($CDCl_3$) δ 2.53 (s, 6 H, SCH_3), 2.68 (s, 6 H, SCH_3), 4.33 (s, 3 H, NCH_3), 6.55 (br s, 2 H, CH=C), 7.73–8.33 (m, 3 H, arom H). Anal. ($C_{14}H_{20}INS_4$) C, H, N.

The following procedure is representative of the formation of the *S*-alkyl derivatives (larger than methyl).

1-Methyl-2-[2,2-bis(2-ethylthio)vinyl]pyridinium Iodide. To a stirred suspension of picolinium methiodide (3.5 g, 15 mmol) in toluene (100 mL) were added potassium *tert*-butoxide (2 g) and 10–15 drops of 95% EtOH. The mixture was stirred 20 min, and the clear supernatant liquid was decanted. This process was repeated five times with 50 mL of toluene, 0.5 g of potassium *tert*-butoxide, and 5–10 drops of 95% EtOH. To the combined toluene solutions was added CS_2 (5 mL, 83 mmol), and the mixture was stirred for 30 min at room temperature. It was filtered, and the residue was taken up in DMF (20 mL). An excess of iodoethane (6 mL, 75 mmol) was added, and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo at 60–70 °C, and the residue was recrystallized (H_2O), giving 4.2 g (77%) of yellow needles: mp 143–145 °C; IR ν 1620 (C=C), 1165–1175 (CH_2S), 800 (C=C); ^1H NMR ($CDCl_3$) δ 1.10–1.60 (m, 6 H, C_2H_5), 2.77–3.43 (m, 4 H, C_2H_5), 4.50 (s, 3 H, NCH_3), 6.67 (s, 1 H, CH=C), 7.63–9.07 (m, 4 H, arom H). Anal. ($C_{12}H_{18}INS_2$) C, H, N.

The following procedure is representative of the synthesis of compounds of type **6**.

1-Methyl-2-[2-(methylthio)-2-piperidinovinyl]pyridinium Iodide. 1-Methyl-2-[2,2-bis(2-methylthio)vinyl]pyridinium iodide (3.0 g, 9 mmol) and piperidine (1.53 g, 18 mmol) were added to 20 mL of DMF, and the mixture was heated at 70 °C for 2 h and at 50 °C for 4 days with stirring. After being cooled, the solution was added to 150 mL of ether and swirled, and the ethereal layer was decanted. Ethyl acetate (150 mL) was added to the residual syrup, and after it was chilled, yellow crystals separated and were filtered and recrystallized from 1:1 EtOH/2-PrOH, giving 2.19 g (66%): mp 143–144 °C; IR ν 1630 (C=C), 1160–1170 (CH_2S), 780 (C=C); ^1H NMR ($CDCl_3$) δ 1.40–1.70 (m, 6 H, piperidine), 2.40 (s, 3 H, SCH_3), 3.20–3.60 (d, 4 H, CH_2N), 4.0 (s, 3 H, NCH_3), 5.2 (s, 1 H, CH=C), 7.2–8.6 (m, 4 H, arom H). Anal. ($C_{14}H_{21}IN_2S$) C, H, N.

The following procedure is representative of the synthesis of compounds of type **3**.

1-Methyl-2-[2-(methylthio)-2-[bis(methoxyethyl)amino]vinyl]quinolinium Iodide. 1-Methyl-2-[2,2-bis(methylthio)vinyl]quinolinium iodide[14] (4.0 g, 10 mmol) and aminoacetaldehyde dimethyl acetal (1.05 g, 10 mmol) were added to 40 mL of Me_2SO. The solution was stirred at room temperature for 4 days and mixed with 300 mL of ether, and the ethereal layer was decanted. The solvent was evaporated and 50 mL of 2-PrOH was added to the residue. A solid was filtered and recrystallized (2-PrOH) to give 2.48 g (58%) of yellow crystals: mp 142–143 °C; IR ν 3200 (NH), 1610 (C=C), 820 (C=C); ^1H NMR (Me_2SO-d_6) δ 2.60 (s, 3 H, SCH_3), 3.36 (d, 6 H, OCH_3), 4.0 (s, 3 H, NCH_3), 4.40 (s, 2 H, CH_2N), 5.50 (s, 1 H, CH=C), 7.8–8.6 (m, arom H). Anal. ($C_{17}H_{23}IN_2O_2S$) C, H, N.

2-Methyl-1-[2,2-bis(methylthio)vinyl]isoquinolinium Iodide. To a suspension of 1,2-dimethylisoquinolinium iodide (2.5 g, 8.8 mmol) in 50 mL of toluene were added 1.0 g (8 mmol) of potassium *tert*-butoxide and 5–10 drops of 95% EtOH. The mixture was stirred for 20 min, and the clear supernatant liquid was decanted. To the residue were added toluene (35 mL), potassium *tert*-butoxide (0.5 g), and 95% EtOH (5–10 drops). The mixture was stirred for 20 min, and the supernatant liquid was decanted. The process was repeated, and to the combined toluene solutions was added CS_2 (3 mL, 50 mmol). The solution was stirred at room temperature for 30 min, iodomethane (3 mL, 48 mmol) was added, and the mixture was stirred overnight. Toluene was removed in a rotary evaporator at 50–60 °C, and the residue was recrystallized from water, giving 2.4 g (70%) of yellow needles: mp 204–205 °C; IR ν 1630 (C=C), 1155 (CH_2)S), 815 (C=C); ^1H NMR ($CDCl_3$) δ 2.37 (s, 3 H, SCH_3), 2.80 (s, 3 H, SCH_3), 4.65 (s, 3 H, NCH_3), 7.03 (s, 1 H, CH=C), 7.80–9.10 (m, 6 H, arom H). Anal. ($C_{14}H_{16}INS_2$) C, H, N.

Test for Radiation Protection. Compounds were administered to groups of 10 mice at each dose level 30 min prior to whole-body irradiation with 1000 rads with a ^{60}Co source. Female C57 B16 mice, 18–20 g, were used. Compounds were generally injected intraperitoneally in water or 10–20% aqueous ethanol; in some cases Klucel or a Tween was also required. Animals surviving beyond 30 days were considered protected.

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Registry No. **1** (R = CH_3), 67943-66-2; **2** (R = H), 21804-67-1; **3** (R = CH_3, R_2 = $(CH_2)_2O(CH_2)_2$), 74020-12-5; **3** (R = H, R_2 = $(CH_2)_5$), 88973-10-8; **3** (R = CH_3O, R_2 = SCH_3), 74020-11-4; **5**, 56185-70-7; **7**·Na(6-$CH_2CS_2^-$), 67943-63-9; **8**, 21695-44-3; **9**, 104664-33-7; **10**, 104664-34-8; **11**, 104664-35-9; **12**, 104664-36-0; **13**, 104664-37-1; **14**, 88973-11-9; **15** (R = CH=C$(SCH_3)_2$), 104664-38-2; **15** (R = CH_3), 51843-14-2; **16**, 104664-39-3; **17**, 104664-40-6; **18**, 104664-41-7; **19**, 104664-42-8; **20**, 104664-43-9; **21**, 54254-80-7; **22**, 110-89-4; **23**, 104692-93-5; **24**, 104664-44-0; CS_2, 75-15-0; CH_3I, 74-88-4; H_3CCH_2I, 75-03-6; $H_2NCH_2CH(OCH_3)_2$, 22483-09-6; 1,2-dimethylpyridinium iodide, 872-73-1; picoline, 1333-41-1; 1,2,6-trimethylpyridinium iodide, 2525-19-1; picolinium methiodide, 930-73-4; piperidine, 110-89-4.

Synthesis and Antilipolytic Activities of Quinolyl Carbanilates and Related Analogues

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A series of quinolyl carbanilates was prepared and tested as antilipolytic agents. These compounds inhibited production of glycerol from rat adipocytes and inhibited liberation of free fatty acids from triolein by canine cardiac triglyceride lipases. An extensive structure–activity relationship study indicated that 8-quinolyl 4-methoxycarbanilate (**1**) contained features necessary for maximum potency in vitro. Substituting a benzofuranyl group for the quinolyl group of **1** provided the most interesting compound on the basis of both potency and structural novelty. 7-Benzofuranyl 4-methoxycarbanilate (**44**) has IC_{50}'s of 16 and 0.3 μM in the myocardial lipase and rat adipocyte assays, respectively. In vivo, compound **44** was orally active as an inhibitor (97% at 25 mg/kg) of lipolysis in the rat.

There is much evidence that free fatty acid (FFA) has a detrimental effect on the ischemic heart by disrupting electrical conduction, decreasing myocardial efficiency, and preventing the transfer of ADP and ATP, in and out, respectively, of the mitochondria. It has been shown that interventions which depress myocardial FFA accumulation

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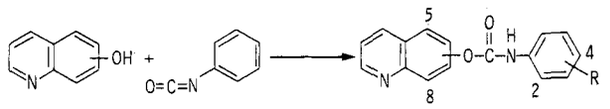
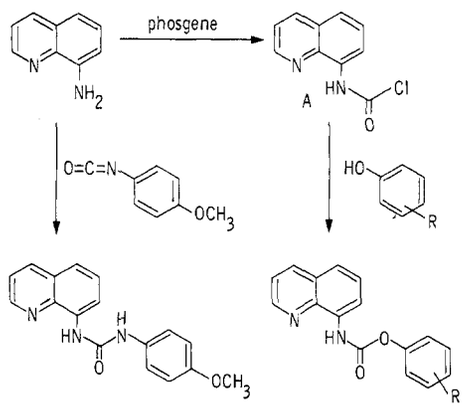
Scheme I



Scheme II



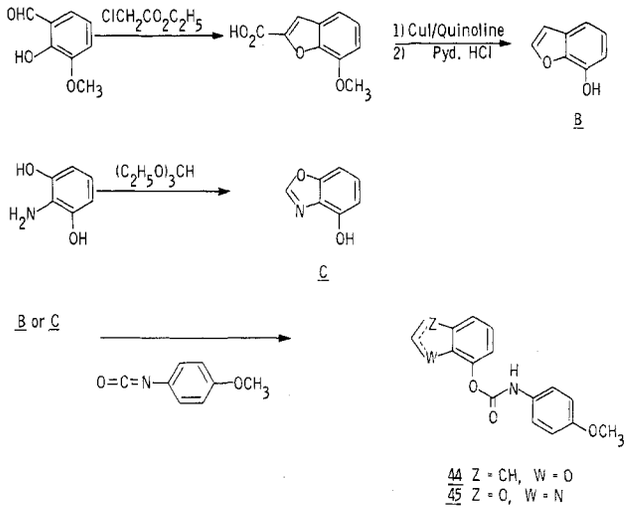
13 11 R = 2 - OCH_3; 12 R = 4 - OCH_3

produce a reduction in myocardial oxygen consumption (MVO_2) in animals[2] and man[3] and provide a protective effect against ischemic injury.[4,5]

Our objective was to discover new compounds capable of inhibiting lipolysis associated with ischemic heart disease. Screens used to uncover antilipolytic activity included the myocardial lipase assay[6] and the rat adipocyte assay.[7] Reported herein are our findings on quinolyl carbanilates, a series of compounds active as antilipolytic agents.

Our interest in quinolyl carbanilates evolved from a chemical lead discovered in our selective screening program. The commercially available 8-quinolyl 2,5-dimethoxycarbanilate (**27**)[8] was found active as an inhibitor of myocardial lipase and rat adipocyte lipolysis in vitro (see Table I). Although quinolines substituted in the 8-position with carbanilates are known as fungicides,[9] pesticides,[10] amebicides,[11] and bactericides,[12,13] we could not find any reference to quinolyl carbanilates as antilipolytic agents. Furthermore, we could not find any references to 5-, 6-, or 7-quinolyl carbanilates or other benzoheterocyclic carbanilates, such as benzoxazoyl or benzofuranyl carbanilates.

Scheme III



44 Z = CH, W = O; 45 Z = O, W = N

Chemistry. The 5- through 8-quinolyl carbanilates (I) (Scheme I) were prepared by reacting the appropriate hydroxyquinoline with various substituted phenyl isocyanates. The procedure that gave the best results involved mixing the two reactants in ethyl ether with a catalytic amount of triethylamine and stirring at room temperature for several days.

As a variation, phenyl esters of 8-quinoline carbamic acid were prepared as shown in Scheme II. Treatment of 8-aminoquinoline with phosgene gave intermediate A. The IR spectrum for A clearly shows a carbamoyl chloride carbonyl absorption at 1800 cm^{-1}, and no isocyanate absorption was observed. Reaction of A with 2- or 4-methoxyphenol at room temperature with 1 equiv of triethylamine produced carbamates **11** or **12**, respectively. *N*-(4-Methoxyphenyl)-*N'*-(8-quinolyl)urea (**13**) was prepared by reacting 8-aminoquinoline with 4-methoxyphenyl isocyanate.

Other variations included the synthesis of 8-quinolyl 4-methoxyacetanilide (**36**), 8-quinolyl 4-methoxyphenylacetate (**42**), and 8-quinolyl 4-methoxybenzoate (**43**). Reaction of 8-hydroxyquinoline with chloro-4-methoxyacetanilide (prepared from chloroacetyl chloride and 4-methoxyaniline), 4-methoxyphenylacetyl chloride, or 4-methoxybenzoyl chloride gave compounds **36**, **42**, or **43**, respectively.

The synthesis of benzofuranyl and the benzoxazoyl carbanilates was carried out as shown in Scheme III. Reaction of 2-vanillin with ethyl chloroacetate followed by base-induced cyclization and hydrolysis gave 7-methoxybenzofuran-2-carboxylic acid; copper-catalyzed decarboxylation and demethylation with pyridine hydrochloride then provided 7-hydroxybenzofuran (B). 4-Hydroxybenzoxazole (C) was prepared by treating 2-aminoresorcinol with triethyl orthoformate. The benzoheterocyclic alcohols B and C were reacted with 4-methoxyphenyl isocyanate to give carbanilates **44** and **45**, respectively.

Biological Results and Discussion

A broad group of quinolyl carbanilates and their variations were synthesized and tested as antilipolytic agents, and the results are summarized in Table I. The most potent inhibitors of lipolysis have the carbanilate group bonded to the 8-position of quinoline. This can be seen by comparing the compounds in group 1–4 and by comparing the compounds in group 5–8. Reversing the car-

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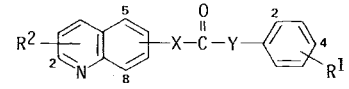
Table I. Inhibition of Myocardial Lipase and Rat Adipocyte Lipolysis



no.	X	Y	R^1	R^2	mp, °C	formula[a]	method[b]	% yield	myocardial lipase IC_{50}, μM,[c] or % inhibn at 100 μM	rat adipocyte IC_{50}, μM,[c] or % inhibn at given concn, μM
1	8-O	NH	4-OCH_3	H	129–130	$C_{17}H_{14}N_2O_3$	1	65	17	0.1
2	7-O	NH	4-OCH_3	H	153–159	$C_{17}H_{14}N_2O_3$	1	86	60%	0% at 30
3	6-O	NH	4-OCH_3	H	139–141	$C_{17}H_{14}N_2O_3$	1	68	64%	8% at 30
4	5-O	NH	4-OCH_3	H	174–177	$C_{17}H_{14}N_2O_3$	1	58	63%	1% at 30
5	8-O	NH	2-OCH_3	H	117–118	$C_{17}H_{14}N_2O_3$	1	90	40	7
6	7-O	NH	2-OCH_3	H	118–120	$C_{17}H_{14}N_2O_3$	1	88	48	80
7	6-O	NH	2-OCH_3	H	112–113	$C_{17}H_{14}N_2O_3$	1	73	42	30
8	5-O	NH	2-OCH_3	H	124–126	$C_{17}H_{14}N_2O_3$	1	27	48	31% at 200
9	8-O	NH	3-OCH_3	H	*d*	$C_{17}H_{14}N_2O_3$			18	7
10	7-O	NH	3-OCH_3	H	136–137	$C_{17}H_{14}N_2O_3$	1	57	52%	25% at 200
11	8-NH	O	4-OCH_3	H	128–129	$C_{17}H_{14}N_2O_3$	11	43	75%	3% at 30
12	8-NH	O	2-OCH_3	H	133–136	$C_{17}H_{14}N_2O_3$	11	38	20	30
13	8-NH	NH	2-OCH_3	H	159–163	$C_{17}H_{15}N_3O_2$	13	42	73	4% at 200
14	8-O	NH	4-$CO_2C_2H_5$	H	200–203	$C_{19}H_{16}N_2O_4$	1	51	200	44% at 200
15	7-O	NH	4-$CO_2C_2H_5$	H	180–182	$C_{19}H_{16}N_2O_4$	1	42	46%	18% at 200
16	8-O	NH	4-Cl	H	*d*				58%	52% at 3
17	8-O	NH	3-Cl	H	*d*				41%	5% at 3
18	8-O	NH	2-Cl	H	*d*				1%	NT[f]
19	7-O	NH	2-Cl	H	152–154	$C_{16}H_{11}F_3N_2O_2$	1	58	6%	NT
20	8-O	NH	4-CH_3	H	*d*				63%	76% at 3
21	8-O	NH	3-CH_3	H	*d*				64%	84% at 3
22	8-O	NH	2-CH_3	H	*d*				7%	40% at 3
23	7-O	NH	2-CH_3	H	145–147	$C_{17}H_{14}N_2O_2$	1	68	45%	20% at 200
24	8-O	NH	3-CF_3	H	*d*				56%	7% at 3
25	7-O	NH	2-CF_3	H	235–238	$C_{17}H_{11}F_3N_2O_2$	1	30	12%	NT
26	8-O	NH	2,4-diOCH_3	H	139–141	$C_{18}H_{16}N_2O_4$	1	65	65%	0.2
27	8-O	NH	2,5-diOCH_3	H	*d*				48	10
28	8-O	NH	4-Br	H	*d*				80	5% at 3
29	8-O	NH	H	H	*d*				69%	28% at 3
30	8-O	NH	H	2-CH_3	149–151		1	57	68%	29% at 3
31	8-O	NH	4-OCH_3	2-CH_3	127–130	$C_{18}H_{16}N_2O_3$	1	86	68%	0.2
32	8-O	NH	4-Br	2-CH_3	*d*				68%	5% at 3
33	8-O	NH	H	5-Cl	*d*				69%	4% at 3
34	8-O	NH	4-OCH_3	5-SO_3H[e]	138–141	$C_{17}H_{14}N_2O_6S$	34	92	83%	14% at 200
35	8-O	NH	H	5,7-diCl	*d*				56	28% at 200
36	8-OCH_2	NH	4-OCH_3	H	125–128	$C_{18}H_{16}N_2O_3$	36	32	7%	26% at 100
37	8-O	$NHCH_2$	4-OCH_3	H	126–129	$C_{18}H_{16}N_2O_3$	1	58	72%	5.8
38	8-O	$NH(CH_2)_2$	4-OCH_3	H	165–167	$C_{19}H_{18}N_2O_3$	1	92	70%	98% at 100
39	7-O	$NH(CH_2)_2$	4-OCH_3	H	112–115	$C_{19}H_{18}H_2O_3$	1	51	97%	84% at 100
40	8-O	(*S*)$NHCHCH_3$	H	H	126–128	$C_{18}H_{16}N_2O_2$	1	56	76%	35
41	8-O	(*R*)$NHCHCH_3$	H	H	126–128	$C_{18}H_{16}N_2O_2$	1	58	74%	35
42	8-O	CH_2	4-OCH_3	H	82–84	$C_{18}H_{15}NO_3$	42	44	0%	74% at 100
43	8-O		4-OCH_3	H	164–167	$C_{17}H_{13}NO_3$	43	50	13%	49% at 200
44[g]					157–159	$C_{16}H_{13}NO_4$	44	71	16	0.3

45[f]		161–162	$C_{15}H_{12}N_2O_4$	44	65	79	2.4
Acipimox							39
nicotinic acid							13
RHC 80,267[h]						4.0	1.0

[a] All compounds had elemental analysis (C, H, N) within 0.4% of their theoretical values except compound **8**. Anal. N: calcd, 9.52; found, 9.99. [b] See compound number in the Experimental Section. [c] All IC_{50}'s were calculated by nonlinear regression analysis and were significant at $p < 0.05$ level. [d] Compounds are commercially available; see ref 8. [e] Triethylamine salt. [f] Not tested. [g] See Scheme III for structure. [h] See ref 20.

bamate function lowers potency (compare **1** with **11**). Substituents on the phenyl portion of the carbanilate that have an electron-donating effect increase the potency of the parent molecule (compare **1** and **20** with **29**), whereas the opposite is true for substituents that have an electron-withdrawing effect (compare compounds **14** and **24** with **29**). Compounds with para-substituted electron-donating groups are more potent than the corresponding ortho-substituted compounds (see pairs **1,5** and **20,22**).

In contrast, substitution on the quinoline has little effect on antilipolytic activity of the quinolyl carbanilates (e.g., see series **29**, **30**, **33**, and **35**, and compare **1** with **31** and **28** with **32**).

Insertion of a methylene between oxygen and carbonyl of the carbanilate produces an inactive compound (**36**), whereas insertion of a methylene or ethylene between nitrogen and phenyl gives active compounds (e.g., **37**, **39**, and **40**); however, they are less potent than compound **1**. Addition of a CH_3CH group lowers potency, and the chirality of the CH_3CH group has little effect on inhibiting lipolysis in that enantiomers **40** and **41** are equipotent. Substituting CH_2 for NH of Y and eliminating NH of Y lower potency.

Many of the quinolyl carbanilates shown in Table I exhibit activity in the myocardial lipase assay and the rat adipocyte assay. The most potent quinolyl carbanilates are compounds **1**, **26**, and **31**. From the structure–activity relationship it appears that an electron-donating group in the para position of the carbanilate is important for the expression of potent antilipolytic activity. Since ortho substituents are less active than the corresponding para substituents, a steric interaction may be implicated. Also important is the quinoline nitrogen vicinal to the carbanilate function.

To determine whether any other benzoheterocyclics substituted with 4-methoxycarbanilate vicinal to a heteroatom would have potent antilipolytic activity, compounds **44** and **45** were synthesized. Although the benzoxazoyl carbanilate **45** only shows modest activity (lipase and adipocyte IC_{50}'s are 79 and 2.4 μM, respectively), the benzofuranyl carbanilate **44** is equipotent (lipase and adipocyte IC_{50}'s are 16 and 0.3 μM, respectively) with quinolyl carbanilate **1**. Since **44** is structurally more novel than **1**, it was decided that **44** should be examined in vivo. The in vivo assay used was essentially the one reported to profile Acipimox.[14] Oral administration of compound **44** to rats inhibited lipolysis by 97% at 25 mg/kg. The complete antilipolytic profile of **44** will be reported elsewhere.

Acipimox has good antilipolytic activity[15] and is being developed as a blood lipid lowering agent for the treatment of atherosclerosis.[16] It is included in Table I along with nicotinic acid for comparison purposes. Compound **44** is 100-fold and 40-fold more potent than Acipimox and nicotinic acid, respectively, in the in vitro adipocyte lipolysis assay. Note, however, that Acipimox does not work by the inhibition of lipase since it does not block lipolysis promoted by either cyclic AMP or dibutyryl cyclic AMP.[15]

A series of quinolyl carbanilates were examined for their ability to inhibit the production of glycerol from rat adi-

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pocytes and to inhibit the liberation of FFA from canine cardiac tissue.[17,18] We have determined structural features for the quinolyl carbanilates that optimize inhibitory potency. This information was used to design the structurally novel 7-benzofuranyl 4-methoxycarbanilate (44).[19] Compound 44 is an orally active antilipolytic agent that has potential in the treatment of ischemic heart disease.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with assigned structures. NMR spectra were recorded on a Varian EM-390 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. All compounds, unless otherwise indicated, had elemental analyses within 0.4% of theoretical values.

Typical Procedure for Scheme I. 8-Quinolyl 4-Methoxycarbanilate (1). To a suspension of 8-hydroxyquinoline (1.45 g, 10.0 mmol) and 4-methoxyphenyl isocyanate (1.49 g, 10.0 mmol) in ethyl ether (100 mL) was added triethylamine (4 drops). The reaction was stirred for 2 days at room temperature. The resulting precipitate was filtered and crystallized from ethyl ether/acetone to give 1.9 g (65% yield) of product, mp 129–130 °C. In a like manner as above using 5-, 6-, 7-, or 8-hydroxyquinoline and the appropriately substituted phenyl isocyanate the following compounds were prepared: **2–8, 10, 14, 15, 19, 23, 25, 26, 31,** and **37–41** (see Table I for percent yield and melting point).

Typical Procedure for Scheme II. 8-Quinolinecarbamoyl Chloride (A). A solution of 8-aminoquinoline (2.0 g, 13.9 mmol) in methylene chloride (10 mL) was added dropwise to a 0 °C solution of 2.2 M phosgene in methylene chloride (7 mL, 15.4 mmol). The resulting precipitate was filtered and dried, giving 3.1 g (92% yield) of product. The dark solid thus obtained was unstable, and in practice it was immediately used in the next reaction.

4-Methoxyphenyl 8-Quinolylcarbamate (11). A suspension of intermediate A (5.7 g, 23.4 mmol) in dry THF (100 mL) was treated with triethylamine (7 mL, 50 mmol). 4-Methoxyphenol (3.5 g, 23.4 mmol) was then added, and the reaction was stirred overnight at room temperature. The solvent was removed in vacuo. The residue was dissolved in chloroform/1.0 N sodium hydroxide and washed with 1.0 N sodium hydroxide (2×) and water; the organic phase was dried ($MgSO_4$) and concentrated to a solid. The solid was dissolved in a 1:1 mixture of ethyl acetate and acetone, treated with charcoal, and filtered through celite and silica gel. A crystalline solid formed, which was filtered and dried to give 3.5 g (43% yield) of product, mp 128–129 °C. In a like manner, using intermediate A and 2-methoxyphenol, compound **12** was prepared, mp 133–136 °C.

***N*-(4-Methoxyphenyl)-*N'*-(8-quinolyl)urea (13).** A solution of 8-aminoquinoline (5.2 g, 36.1 mmol) and 2-methoxyphenyl isocyanate (5.4 g, 36.1 mmol) in ethyl ether (200 mL) was stirred at room temperature overnight. A precipitate formed, which was filtered and dried, giving a solid. The solid was crystallized from ethyl ether/acetone to give 4.7 g (42% yield) of product, mp 159–163 °C.

8-[(4-Methoxyphenyl)carbamoyl]quinoline-5-sulfonic Acid, Triethylamine Salt (34). A solution of 8-hydroxyquinoline-5-sulfonic acid, triethylamine salt (1.9 g, 5.5 mmol) in DMF (25 mL) was treated with 4-methoxyphenyl isocyanate (0.82 g, 5.5 mmol) and the mixture was stirred overnight at room temperature. The mixture was triturated with ethyl ether (3×), and a solid formed that was filtered, washed with ethyl ether, and dried to give 2.3 g (92% yield) of product, mp 138–141 °C.

8-Quinolyl 4-Methoxyacetanilide (36). A mixture of α-chloro-4-methoxyacetanilide (5.0 g, 25.1 mmol) (prepared by treating 4-methoxyaniline with chloroacetyl chloride in THF with triethylamine), 8-hydroxyquinoline (3.6 g, 25.1 mmol), cesium carbonate (16.2 g), cesium iodide (20 mg), and acetone (200 mL) was refluxed overnight. The reaction was filtered, and the solvent was removed in vacuo. The remaining oil was dissolved in methylene chloride, washed with 1.0 N sodium hydroxide and water, dried ($MgSO_4$), and concentrated. The remaining oil was crystallized from methylene chloride to give 2.5 g (32% yield) of product, mp 125–128 °C.

8-Quinolyl 4-Methoxyphenylacetate (42). To a solution of 8-hydroxyquinoline (3.9 g, 26.2 mmol) and triethylamine (2.6 g, 26.2 mmol) in dry THF (300 mL) was added 4-methoxyphenylacetyl chloride. The solution was stirred for 2 days at room temperature. The reaction was filtered, and the solvent was removed in vacuo. The remaining solid was crystallized in ethyl ether to give 3.5 g (44% yield) of product, mp 82–84 °C. In a like manner, using 4-methoxybenzoyl chloride, compound **43** was prepared, mp 164–167 °C.

Procedures for Scheme III. 7-Methoxybenzofuran-2-carboxylic Acid. A mixture of 2-vanillin (42 g, 276 mmol), ethyl chloroacetate (45 g, 367 mmol), potassium carbonate (75 g), and DMF (500 mL) was heated at 80 °C for 4 h. The reaction was poured into ice and extracted with methylene chloride. The aqueous layer was separated and acidified with concentrated hydrochloric acid. A precipitate formed, which was filtered and dried, giving 27 g (51% yield) of solid, mp >200 °C.

7-Methoxybenzofuran (B). To a solution of 7-methoxybenzofuran-2-carboxylic acid (2.6 g, 13.5 mmol) in quinoline (10 mL) was added finely ground copper metal (50 mg). The reaction was slowly heated until the evolution of gas was noted. After termination of gas evolution, the mixture was cooled and diluted with methylene chloride. The solution was washed with 5% aqueous hydrochloric acid (6×), dried ($MgSO_4$), and concentrated to give 1.8 g (90% yield) of oil.

7-Hydroxybenzofuran (C). A mixture of 7-methyloxybenzofuran (1.8 g, 12.2 mmol) and pyridine hydrochloride (4.6 g, 40.0 mmol) was heated at 200 °C for 2.5 h. The reaction was cooled and diluted with methylene chloride. The solution was washed with 5% aqueous hydrochloric acid (6×), dried ($MgSO_4$), and concentrated to give 0.8 g (50% yield) of oil.

4-Hydroxybenzoxazole. A mixture of 2-aminoresorcinol (2.1 g, 17.1 mmol), triethyl orthoformate (3.7 g, 25 mmol), and sulfuric acid (4 drops) was heated at 130 °C for 0.5 h. After cooling, a solid formed which was crystallized from ethyl acetate to give 1.4 g (62% yield) of product.

7-Benzofuranyl 4-Methyloxycarbanilate (44). To a solution of 7-hydroxybenzofuran (0.7 g, 5.2 mmol) in ethyl ether (25 mL) and triethylamine (2 drops) was added 4-methoxyphenyl isocyanate (0.8 g, 5.2 mmol). The reaction was stirred at room temperature for 3 days. The resulting precipitate was filtered and dried to give 0.8 g (54% yield) of product, mp 157–159 °C. In the same manner as above, using 4-hydroxybenzoxazole, 4-benzoxazoyl 4-methoxycarbanilate (**45**) was prepared, mp 161–162 °C.

Compounds **9, 16–18, 20–22, 24, 27–30, 32, 33,** and **35** are commercially available.[8]

Myocardial Lipase Assay.[6] All compounds were dissolved in Me_2SO (final concentration 3.0%) and tested in duplicate at a concentration of 100 μM. Canine cardiac lipases were obtained by extracting washed heart membranes with buffer plus heparin and a small amount of Triton X-100 detergent. Because these enzymes are only active at an oil–water interface, the enzyme reaction is run in an oil–water emulsion that contains triolein substrate, Tris buffer (50 mM, pH 6.8), and a small amount of bovine serum albumin (0.5%) added to stabilize the emulsion. A small amount of tritiated triolein was added to the unlabeled triolein substrate. Tritium-labeled oleic acid released by the lipases was extracted into hexane, separated from unreacted triolein, and counted in a scintillation counter. Inhibitory agents reduce the amount of radioactivity appearing in the free fatty acid fraction isolated in the extraction procedure.

Rat Adipocyte Assay.[7] Abdominal fat pads were removed from male rats weighing 200–250 g and placed in Krebs–bicarbonate buffer gassed with 95:5 O_2/CO_2. The fat pads were digested with collagenase for 1 h at 37 °C, washed twice with Krebs–bicarbonate buffer, and distributed among a set of 20-mL plastic counting vials. Two such vials received only buffer and cells (4 mL) but no agonists or antagonists. The remaining vials

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received epinephrine (3 μM) plus the phosphodiesterase inhibitor methylisobutylxanthine (10 μM). Test compounds were dissolved in Me_2SO or water to a concentration of 20 mM, and 40 μL was added to the buffer plus cells in the counting vials. The final compound concentration for routine screening was 200 μM (final concentration of Me_2SO = 1%).

The cells were incubated for 1 h at 37 °C under a 95:5 O_2/CO_2 atmosphere. The incubation was stopped by placing the vials in crushed ice. The cells and the medium were transferred to test tubes and centrifuged, and the cell layer was removed by aspiration. The aqueous phase was assayed for glycerol using the enzyme glycerol dehydrogenase.

The glycerol dehydrogenase assay for glycerol depends on the enzyme-catalyzed conversion of glycerol to glyceraldehyde and NAD to NADH. The assay can detect as little as 5–10 nmol of glycerol. The aqueous phase, following removal of the cells, usually contained about 50–80 nmol of glycerol/300 μL of assayed samples if no inhibitory activity was present. Samples from the control tubes (no agonist) usually contained 0–5 nmol of glycerol/300 μL of sample.

Registry No. **1**, 20842-55-1; **2**, 100926-71-4; **3**, 100926-72-5; **4**, 100926-73-6; **5**, 20842-55-1; **6**, 100926-71-4; **7**, 100926-72-5; **8**, 100926-76-9; **9**, 59741-09-2; **10**, 100926-77-0; **11**, 99541-10-3; **12**, 99541-11-4; **13**, 104531-64-8; **14**, 59741-07-0; **15**, 100926-78-1; **16**, 14628-09-2; **17**, 14628-08-1; **18**, 14628-13-8; **19**, 100926-79-2; **20**, 99541-00-1; **21**, 99541-01-2; **22**, 14577-73-2; **23**, 100926-80-5; **24**, 14628-11-6; **25**, 100926-81-6; **26**, 59741-06-9; **27**, 99541-02-3; **28**, 99541-03-4; **29**, 6329-08-4; **30**, 14577-80-1; **31**, 20843-96-3; **32**, 99541-04-5; **33**, 99541-05-6; **34**, 99541-14-7; **35**, 83685-83-0; **36**, 99541-15-8; **37**, 99541-06-7; **38**, 99541-07-8; **39**, 100926-82-7; **40**, 99541-08-9; **41**, 99541-09-0; **42**, 104531-65-9; **43**, 28507-33-7; **44**, 94242-00-9; **45**, 94242-03-2; 4-$MeOC_6H_4NCO$, 5416-93-3; 2-$MeOC_6H_4NCO$, 700-87-8; 3-$MeOC_6H_4NCO$, 18908-07-1; 4-$EtOCOC_6H_4NCO$, 30806-83-8; 2-ClC_6H_4NCO, 3320-83-0; 2-$CH_3C_6H_4NCO$, 614-68-6; 2-$F_3CC_6H_4NCO$, 2285-12-3; 4-$MeOC_6H_4CH_2NCO$, 56651-60-6; 4-$MeOC_6H_4(CH_2)_2NCO$, 52634-59-0; (*S*)-$PhCH(CH_3)NCO$, 14649-03-7; (*R*)-$PhCH(CH_3)NCO$, 33375-06-3; 4-$MeOC_6H_4OH$, 150-76-5; 2-$MeOC_6H_4OH$, 90-05-1; 4-$ClCH_2CONHC_6H_4OMe$, 22303-36-2; 4-$MeOC_6H_4NH_2$, 104-94-9; $ClCH_2COCl$, 79-04-9; 4-$MeOC_6H_4CH_2COCl$, 4693-91-8; 4-$MeOC_6H_4COCl$, 100-07-2; 8-hydroxyquinoline, 148-24-3; 7-hydroxyquinoline, 580-20-1; 6-hydroxyquinoline, 580-16-5; 5-hydroxyquinoline, 578-67-6; 2,4-dimethoxyphenylisocyanate, 33904-03-9; 8-hydroxy-2-methylquinoline, 826-81-3; 8-aminoquinoline, 578-66-5; phosgene, 75-44-5; 8-quinoline carbamoyl chloride, 99541-17-0; 8-hydroxyquinoline-5-sulfonic acid triethylamine salt, 104531-67-1; 2-vanillin, 148-53-8; ethyl chloroacetate, 105-39-5; 7-methoxybenzofuran-2-carboxylic acid, 4790-79-8; 7-methoxybenzofuran, 7168-85-6; 7-hydroxybenzofuran, 4790-81-2; 2-aminoresorcinol, 3163-15-3; triethylorthoformate, 122-51-0; 4-hydroxybenzoxazole, 89590-22-7.

(5*Z*)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic Acid: A Specific Thromboxane A_2 Receptor Antagonist

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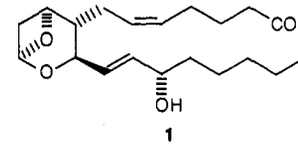
(5*Z*)-7-(2,2-Dimethyl-4-phenyl-1,3-dioxan-*cis*-5-yl)heptenoic acid (**2**) was found to be a specific, competitive thromboxane A_2 receptor antagonist that acts at platelet, vascular, and pulmonary receptors. No antagonism was detected at receptors for prostacyclin, SRSA, norepinephrine, and serotonin. The synthesis of a series of analogues is described; activity at the thromboxane receptor was observed in cis-substituted compounds but not in their trans counterparts. Compound **2** inhibited the bronchoconstriction induced by a stable thromboxane mimetic in the anesthetized guinea pig.

The short-lived arachidonic acid metabolite thromboxane A_2[1] (TxA_2, **1**) has been shown to be a potent inducer of platelet aggregation[2] and of vascular[3] and pulmonary[4] smooth muscle contraction. The possibility that an abnormal production of TxA_2 may be involved in a number of disease processes is now well-recognized,[5] and in recent years considerable effort has been devoted to the development of new therapeutic agents that have as their mode of action either the inhibition of the enzyme thromboxane synthase[6] or the antagonism of TxA_2 at the receptor level.[7]

The latter approach is particularly attractive because it has been established that several prostanoids, including PGH_2 and PGD_2, exert an effect via the thromboxane receptor;[8] thus an agent that modifies TxA_2 receptor binding could also inhibit the potentially deleterious effect of a variety of prostanoids in certain tissues, e.g., the lung. It follows that a thromboxane antagonist could be of value in the treatment of asthma.



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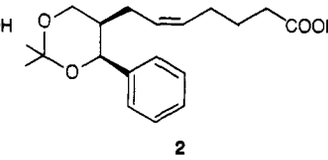

2

In an attempt to design a thromboxane antagonist, we decided to retain certain structural features of TxA_2, no-

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