 8. 2-(Methylsulfinyl)-5-ethyl-4′-methylbenzophenone (55). Compound **53** (2.7 g, 0.01 mol) and 30% H_2O_2 (1.14 mol) were refluxed together for 1 h in AcOH (100 mL) under N_2. The mixture was poured into ice/water (ca. 500 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 was washed with H_2O, dried ($MgSO_4$), and evaporated to give the product. This was purified by treatment in hexane with C and subsequent chromatography of the product of evaporation of the hexane on preparative thin-layer chromatography (PTLC) using $CHCl_3/Et_2O$ (3:1) as eluent. The product from this process was purified by crystallization from $COMe_2$.

Method 9. 2-(Methylsulfonyl)-5-ethyl-4′-chlorobenzophenone (57). Compound **52** (2.91 g, 0.01 mol) and 30% H_2O_2 (3.4 mL, 0.03 mol) were refluxed in AcOH (20 mL) for 3 h. The solution was poured into ice/water (100 mL) and the resulting precipitate recrystallized from $CHCl_3$/hexane. The product was further purified by using PTLC to give a material that was crystallized from $COMe_2$ to give the product.

Method 10. 4-Ethyl-2-(phenylsulfinyl)phenol (68). Compound **66** (2.3 g, 0.01 mol) was refluxed for 1 h in AcOH (100 mL) with 30% H_2O_2 (14 mL, 0.01 mol) under N_2. The cooled mixture was poured into ice/water to give a solid, which was crystallized from hexane/$CHCl_3$ to give the product.

Method 11. 4-Ethyl-2-(phenylsulfonyl)phenol (70). Compound **66** (2.3 g, 10 mmol) was refluxed for 3 h with 30% H_2O_2 (4.54 mL, 40 mmol) in AcOH (40 mL). The cooled mixture was poured onto crushed ice to give a solid, which was filtered off, dried, and recrystallized from hexane (charcoal) to give the product.

Method 12. 2-Furoyl-4-ethylphenol (80). 4-Ethylphenol (12.2 g, 0.1 mol), 2-furoyl chloride (13.05 g, 0.1 mol) and pyridine (40 mL) were heated at 100 °C for 15 min. The pyridine was evaporated and the residue treated with H_2O and extracted with $CHCl_3$. The latter was washed with saturated $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$), filtered, and evaporated to give the 4-ethylphenyl ester of furoic acid (37.3 g), bp 114–116 °C (0.16 mm). Anal. ($C_{13}H_{12}O_3$) C, H. (The 4-ethylphenyl ester of 3-thenoic acid, bp 131–133 °C (0.4 mm), was similarly prepared for **84**. Anal. ($C_{13}H_{12}O_2S$) C, H.) The ester (5.74 g, 0.026 mol), $AlCl_3$ (5 g, 0.037 mol), and CS_2 were refluxed for 30 min, the CS_2 was removed, and the residue was heated at 120–130 °C for 1.5 h. The cooled material was treated with ice and HCl and extracted with $CHCl_3$. The $CHCl_3$ was washed with saturated $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$), filtered, and evaporated to give **80** after distillation.

Method 13. 2-Thenoyl-4-ethylphenol (81). 2-Hydroxy-5-ethylbenzoic acid (16.6 g, 0.1 mol) was converted to its acid chloride in petroleum ether (bp 40–60 °C, 75 mL) with pyridine (0.1 mL) and $SOCl_2$ (12.49 g, 0.1 mol) with refluxing for 6 h. After evaporation of the solvent, the product was stirred in CS_2 (120 mL) with $AlCl_3$ (26.6 g, 0.2 mol) with cooling to 2 °C. Then thiophene (8.4 g, 0.1 mol) in CS_2 (25 mL) was added at a rate that maintained the temperature at 3 °C. The mixture was stirred at room temperature overnight and refluxed for 3.5 h. Processing in the usual way and distillation gave **81**. For the preparation of **4**, 2-hydroxy-3-*n*-propylbenzoic acid (79% yield, mp 87–89 °C, anal. ($C_{10}H_{12}O_3$) C, H) was formed from 2-*n*-propylphenol by reaction with CO_2 at 200 °C/140 atm in the presence of K_2CO_3, with subsequent acidification, and the resulting acid was converted to its acid chloride and reacted with C_6H_6 with $AlCl_3$ as before to give **4**. For **2**, CS_2 was omitted in the corresponding Friedel–Crafts reaction.

Method 14. 2-Hydroxy-4-ethyl-4′-fluorobenzophenone Acetate (14). Compound **12** (5 g, 0.02 mol) was refluxed for 5 h with Ac_2O (20 mL). After evaporation of Ac_2O, treatment with 2 N NaOH, the product was extracted with $CHCl_3$. After evaporation of the $CHCl_3$, the residue was crystallized from *n*-hexane to give **14**.

Method 15. (2-Hydroxy-5-ethylphenyl)(4-chlorophenyl)methanol (42). To a stirred suspension of $LiAlH_4$ (1.45 g, 0.038 mol) in Et_2O (150 mL) was added dropwise compound **20** (9.7 g, 0.037 mol) in Et_2O (75 mL). The mixture was refluxed for 0.5 h and cooled in an ice bath and 2 N HCl (4 mL) added, followed by H_2O. The mixture was separated and the pH of the aqueous layer adjusted to 4 by addition of 1 N HCl. This was extracted with Et_2O (3×), and the combined Et_2O extracts were dried ($MgSO_4$) filtered, and evaporated. The residue solidified to give **42**. $NaBH_4$ in 2-propanol, instead of $LiAlH_4$ in Et_2O, was used for the preparation of **43**, and aluminum isopropoxide was the reductant for **46**.

Method 16. (2-Methoxy-5-ethylphenyl)(4-chlorophenyl)methyl Methyl Ether (45). To **43** (3 g, 0.011 mol) was added 60% HBr solution (20 mL), and the mixture was refluxed for 0.5 h. The cooled solution was extracted with Et_2O, which was washed with 10% Na_2CO_3 solution, dried ($MgSO_4$), filtered, and evaporated to give a brown oil (3.63 g). The oil was dissolved in MeOH and added to a stirred solution of NaOH (0.8 g, 0.02 mol) in MeOH (30 mL), and the solution was refluxed for 1.5 h. This was acidified with dilute HCl, extracted with $CHCl_3$, dried, and evaporated to give an oil, which crystallized and gave **45** on recrystallization from MeOH.

Method 17. 5-Chloro-4-ethyl-2-[(4-methylphenyl)sulfinyl]phenol (61). Cl_2 was passed into a stirred, ice-cooled solution of 4-ethylphenol (44.4 g, 0.3 mol) and 4-thiocresol (36.1 g, 0.25 mol) in CH_2Cl_2 (150 mL) for 4 h. After standing at room temperature overnight, the solvent was distilled off in vacuo to give two fractions (35.3 g), which were chromatographed on SiO_2 (20% $CHCl_3$/hexane as eluent) to give four fractions, the fourth (10 g) being 77% pure 5-chloro-4-ethyl-2-(4-tolylthio)phenol (as estimated by GC). The latter material (3.17 g) and 30% H_2O_2 (1.14 mL, 0.01 mol) were refluxed for 1 h in HOAc (100 mL) under N_2. The cooled mixture was poured into ice to give a gummy solid, which was recrystallized from $CHCl_3$/hexane to give **61**.

Method 18. 4-Ethyl-2-(4-chlorobenzyl)phenol (39). Ninety-five percent hydrazine (8 mL) was added to a slightly warm solution of compound **20** (7.8 g, 0.03 mol) in diethylene glycol (40 mL), and the solution was heated at 150 °C for 30 min. A solution of KOH (5.6 g, 0.03 mol) in hot diethylene glycol (40 mL) was added, and the solution was heated at 150 °C for a further 30 min. Some of the vapor was allowed to escape until the internal temperature of the reaction reached 210 °C. The clear solution was kept at this temperature for 3 h, half of the solvent was removed by evaporation, and the remainder was poured into an excess of ice and 2 N HCl. The mixture was extracted with Et_2O (3×), and the organic extracts were washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was distilled to yield the expected product, which solidified on standing.

Method 19. 1-(2-Hydroxy-4-ethylphenyl)-1-(4-fluorophenyl)ethylene (49). A solution of 5-ethyl-2-(4-fluorobenzoyl)phenol (6.8 g, 0.028 mol) in anhydrous Et_2O (50 mL) was added dropwise during 30 min to a stirred solution of MeMgI

(0.060 mol) in Et_2O (100 mL). The reaction mixture was stirred under reflux for 16 h, cooled, and poured into an excess of 1 N HCl. The product was extracted into Et_2O (3×), and the organic solution was washed with H_2O, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the ethylenic compound.

Method 20. 1-(5-Ethyl-2-methoxyphenyl)-1-(4-pyridyl)-methanone (75). The Grignard reagent from 0.1 mol of 2-bromo-4-ethylanisole in anhydrous Et_2O (200 mL) was prepared in the conventional way. To this was added, dropwise, a solution of 4-cyanopyridine (10.4 g, 0.1 mol) in Et_2O (100 mL). A yellow precipitate formed. The reaction mixture was stirred under reflux for 1.5 h, cooled, and poured into 2 N HCl (250 mL). The Et_2O layer was separated and discarded. The aqueous layer was basified with 5 N NaOH and extracted with Et_2O (3×). The Et_2O extracts were washed with H_2O, dried (Na_2SO_4), and evaporated. Distillation of the residue gave the expected product.

Method 21. 1-(5-Ethyl-2-hydroxyphenyl)-1-(4-pyridyl)-methanone Hydrobromide (73). A solution of compound **75** (7.5 g, 0.031 mol) in 48% HBr (40 mL) was heated at 90 °C for 18 h, and the excess of HBr was removed under reduced pressure. The residue was recrystallized from a small quantity of EtOH/petroleum ether (bp 60–80 °C) to give yellow crystals to the hydrobromide. For compounds **72** and **77**, the free bases were liberated from the hydrobromide in the conventional way and purified by distillation in vacuo.

Method 22. 4-(5-Ethyl-2-methoxybenzoyl)pyridine *N*-Oxide (76). A solution of 85% *m*-chloroperbenzoic acid (100 g, 0.0492 mol) and compound **75** (9.3 g, 0.0386 mol) was dissolved in $CHCl_3$ (150 mL) and kept at room temperature for 3 days. The solution was shaken successively with 2 N NaOH (50 mL) and H_2O (4×). The dried (Na_2SO_4) $CHCl_3$ layer was evaporated, and the residue was distilled.

Biological Methods. The Guinea Pig Chopped Lung Test (GPCL). Guinea pigs (male, 250–350 g, body weight) were sensitized with ovalbumin (Sigma, Grade 11, 100 mg ip and sc). Their lungs were removed 3 weeks later, perfused with Tyrode solution to remove blood, and chopped into 0.5-mm cubes: 100-mg aliquots were suspended in Tyrode solution (4.5 mL) in each tube, incubated for 5 min (37 °C) before addition of compound or Tyrode and the challenging solution of ovalbumin (5 mg in 0.1 mL, Sigma Grade 111). One control group was not challenged and was used to assess spontaneous mediator release. Following incubation with rocking at 37 °C for 15 min, each supernatant was removed and bioassayed. Results are expressed as the percentage inhibition of mediator release. Each result is the mean of at least four samples, and the usual variance is 5–10%. Significance of differences was calculated from the absolute values by Student's *t* test. Bioassay: SRS-A was assayed on segments of guinea pig ileum treated with mepyramine (0.4 μg/mL) against partially purified SRS-A from guinea pig lung. Histamine was assayed similarly by using normal segments by guinea pig ileum.

All compounds were sufficiently soluble in the physiological solution to be used at the concentrations described for the GPCL and human chopped lung studies. In the Herxheimer test, compounds either were dissolved in 0.9% solution of sodium chloride or, if insoluble, were suspended in 0.5% sodium carboxymethylcellulose solution.

Human Chopped Lung Test. Samples of healthy human lung were placed in ice-cold Tyrode solution within 45 min of removal during operations for carcinoma of the lung. Within 2 h, the lung samples were washed in Tyrode, chopped with a McIlwain chopper into 0.5-mm cubes, and then incubated for 18 h at 18 °C with atopic serum derived from patients allergic to cocksfoot (*Dactylis glomerata*) pollen. The chopped tissue was incubated, challenged, and bioassayed in a similar manner as was employed for guinea pig chopped lung, except that the tissue was challenged, after preincubation for 5 min with the compound under test, with specific antigen (pollen extract 0.1 mL, 1000 noon units).

Modified Herxheimer Test. Male guinea pigs were sensitized as described for the chopped test. Three weeks later they were exposed to ovalbumin (1% w/v solution, as an aerosol) in an observation chamber. The animals were kept in the chamber until symptoms of respiratory distress, terminating in a characteristic convulsive cough, were observed. The time of onset of the cough immediately preceding convulsions was known as the "collapse time". Exposure beyond this end point resulted in convulsions and death from severe bronchospasm. Pretreatment with antihistamines, such as mepyramine, reveals that a non-histamine component, which may be assumed to be largely due to SRS-A,[12] is responsible for the remainder of the response. Accordingly, the response to each compound in the presence of mepyramine (0.5 mg/kg sc), given 0.5 h before challenge, was studied. The compound was given orally at doses of 25, 50, or 100 mg/kg 2 or 4 h before antigen challenge. The dose was based on the amount of compound required to produce observable side effects in pilot studies in mice and guinea pigs, the dose used for the test being at least one-eighth of this amount. The protection ratios of a compound were related to the protection that the compound gave against (i) the histamine component of bronchospasm and (ii) the non-histamine component. They were defined as mean collapse time after pretreatment with compound divided by mean collapse time of untreated control animals (*D*) and as mean collapse time after pretreatment with compound and mepyramine divided by mean collapse time of mepyramine-dosed control animals (*M* + *D*).

Acknowledgment. We thank D. Brockwell for the guinea pig chopped lung results, C. H. Marsden and J. Shephard for Herxheimer results, and G. Maciak of Lilly Research Laboratories, Indianapolis, for microanalytical data. Dr. W. J. Ross is thanked for helpful discussions and Dr. D. M. Rackham for NMR and IR data and interpretations. In addition we thank Dr. J. W. Jackson and J. DeMulder of Harefield Hospital, Middlesex, for help in obtaining specimens of human lung and Dr. L. M. McEwen, London, for pollen extract. We thank Sandoz Ltd., Basel, Switzerland, for a generous gift of ketotifen hydrogen fumarate. We thank Ann Gracey for experimental assistance and T. A. Hicks for preparing compound **27**.

Registry No. 1, 117-99-7; **2**, 4072-08-6; **2a**, 108295-07-4; **3**, 56394-91-3; **3a**, 108295-08-5; **4**, 108294-70-8; **5**, 2985-79-7; **6**, 6279-04-5; **6a**, 65975-46-4; **7**, 61466-80-6; **8**, 61466-78-2; **9**, 107622-28-6; **9a**, 108295-09-6; **10**, 56394-72-0; **10a**, 61466-74-8; **11**, 108294-71-9; **11a**, 65975-45-3; **12**, 56394-78-6; **13**, 61466-88-4; **14**, 78473-40-2; **15**, 1470-57-1; **16**, 3132-42-1; **17**, 6279-05-6; **17a**, 61466-69-1; **17b**, 61466-70-4; **18**, 108294-72-0; **19**, 61466-85-1; **20**, 56394-67-3; **20a**, 61466-72-6; **21**, 61750-27-4; **22**, 61750-28-5; **23**, 108294-73-1; **24**, 108294-74-2; **25**, 108294-75-3; **26**, 61750-25-2; **27**, 108294-76-4; **28**, 108294-77-5; **29**, 108294-78-6; **30**, 61466-83-9; **30a**, 108295-10-9; **31**, 61466-87-3; **31a**, 108295-11-0; **32**, 108294-79-7; **33**, 61466-81-7; **33a**, 108295-12-1; **34**, 108294-80-0; **35**, 108294-81-1; **36**, 108294-82-2; **37**, 61516-21-0; **38**, 108294-83-3; **39**, 108294-84-4; **40**, 108294-85-5; **41**, 108294-86-6; **42**, 78473-42-4; **43**, 78473-45-7; **43** (X = CO), 78473-44-6; **44**, 78473-39-9; **45**, 78473-46-8; **46**, 108294-87-7; **47**, 78473-43-5; **47** (X = CO), 108295-16-5; **18**, 108294-88-8; **49**, 108294-89-9; **50**, 108294-90-2; **51**, 108294-91-3; **52**, 69738-08-5; **53**, 69738-06-3; **54**, 69738-09-6; **55**, 69738-15-4; **56**, 69738-14-3; **57**, 69738-11-0; **58**, 108294-92-4; **59**, 69738-13-2; **59** (X = S), 69738-07-4; **60**, 69738-10-9; **61**, 108294-93-5; **61** (X = S), 108295-17-6; **62** (R^2 = 4-Et), 108294-94-6; **62** (R^2 = 5-Et), 108295-13-2; **63**, 69738-12-1; **64**, 69738-07-4; **65**, 108294-95-7; **66**, 66784-32-5; **67**, 66784-33-6; **68**, 64790-84-7; **69**, 66784-34-7; **70**, 108294-96-8; **71**, 108294-97-9; **72**, 108294-98-0; **73**, 108294-99-1; **74**, 108295-00-7; **75**, 108295-01-8; **76**, 108295-02-9; **77**, 108295-03-0; **77** (R^1 = OMe), 108295-18-7; **78**, 108295-04-1; **79**, 108295-05-2; **80**, 108295-06-3; **81**, 69582-62-3; **82**, 69582-64-5; **83**, 69582-63-4; **84**, 69582-65-6; **85**, 69582-67-8; 4-EtC_6H_4SMe, 31218-75-4; 4-ClC_6H_4COCl, 122-01-0; PhCl, 108-90-7; 4-EtC_6H_4OH, 123-07-9;

(12) Dawson, W.; Sweatman, W. J. F. *Br. J. Pharmacol.* **1980**, *71*, 387.
(13) Graebe, C.; Ullman, F. *Ber. Dtsch. Chem. Ges.* **1986**, *29*, 824.
(14) Reich, D. A.; Nightingale, D. V. *J. Org. Chem.* **1956**, *21*, 825.
(15) Koskov, V. K.; Naumov, Y. A. *Zh. Obshch. Khim.* **1961**, *31*, 54.
(16) Kulka, M. *J. Am. Chem. Soc.* **1951**, *73*, 2483.
(17) Huston, R. C.; Robinson, K. R. *J. Am. Chem. Soc.* **1951**, *73*, 2483.
(18) Kindler, K.; Oelschläger, H.; Henrich, P. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1954**, *287*, 210.

C_6H_5SH, 108-98-5; 3-NCC_6H_4COCl, 1711-11-1; 5-Ac-2-OHC_6H_3COCl, 108295-15-4; 5-Et-2-$OHC_6H_3CO_2H$, 51-27-4; 2-*n*-PrC_6H_4OH, 644-35-9; 4-MeC_6H_4SH, 106-45-6; 2-Br-4-EtC_6H_3OMe, 99179-98-3; 3-Me-2-$OHC_6H_3CO_2H$, 83-40-9; C_6H_6, 71-43-2; 3-Pr-2-$OHC_6H_3CO_2H$, 22890-52-4; 2-$OHC_6H_4CO_2H$, 69-72-7; 4-MeC_6H_4COCl, 874-60-2; C_6H_5COCl, 98-88-4; 4-ClC_6H_4SH, 106-54-7; 4-ethylphthalic anhydride, 35081-12-0; 4-ethylphenyl 3-cyanobenzoate, 108295-14-3; 2-furoyl chloride, 527-69-5; 4-ethylphenyl 2-furoate, 108319-34-2; 4-ethylphenyl 3-thenoate, 69582-66-7; thiophene, 110-02-1; 4-cyanopyridine, 100-48-1; 2-cyanopyridine, 100-70-9; 2-chlorothiophene, 96-43-5; 1-methylpyrrole, 96-54-8.

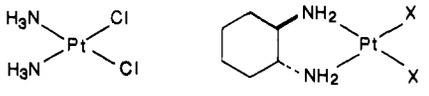
Stereocontrolled Syntheses for the Six Diastereomeric 1,2-Dihydroxy-4,5-diaminocyclohexanes: Pt^{II} Complexes and P-388 Antitumor Properties[1]

Donald T. Witiak,*† David P. Rotella,† Joyce A. Filppi,‡ and Judith Gallucci§

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, and Adria Laboratories, Columbus, Ohio 43216. *Received September 10, 1986*

Stereocontrolled syntheses for the six diastereomeric 1,2-dihydroxy-4,5-diaminocyclohexanes **3a–f** from cyclohexene diamines *cis*-**4** and *trans*-**5** are described. Cbz-protected species *cis*-**9** and *trans*-**11**, respectively, served as a source of stable Cbz-protected precursors to these cyclohexanediol diamines (CDD), which were liberated upon catalytic (H_2, Pd/C) hydrogenation. Catalytic osmylation of **9** afforded a mixture of diastereomeric diols **13** and **14**, which served as precursors to cis-anti-cis CDD **3b** and cis-syn-cis CDD **3a**, respectively, whereas osmylation of **11** yielded the expected single product **12**, the precursor to cis-anti-trans CDD **3d**. Epoxidation of olefins **9** and **11** afforded oxiranes **15** and **17**, respectively, which upon acid-catalyzed hydrolysis produced the corresponding Cbz-protected diols **16** and **18**, which served as precursors to CDD trans-anti-cis **3c**, and trans-anti-trans **3e**. Formation of diol **18** from oxirane **17** was accompanied by formation of 2-oxa-4-azabicyclo[3.3.1]nonan-3-one **19**. CDD trans-syn-trans **3f** was prepared from diol **12** via regioselective monoacetylation, yielding **22**, followed by oxidation to afford ketone **24**. Sodium borohydride reduction and acetylation produced diacetate precursor **26**. $Pt^{II}Cl_2$ complexes of five of the diamines (**3a–d,f**) are described, and their activities were compared with cisplatin (**1**) by employing P-388 leukemia implanted CDF_1 mice. The data indicate that stereochemistry of the amino groups on the cyclohexanediamine ligand modulate the expression of toxic effects, and depending upon hydroxyl and amino group stereochemistry, there is a marked effect on complex formation (e.g., Cl_2Pt^{II}-**3e**) and solubility characteristics (e.g., Cl_2Pt^{II}-**3c**). Acetylation of the hydroxyl functions in selected isomers (**28a–c**) rendered the Pt^{II} complexes inactive. A single-crystal X-ray structure of compound **3a** was determined at room temperature and indicated the cis-syn-cis arrangement of the OH and NH_2 groups.

The clinical utility of antineoplastic platinum complexes, typified by cisplatin (**1**), has engendered numerous studies directed toward understanding the unique biological properties exhibited by such species.[2] Additionally, congeners of **1** are desired that do not share its severe nephrotoxicity and emetic potential thereby limiting the effective therapeutic use of the drug.[2b,3] Second-generation organoplatinum compounds include 1,2-diaminocyclohexane–Pt^{II} complexes (**2**),[4] which display less nephrotoxicity, decreased cross resistance with cisplatin, or a somewhat expanded antitumor spectrum when compared to **1**.[2a] Structure–activity studies[4–9] of **2** have focused on the labile ligands which modify aqueous solubility,[10] reactivity in vivo with DNA bionucleophiles[2e–g,i,j] such as the N-7 position of guanine,[2c,d,j] and toxicity.[11] Although numerous efficacious and sometimes water-soluble drugs have been prepared,[4–9] problems[5,12] associated with modification of the leaving group in **2** are exemplified by complexes having inadequate water solubility (**2a**) or chemical instability (**2c,d**), thus producing unacceptable



1 **2a**, X = Cl; **b**, X = malonate; **c**, X = SO_4; **d**, X = NO_3

† The Ohio State University, Department of Medicinal Chemistry.
‡ Adria Laboratories.
§ The Ohio State University, Department of Chemistry.

(1) A preliminary account of this work was presented to the Division of Medicinal Chemistry, 191st National Meeting of the American Chemical Society, New York, NY: Rotella, D. P.; Witiak, D. T.; MEDI-65, 1986. This article was abstracted in part from a Ph.D. dissertation (1985) presented by D.P.R. to The Ohio State University. Present address for D.P.R. is Department of Chemistry, Pennsylvania State University, University Park, PA 16802.

(2) For mechanistic studies and the antitumor spectrum of cisplatin, see: (a) Hill, J. M.; Speer, R. J. *Anticancer Res.* **1982**, 2, 173–186; (b) Loehrer, P. J.; Einhorn, L. H. *Ann. Intern. Med.* **1984**, *100*, 704–713; (c) Pinto, A. L.; Lippard, S. J. *Biochim. Biophys. Acta* **1985**, *780*, 167–180; (d) Sherman, S. E.; Gibson, D.; Wang, A. H.-J.; Lippard, S. J. *Science (Washington, D.C.)* **1985**, *230*, 412–417; (e) Roberts, J. J.; Thomson, A. J. *Prog. Nucleic Acid Res. Mol. Biol.* **1979**, *22*, 71–133; (f) Roberts, J. J. In *Molecular Actions and Targets for Cancer Chemotherapeutic Agents*; Sartorelli, A. C., Lazo, J. S. Bertino, J. R., Eds; Academic: New York, 1981; pp 17–43; (g) *Cisplatin: Current Status and New Development*; Prestayko, A. W., Crooke, S. T., Carter, S. K., Eds.; Academic: New York, **1980**; (h) *Platinum Coordination Complexes in Cancer Chemotherapy*; Hacker, M. P., Douple, E. B., Krakoff, I. H., Eds.; Martinus Nijhoff: Boston, 1984; (i) *Platinum, Gold and Other Metal Chemotherapeutic Agents, Chemistry and Biochemistry*; Lippard, S. J., Ed.; ACS Symposium Series 209; American Chemical Society: Washington, DC, 1983; (j) Haghighi, S.; McAuliffe, C. A.; Friedman, M. E. *Rev. Inorg. Chem.* **1981**, *3*, 291–351.

(3) (a) Kociba, R. J.; Sleight, S. D. *Cancer Chemother. Rep., Part 1* **1971**, *55*, 1–8; (b) Burchenal, J. H.; Kalaher, K.; Dew, K.; Lokys. L. *Cancer Treat. Rep.* **1979**, *63*, 1493–1498.

0022-2623/87/1830-1327$01.50/0