Pyranenamines: A New Series of Antiallergic Compounds[1a]

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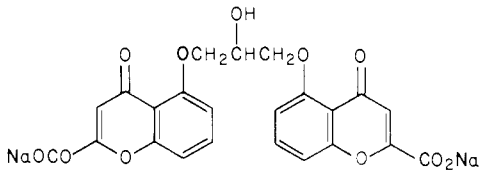
Condensation of 3,5-diacylpyrantriones with various aromatic amines gave a new class of potent, orally active, antiallergic compounds, the 3-[(arylamino)ethylidene]-5-acylpyrantriones, hereafter referred to as pyranenamines, as evaluated not only in the traditional rat passive cutaneous anaphylaxis (PCA) assay but also in the in vitro fragmented rat and primate lung assay. Potencies in the PCA system, when measured intravenously, reached a maximum ID_{50} of 0.9 μg/kg (1000 times more potent than disodium chromoglycate) with 5-acetyl-4-hydroxy-3-[1-[(3,5-bisglyceramoylphenyl)amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione (**100**), as predicted by structure–activity relationship (SAR) analyses. Potencies in the iv PCA system correlated well with potencies in the in vitro rat lung system but not with potencies in the oral PCA system or the in vitro primate lung system. Several compounds had good oral potency, and one analogue, 3-acetyl-4-hydroxy-3-[1-[3-amino-4-hydroxyphenyl)amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione hydrochloride (**78**), reached an oral ID_{50} of less than 1 mg/kg and was better than 10 times more effective than disodium chromoglycate at inhibiting the release of histamine and slow-reacting substance of anaphylaxis in the fragmented primate lung assay.

The disclosure of disodium chromoglycate (DSCG, 1)



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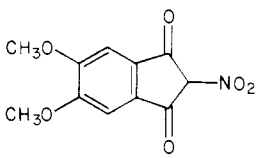

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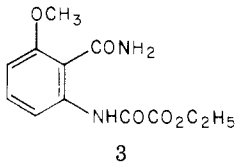

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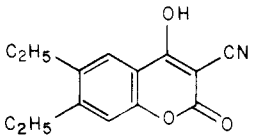

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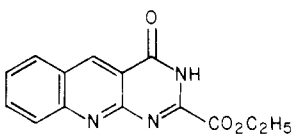

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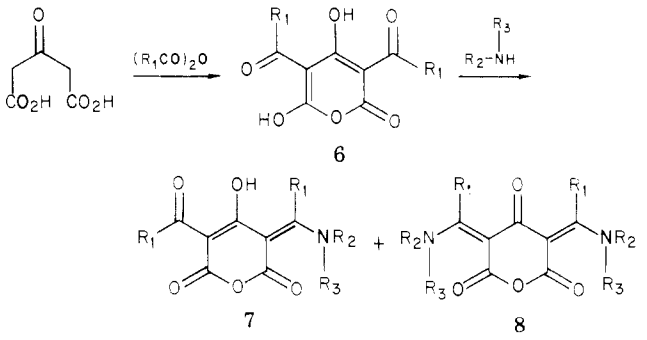
with its unique antiallergic activity[2a] has prompted an intensive search for more potent, orally active compounds.[2b] Many of the most active compounds have been carboxylic acids or their tetrazole analogues, and only recently have a few noncarboxylic acids, such as BRL 10833 (**2**),[3] Wy 16922 (**3**),[4] 3-cyano-4-hydroxy-6,7-diethylcoumarin (**4**),[3] and 2-carboethoxypyrimido[4,5-*b*]quinoline (**5**),[5] exhibited this antiallergic activity.

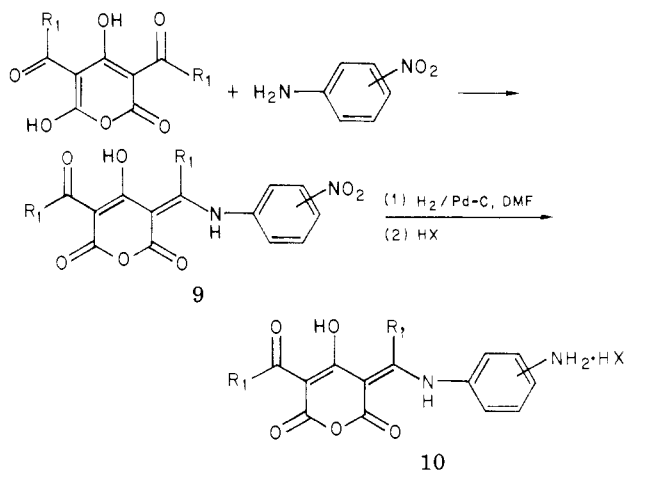
Our objective was to find potent, orally active antiallergic compounds which inhibited the release of mediators of the allergic response such as histamine and slow reacting substance of anaphylaxis (SRS-A). In 1976 we reported on a new series of weakly acidic compounds with this mechanism of activity, the 3,5-diacylpyrantriones, **6**.[6] We now report the extension of that series to the amine adducts, the 3-[(arylamino)ethylidene]-5-acylpyrantriones, **7**, hereafter referred to as pyranenamines for convenience. These compounds are potent, orally active, inhibitors of the release of the mediators of immediate hypersensitivity as demonstrated both in the rat passive cutaneous anaphylaxis (PCA) test system and in the rat and primate in vitro systems which measure antigen–IgE induced release of histamine and SRS-A.

Chemistry. The pyrantrione **6**, whose structure was corrected by Lansing and White,[7] can be easily prepared

Scheme I



Scheme II



from a suitable anhydride and acetone dicarboxylic acid as shown in Scheme I. Condensation of **6** with primary aromatic or aliphatic amines gives the monoenamine **7**, whose general structure was reported by Kiang and coworkers[8a] and which was later confirmed.[8b]

The bisenamine **8** is formed under forcing conditions such as elevated temperature and azeotropic removal of water; however, in most cases the monoenamine is readily obtained in good yield by precipitation from the reaction media. The monoenamines formed from primary aromatic amines (R_3 = H) are more stable than simple enamines, and many of the amino-substituted analogues, **10**, can be prepared by catalytic reduction of the nitroenamines, **9**, as in Scheme II. The enamines are even stable to mild acid, since **25** can be nitrated directly to give **113**.

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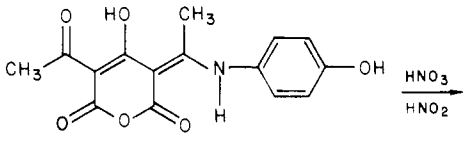

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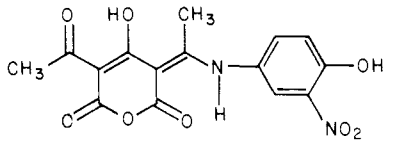

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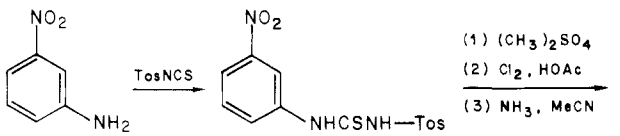
Preparation of most of the monoenamines in Table I was accomplished by condensing a suitable aniline, many of which are reported, with **6** (R_1 = CH_3) in methanol at reflux temperature according to Scheme I. Frequently, it was convenient to generate the aniline by catalytic reduction and carry out the condensation without isolation. Compound **115** was prepared from 3-nitroaniline according



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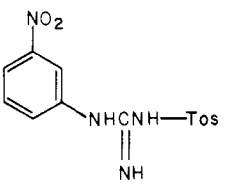
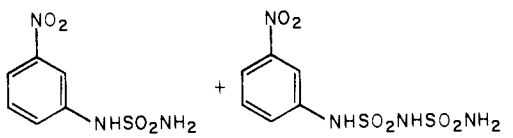


115

to the method described by Bosin et al.[9] and was condensed via Scheme I to give **45**; however, it was not possible to remove the tosyl blocking group without destroying the pyran. Treatment of 3-nitroaniline with 3,5-dimethyl-1-guanylpyrazole nitrate[10] gave **116**, which was catalytically



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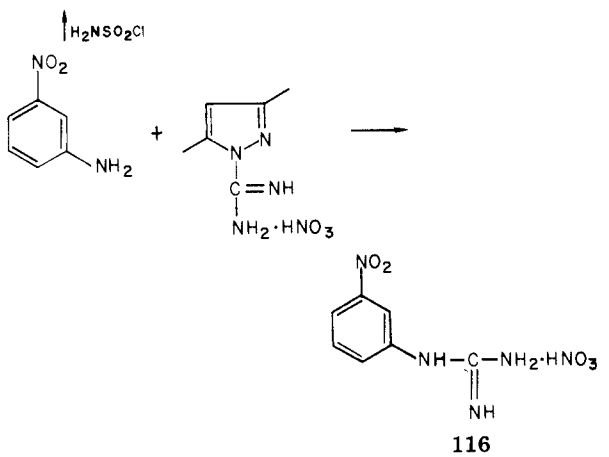
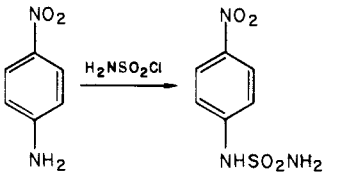


116

reduced and condensed with **6** (R_1 = CH_3) in situ to give **46**. Treatment of 4-nitroaniline with sulfamyl chloride gave **117**, which was easily reduced and condensed to give **67**. The same reaction with 3-nitroaniline gave equal amounts of **118** and **119**, which were separated by gel permeation chromatography on μ-styragel. Oxidation of **120** with alkaline permanganate gave **121** and **122**, each



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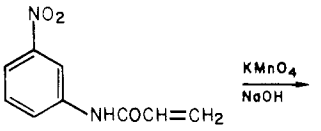

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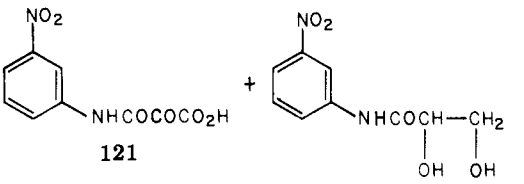
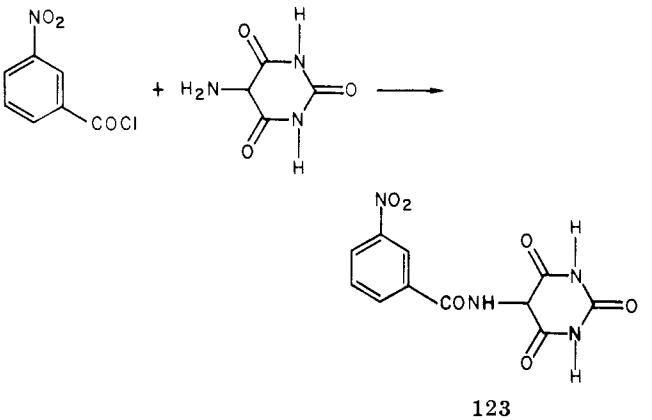


121 122

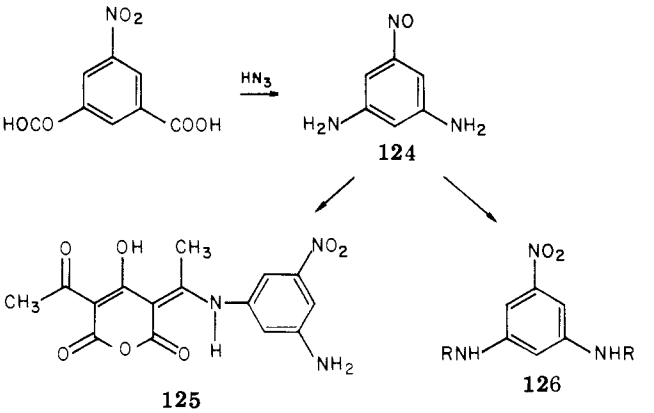
of which was reduced to the aniline and condensed in situ to give **69** and **70**. Treatment of 3-nitrobenzoyl chloride with uramil[11] gave **123**, which was easily reduced and



123

condensed to give **76**.

The multiply substituted pyranenamines listed in Tables II and III were also prepared from the suitable anilines and **6** (R_1 = CH_3). Preparation of the 3',5'-disubstituted pyranenamines centered on the common intermediate **124**,

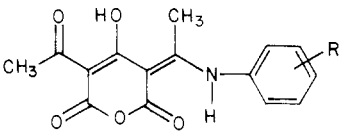


125 126

which was most conveniently prepared (with the precaution of careful temperature control) via a double Schmidt reaction on 5-nitroisophthalic acid. Intermediate **124** can then be condensed with **6** (R_1 = CH_3) and carried on to the unsymmetrical product **125**, or it can be derivatized directly to give **126** which can be carried on to the symmetrical analogues **94–102**.

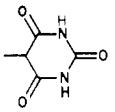
Table IV includes a small group of N-alkylated analogues which can be prepared from the corresponding

Table I. Monosubstituted Pyranenamines



compd	R	% yield	mp, °C	crystn solv	synth route	anal.	iv PCA dose[a]	iv PCA % inhibn[b]	po PCA dose[a]	po PCA % inhibn[b]
DSCG							0.9[e]	50		
11	H	77	184-186[f]	PhH	Ia	C, H, N	10	76		
12	2-Cl	57	143-145	MeOH	Ia	C, H, N, Cl	10	36		
13	3-Cl	56	163-164	EtOH	Ia	C, H, N	10	74		
14	4-Cl	52	205-206	MeOH	Ia	C, H, N	10	84		
15	4-F	90	199-201	MeOH	Ia	C, H, N, F	10	54		
16	4-Br	91	199-201	MeOH	Ia	C, H, N, Br	0.5	0 (NS)[c]		
17	4-NO_2	58	231-233	toluene	Ia	C, H, N	10	17 (NS)		
18	2-$CO_2C_2H_5$	51	142-243	EtOH	Ia	C, H, N	5	18 (NS)		
19	4-CO_2CH_3	48	205-207	MeOH	Ia	C, H, N	5	6 (NS)		
20	3-SO_2NH_2	95	237	MeOH	Ia	C, H, N, S	0.5	45		
21	4-SO_2NH_2	98	260	MeOH	Ia	C, H, N, S	0.5	12 (NS)		
22	4-CH_3	68	190-192	MeOH	Ia	C, H, N	10	33		
23	2-OH	46	210-192	MeOH/$CHCl_3$	Ia	C, H, N	2.8[e]	50	25	-12 (NS)
24	3-OH	74	213-216	MeOH	Ia	C, H, N	1.6[e]	50	25	0 (NS)
25	4-OH	53	223-225	MeOH	Ia	C, H, N	1.3[e]	50	29[e]	50
26	4-$OCOCH_3$	38	199-201	$CHCl_3$/MeOH	Ia	C, H, N	0.5	41		
27	4-$OCOCH_2CH_3$	53	168-170	$CHCl_3$/MeOH	Ia	C, H, N	0.5	16 (NS)		
28	4-$OCO(CH_2)_2CH_3$	62	158-160	$CHCl_3$/MeOH	Ia	C, H, N	1.5[e]	50		
29	4-$OCO(CH_2)_3CH_3$	44	155-157	$CHCl_3$/MeOH	Ia	C, H, N	0.5	34	25	36
30	4-$OCO(CH_2)_4CH_3$	25	148-149	$CHCl_3$/MeOH	Ia	C, H, N	12.1[e]	50		
31	4-$OCO(CH_2)_5CH_3$	64	148-149	$CHCl_3$/MeOH	Ia	C, H, N	0.5	21		
32	4-$OCOC(CH_3)_3$	27	187-188	$CHCl_3$/Et_2O	Ia	C, H, N	0.5	3 (NS)		
33	4-$OCOC_6H_3$	43	220-223	$CHCl_3$	Ia	C, H, N	0.5	10 (NS)		
34	4-$OCONH_2$	40	213-215	THF	Ia	C, H, N	0.5	19		
35	4-$OCONHC_7H_7$	88	195-197	$CHCl_3$	Ia	C, H, N	0.5	22		
36	4-OCH_3	80	212-214	PhH	Ia	C, H, N	5	27		
37	3-OCH_2COOH	55	186-187	MeOH	Ia	C, H, N	0.5	6 (NS)		
38	4-OCH_2COOH	86	213-214	MeOH	Ia	C, H, N	0.5[e]	50	25	2 (NS)
39	4-SH	30	207-210	MeOH	Ia	C, H, N, S	1.9[e]	50		
40	2-NH_2	35	182-184	EtOH/PhH	II	C, H, N	27.5[e]	50		
41	3-NH_2	25	165-167	MeOH	II	C, H, N	0.3[e]	50		
42	3-$NHCH_3$	38	180-181	EtOH	Ia	C, H, N	0.5	-8 (NS)		
43	4-NH_2	8	215-218	MeOH/$CHCl_3$	II	C, H, N	0.5	58	25	23
44	4-$N(CH_3)_2$	25	198[g]	PhH	Ia	C, H, N	100	11 (NS)		
45	3-NHC(NH)NHT_S	53	240	MeOH	Ia	C, H, N, S	0.5	2 (NS)		
46	3-NHC(NH)NH_2·HNO_3	90	208[h]	MeOH/THF	Ia	C, H, N	0.9[e]	50	25	-7 (NS)
47	2-NHCHO	45	197-198	EtOH	Ia	C, H, N	0.5	52	25	31
48	3-NHCHO	14	189-190	$CHCl_3$	Ia	C, H, N	0.5	22 (NS)		
49	4-NHCHO	34	247-248	THF	Ia	C, H, N	0.5	49	25	-6
50	2-$NHCOCH_3$	31	225-226	THF	Ia	C, H, N	0.5	-12 (NS)		
51	3-$NHCOCH_3$	67	220-221	dioxane	Ia	C, H, N	0.25	65	25	53
52	4-$NHCOCH_3$	96	249-251	MeOH	Ia	C, H, N	5	19		
53	3-$NHCONH_2$	76	248-249	MeOH	Ia	C, H, N	0.5	45	25	6 (NS)
54	4-$NHCONH_2$	59	250-253	TFA/MeOH	Ia	C, H, N	0.5	38	25	-17 (NS)
55	3-$NHCOCH_2CH_3$	50	202-203	EtOH	Ia	C, H, N	0.2[e]	50	25	70
56	4-$NHCOCH_2CH_3$	54	238-239	THF/Et_2O	Ia	C, H, N	1.6[e]	50		
57	3-$NHCOCH(CH_3)_2$	59	219-231	EtOH	Ia	C, H, N	0.5	72	25	46
58	4-$NHCOCH(CH_3)_2$	84	358-359	THF	Ia	C, H, N	0.5	64	25	4 (NS)
59	3-$NHCO(CH_2)_2CH_3$	41	193-194	MeOH	Ia	C, H, N	0.5	58		
60	3-$NHCO(CH_2)_2$-CO_2CH_3	82	208-110	MeOH	Ia	C, H, N	0.4[e]	50		
61	3-NSucc[d]	68	230-232	MeOH	Ib	C, H, N	0.5	22		
62	3-$NHSO_2CH_3$	95	196	EtOH	Ib	C, H, N, S	0.5	28		
63	4-$NHSO_2CH_3$	98	235	EtOH	Ib	C, H, N, S	0.5	20 (NS)		
64	3-$NHSO_2C_6H_5$	95	209	EtOH	Ib	C, H, N, S	1.3[e]	50	25	7 (NS)

Table I (*Continued*)

compd	R	% yield	mp, °C	crystn solv	synth route	anal.	iv PCA dose[a]	iv PCA % inhibn[b]	po PCA dose[a]	po PCA % inhibn[b]
65	4-$NHSO_2C_6H_5$	90	223-224	EtOH	Ib	C, H, N, S	0.5	4 (NS)		
66	3-$NHSO_2NH_2$	20	153-155	THF	Ib	C, H, N, S	0.5	45	25	13 (NS)
67	4-$NHSO_2NH_2$	50	221	THF	Ib	C, H, N, S	0.3[e]	50	25	10 (NS)
68	3-$NHCO_2C_2H_5$	47	162-164	EtOH	Ib	C, H, N	0.4[e]	50		
69	3-$NHCOCOCO_2H$	66	218	MeOH	Ib	C, H, N	0.03[e]	50	25	21 (NS)
70	3-$NHCOCH(OH)CH_2OH$	85	218	MeOH	Ib	C, H, N	0.05[e]	50	25	55
71	3-$CH_2NHCOCH_3$	83	202-4	MeOH	Ib	C, H, N	0.5	4 (NS)		
72	3-$CONH_2$	84	223.5-225	MeOH	Ib	C, H, N	0.5	-16 (NS)		
73	3-$CONHCH_3$	88	208-209.5	dioxane	Ib	C, H, N	0.5	24		
74	3-$CONHC_2H_5$	86	216-218	MeOH	Ib	C, H, N	0.5	-4 (NS)		
75	3-$CON(CH_3)_2$	82	186-188.5	MeOH	Ib	C, H, N	0.5	10 (NS)		
76	3-CONH- 	81	256	H_2O	Ib	C, H, N	0.5	39		

[a] Dose in mg/kg. [b] $p < 0.05$, except where noted; [c] NS = not statistically significant. [d] *N*-Succinimido. [e] Calculated ID_{50}. [f] Lit. value 182-184 °C.[14] [g] Lit. value 198 °C.[14] [h] Decomposition.

secondary amines provided forcing conditions, such as elevated temperature and azeotropic removal of water, are used.

Results and Discussion

A broad group of aryl-substituted pyranenamines was tested in the rat passive cutaneous anaphylaxis (PCA) system,[12] and the results are shown in Tables I–IV. A smaller number of substituted 3,5-diacylpyrantriones were also tested, and these are shown in Table V. All compounds were tested by intravenous administration 30 s prior to antigen challenge. When substantial iv activity was observed, the compound was tested orally, at an initial dose of 25 mg/kg administered 15 min before antigen challenge. Full dose range studies were performed on the more active compounds, and an ID_{50} was determined. The inhibition was evaluated statistically by Student's *t* test. In addition, any compound which showed substantial inhibition of the PCA reaction was tested for its ability to inhibit a direct intradermal challenge of histamine or serotonin and, in general, was devoid of any significant end-organ antagonist activity.

Evaluation of the data generated by intravenous administration was most readily adaptable to structure–activity relationship (SAR) interpretation. In some cases only weak activity was observed, and, therefore, the compound was tested at a single dose. For comparison of potencies, an estimated ID_{50} was calculated using dose range curves from the more active analogues. Single aromatic substitutions indicated that electron-withdrawing groups had either no effect, as in the case of the halogen analogues **12–16**, or were detrimental, as in the case of the nitro analogue **17**. Hydrophilic groups such as hydroxyls, **23–25**, enhanced activity. Ortho derivatives tended to be less active than their meta or para isomers. Some esters, **26–33**, showed slight improvement in potency, reaching an optimum with the valerate ester **29**. Of the various ethers and urethanes, only **38** gave any significant improvement in potency over the hydroxyl, but it had poor oral activity. Substitution with primary amine groups greatly improved the PCA activity, whereas secondary and tertiary amine substitution was not beneficial, as exemplified by **42** and **44** which were inactive at the doses tested. Similarly, the "primary" guanidine **46** showed good inhibition when tested intravenously, as was suggested by our early SAR studies, but was inactive orally, probably due to its high polarity.

Amide substitution produced the most potent of the simple monosubstituted pyranenamines. The most active of the simpler amides was **55**, but it was surpassed by **69** which was almost tenfold more potent by iv administration but inactive when given orally. The most effective substituent of all was the glyceramide **70**, which was roughly equipotent to **69** but retained reasonable oral activity. This particular grouping was suggested by QSAR work.

Other single substitution patterns did not improve the activity. The homologation of the active propionamide **55** in the form of **71** and **73–75** all reduced the activity of the parent. Similarly, alkylation of the enamine nitrogen atom as in **108** and **109** did not improve the PCA activity.

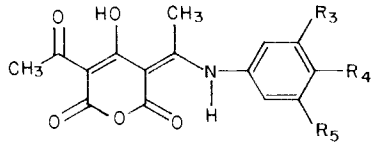
Assembly of multiple aromatic substitutions was the next step in optimizing potency, and 3,4 and 3,5 bissubstitution showed the most promise. Again the more active derivatives were hydroxy and amine or amide analogues. The 3-amino-4-hydroxy analogue **78** was most interesting, since the ratio of iv potency to po potency approached 1.0. A surprising activity profile was observed with the propionamide **86**, whose iv and po potency were essentially the same as the amine **78**, even though the acetamide **82** did not have substantial oral activity and the easily cleaved benzoxazoline **83** did not have the potency of its hydrolysis product **82**.

The 3,5-disubstituted analogues were the most potent compounds when tested by intravenous administration. Simple amides reached maximal PCA activity with the propionamide **95** but was accompanied by a disappointing loss of oral activity. Oxamates **98** and **99** had very good potencies and, as has been reported,[4] the ester **98** was more potent than the acid **99** in the oral test. The diglyceramide **100**, whose iv potency was 1000 times that of DSCG, was our most potent compound, and even though the oral activity was not as great as some other analogues, nevertheless, it was quite substantial. This was satisfying, since QSAR analysis had suggested this particular substituent. Additional multiple substitutions, **103–107**, had a detrimental effect on PCA activity.

Examples of modified pyrones are presented in Table V. In general, elongation of the side chain, R, in **6** did not substantially improve the PCA activity, and compounds **6b**, **6d**, and **6g** showed substantial antihistamine activity.

The antiallergic activity of our best candidates was studied further in an in vitro system of passively sensitized lung tissue from rats or primates.[12] A compound's activity was measured by its ability to inhibit the liberation of two

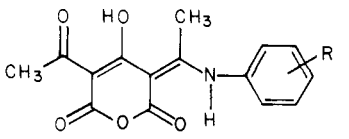
Table II. Multiply Substituted Pyranenamines



no.	R_3	R_4	R_5	% yield	mp, °C	crystn solv	synth route	anal.	iv PCA dose[a]	iv PCA % inhibn[b]	po PCA dose[a]	po PCA % inhibn[b]
77	Cl	Cl	H	42	214–216	MeOH	Ia	C, H, N, Cl	10	10 (NS)		
78	$NH_2 \cdot HCl$	OH	H	95	244–246	THF	II	C, H, N, Cl	0.7	50	0.8[d]	50
79	OH	$NH_2 \cdot HCl$	H	82	220–221[e]	DMF/H_2O	II	C, H, N, Cl	3.4	50	25	40
80	$NHCH_3$	OH	H	32	227–229[e]	EtOH	Ib	C, H, N	0.5	−6 (NS)		
81	$CH_2NHCOCH_3$	OH	H	32	212–213[e]	THF	Ia	C, H, N	0.5	1 (NS)		
82	$NHCOCH_3$	OH	H	12	248–250[e]	dioxane/MeCN	Ia	C, H, N	0.2	50	25	50
83	$-N{=}C(CH_3)O-$		H	52	218–220	MeOH	Ia	C, H, N	0.5	13 (NS)		
84	$NHCOCH_3$	OCH_3	H	72	252–253[e]	MeOH	Ia	C, H, N	0.5	27		
85	$CONHCH_3$	OH	H	40	238–240	DMF/H_2O	Ia	C, H, N	0.5	38		
86	$NHCOCH_2CH_3$	OH	H	42	228–229[e]	EtOH	Ia	C, H, N	0.4[d]	50	0.6[d]	50
87	$NHCOCH(CH_3)_2$	OH	H	63	208–209[e]	EtOH	Ia	C, H, N	0.2[d]	50	3.3[d]	50
88	$NHSO_2CH_3$	OH	H	96	223–224.5	acetone	Ia	C, H, N	5.0	38		
89	CF_3	H	CF_3	45	229	MeOH	Ia	C, H, N	5.0	14		
90	OH	H	$NH_2 \cdot HCl$	75	210[e]	EtOH	II	C, H, N	0.5[d]	50	8.0[d]	50
91	OH	H	$NHCOCH_3$	19	257–258[e]	dioxane	Ia	C, H, N	0.02[d]	50	25	2 (NS)
92	NH_2	H	$NHCOCH_3$	45	227–230	DMF/H_2O	II	C, H, N	0.1[d]	50	25	11 (NS)
93	NH_2	H	NH_2	92	>350	DMF/H_2O	II	C, H, N	0.5[d]	50	0.9[d]	50
94	$NHCOCH_3$	H	$NHCOCH_3$	62	265–267[e]	MeOH	Ia	C, H, N	0.01[d]	50	50	−1 (NS)
95	$NHCOCH_2CH_3$	H	$NHCOCH_2CH_3$	42	239–241	MeOH	Ia	C, H, N	0.003[d]	50	50	14 (NS)
96	$NHCO(CH_2)_2CH_3$	H	$NHCO(CH_2)_2CH_3$	31	214–216[e]	$MeOH/H_2O$	Ia	C, H, N	0.05[d]	50	25	7 (NS)
97	$NHCO_2C_2H_5$	H	$NHCO_2C_2H_5$	57	234–235	EtOH	Ia	C, H, N	0.25[d]	50	25	−18 (NS)
98	$NHCOCO_2C_2H_5$	H	$NHCOCO_2C_2H_5$	77	195	MeOH/THF	Ia	C, H, N	0.03[d]	50	6.5[d]	50
99	$NHCOCO_2H$	H	$NHCOCO_2H$	79	>325	MeOH	Ia	C, H, N	0.05[d]	50	19[d]	50
100	$NHCOCH(OH)CH_2OH$	H	$NHCOCH(OH)CH_2OH$	77	231	MeOH	Ia	C, H, N	0.0009[d]	50	2.9[d]	50
101	$NHSO_2CH_3$	H	$NHSO_2CH_3$	30	260	MeOH	Ia	C, H, N, S	0.3[d]	50	50	9 (NS)
102	$NHSO_2C_6H_5$	H	$NHSO_2C_6H_5$	79	261	MeOH	Ia	C, H, N, S	0.5	−9 (NS)		
103	OH	OH	OH	53	208	MeOH	Ia	C, H, N	0.4[d]	50	25	−3 (NS)

[a] Dose in mg/kg. [b] $p < 0.05$ except where noted. [c] NS = not statistically significant. [d] Calculated ID_{50}. [e] Decomposition.

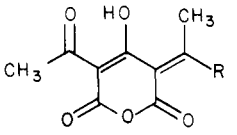
Table III. Ortho Substituted Pyranenamines

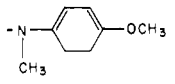
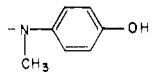


no.	R	% yield	mp, °C	crystn solvent	synth route	anal.	iv PCA dose[a]	iv PCA % inhibn[b]	po PCA dose[a]	po PCA % inhibn[b]
104	2,6-$(Cl)_2$	21	208-210	MeOH	Ia	C, H, N, Cl	10	3 (NS)[c]		
105	2,6-$(OH)_2$	23	225-227	MeOH	Ia	C, H, N	0.5	-22 (NS)		
106	2-OH-5-$NHCOCH_3$	17	253-254[d]	dioxane/MeCN	Ia	C, H, N	0.5	40	25	4 (NS)
107	2-NH_2-5-OH	100	220-221	DMF/H_2O	II	C, H, N	5	47		

[a] Dose in mg/kg. [b] $p < 0.05$, except where noted. [c] NS = not statistically significant. [d] Decomposition.

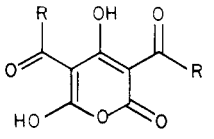
Table IV. Miscellaneous Pyranenamines



no.	R	% yield	mp, °C	crystn solv	synth route	anal.	iv PCA dose[a]	iv PCA % inhibn[b]
108		26	212-214[a]	MeOH	Ia	C, H, N	5	37
109		13	226-227[a]	MeOH/$PhCH_3$	Ia	C, H, N	5	42
110	c-$O(CH_2CH_2)_2N$	21	196-197[a]	*i*-PrOH	Ia	C, H, N	0.5	2 (NS)[c]
111	$-NH_2$	48	228	Ph_2O	Ia	C, H	5	17 (NS)
112	-NH-c-C_5H_4N	29	175-176	MeOH	Ia	C, H, N	10	60

[a] Dose in mg/kg. [b] $p < 0.05$ except where noted. [c] NS = not statistically significant.

Table V



no.	R	% yield	mp, °C	crystn solv	anal.	iv PCA dose[a]	iv PCA % inhibn[b]
6a	CH_3	75	154-155	MeOH	C, H	14[d]	50
6b	CH_2CH_3	52	114-115	MeOH	C, H	10	39
6c	$CH_2CH_2CH_3$	48	80-82	MeOH	C, H	10	3 (NS)
6d	$(CH_2)_3CH_3$	64	84-85	MeOH	C, H	10	69
6e	$CH_2CH(CH_3)_2$	33	74-75	MeOH	C, H	10	23
6f	$(CH_2)_4CH_3$	8	86-88	MeOH	C, H	6[d]	50
6g	$(CH_2)_5CH_3$	74	88-89	MeOH	C, H	10	27

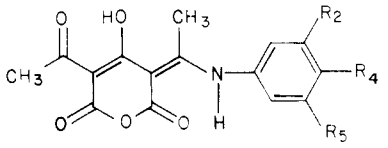
[a] Dose in mg/kg. [b] $p < 0.05$ except where noted. [c] NS = not statistically significant. [d] Calculated ID_{50}.

mediators, histamine and slow reacting substance of anaphylaxis (SRS-A) in primate tissue and histamine alone in rat tissue. Two criteria determined which compounds were tested in this system: (1) reasonable activity in the rat PCA test and (2) sufficient solubility in the culture media used for the lung tissue.

Table VI lists the activity of a group of pyranenamines when tested for their ability to inhibit histamine secretion from fragmented rat lung. Calculation of ID_{50} values was frequently impossible in these tests, since the dose–response pattern was not always linear, especially at the higher drug concentrations. Examination of the various derivatives, however, did indicate an approximate correlation between the rat PCA activity (iv) and the in vitro potency in this same species. For example, the rank order of increasing potency in the PCA test was **25**, **78**, **58**, **86**, **82**, and **87** and was the same in the rat lung in vitro test with the qualification that **82** and **87** are roughly equipotent at 10^{-6} M, as are **58** and **78**.

Table VII lists the results with passively sensitized primate lung tissue where inhibition of both histamine and SRS-A were measured. In this system, inhibition of both mediators usually did not follow the same dose–response pattern and frequently a compound was more effective at inhibiting histamine release than it was at inhibiting SRS-A release. Also, there did *not* appear to be any correlation between the in vivo rat PCA data and the in vitro primate lung data. Consequently, those compounds which were very potent in the rat PCA test system, **90–92** and **100**, were not as promising as clinical candidates as **78**, which had an ID_{30} of 1.3×10^{-5} M against histamine release and 3.3×10^{-5} M against SRS-A release in the

Table VI. Inhibition of Antigen-Induced Histamine Release in Passively Sensitized Fragmented Rat Lung



compd	R_3	R_4	R_5	in vitro concn, M	% inhibn of histamine[a]
DSGG				1.3×10^{-3}	56 (10)
				2.7×10^{-4}	47 (4)
				5.3×10^{-5}	32 (3)
25	H	OH	H	1.6×10^{-4}	45 (5)[a]
				6.6×10^{-6}	44 (7)
				6.6×10^{-7}	34 (4)
58	H	$NHCOCH(CH_3)_2$	H	1×10^{-5}	92 (1)
				1×10^{-6}	60 (1)
78	$NH_2 \cdot HCl$	OH	H	1×10^{-5}	47 (4)
				1×10^{-6}	61 (5)
				1×10^{-7}	42 (4)
				1×10^{-8}	26 (4)
82	$NHCOCH_3$	OH	H	1×10^{-5}	86 (5)
				1×10^{-6}	76 (5)
				1×10^{-7}	88 (5)
				1×10^{-8}	53 (1)
				1×10^{-9}	43 (1)
86	$NHCOCH_2CH_3$	OH	H	1×10^{-5}	65 (4)
				1×10^{-6}	66 (4)
				1×10^{-7}	70 (4)
				1×10^{-8}	41 (2)
87	$NHCOCH(CH_3)_2$	OH	H	1×10^{-6}	78 (1)
				1×10^{-7}	81 (1)

[a] Values in parentheses are the number of different lung preparations.

primate lung assay. These data, together with its favorable iv to po potency ratio makes this analogue, designated SK&F 78729-A, the compound of greatest interest as a potential antiallergic candidate.

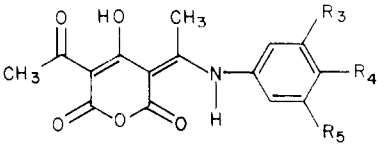
Conclusions. In this study, we report a new class of compounds, the pyranenamines, which are potent oral antiallergic compounds as evaluated not only in the traditional rat PCA assay but also in the in vitro rat or primate lung assay. The results of the iv PCA assay and the in vitro rat lung assay correlated well with SAR analyses but oral test results in the rat PCA assay and in vitro primate lung assay results did not. With compound **100** we observed potencies of 1000 times that of DSCG via iv administration in the rat PCA assay, and with compound **78** we reached oral potencies of less than 1 mg/kg and still retained the desired mechanism of activity.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline & French Laboratories, and where analyses are indicated by the symbol of the elements analytical results for those elements were within ±0.4% of the theoretical values. The structure of all compounds was confirmed by IR and ^1H NMR spectroscopy.[8] Mass spectra were obtained on a Hitachi Perkin-Elmer RMN 6E spectrometer, IR spectra were obtained on a Perkin-Elmer 137 spectrometer as Nujol mulls, and ^1H NMR spectra were obtained on a Varian T60 spectrometer as a solution in $CDCl_3$, Me_2SO-d_6, or mixtures of the two using tetramethylsilane as an internal standard. Where relevant, the ^{13}C NMR spectra were obtained on a Varian FT 80 spectrometer as a solution in $CDCl_3$, Me_2SO-d_6, TFA-d_1, or mixtures of these using tetramethylsilane as an internal standard.

Biological Test Procedure. The PCA test was performed in a manner similar to that described by Goose and Blair.[12] The backs of unanesthetized rats were shaved and 0.1 mL of a dilution of antiserum sufficient to produce an average wheal of 12 × 12 mm was injected intradermally at four sites on the back. After 48 h, the test compound was administered either iv or po and was followed by 0.5 mL (iv) of saline containing 5 mg of Evans blue dye and 5 mg of egg albumin. For iv administration the delay between test compound and antigen challenge was 0.5 min, and

Table VII. Inhibition of IgE-Antihuman IgE Release of Histamine and SRS-A from Passively Sensitized Fragmented Rhesus Monkey Lung Tissue



no.	R_3	R_4	R_5	concn, M	% inhibn of histamine[a]	% inhibn of SRS-A[a]
DSCG				1.3×10^{-3}	54 (4)	27 (4)
				2.7×10^{-4}	37 (4)	36 (4)
				5.3×10^{-5}	11 (4)	24 (4)
25	H	OH	H	1.6×10^{-4}	59 (7)	51 (7)
				3.3×10^{-5}	50 (10)	33 (10)
				6.6×10^{-6}	18 (5)	8.6 (5)
78	$NH_2 \cdot HCl$	OH	H	1×10^{-4}	66 (9)	56 (7)
				5×10^{-5}	49 (5)	40 (4)
				1×10^{-5}	22 (9)	1 (7)
				1×10^{-6}	4 (7)	−24 (5)
82	$NHCOCH_3$	OH	H	5×10^{-5}	25 (4)	33 (4)
				1×10^{-5}	−31 (4)	5 (4)
				5×10^{-6}	−32 (4)	−11 (4)
90	OH	H	$NH_2 \cdot HCl$	1×10^{-4}	24 (3)	18 (2)
				1×10^{-5}	−0.7 (3)	5 (2)
91	OH	H	$NHCOCH_3$	1×10^{-4}	57 (2)	22 (2)
				1×10^{-5}	17 (2)	6 (2)
92	NH_2	H	$NHCOCH_3$	1×10^{-4}	17 (1)	8 (1)
100	$NHCOCH(OH)CH_2OH$	H	$NHCOCH(OH)CH_2OH$	1×10^{-4}	7 (2)	7 (2)
				1×10^{-5}	−20 (2)	−0.5 (2)
				1×10^{-6}	−30 (2)	−7 (2)

[a] Values in parentheses are the number of different lung preparations.

for po administration the delay was 15 min. After 30 min, the animal was sacrificed, the dorsal skin was reflected, and the extent of cutaneous anaphylaxis (bluing) was measured along two axes (mm × mm) of each of the four wheals and averaged for each animal. Six animals per test compound per dose constitute a drug-treated group. A minimum of six control animals, receiving an equivalent volume of vehicle, was used. Percent inhibition was calculated from the difference in mean wheal size. The data were statistically evaluated using a one-sided Student's t test.

The in vitro tests in passively sensitized rat and primate lung tissue were performed in a manner previously described[13] using tissue from a young adult male Rhesus monkey or adult male Charles River albino rats. The histamine liberated on challenge was measured fluorometrically, and the SRS-A (in the case of primate tissue) was estimated by bioassay using guinea pig ileum. The net immunological release of histamine in these primate experiments in the absence of any drugs accounted for approximately 8.5% [2.2 ± 0.22 μg/g $\bar{x}$ ± SE (n = 30)] of the tissue content of 25.01 ± 2.58 μg/g $\bar{x}$ ± SE (n = 30). The immunological release of SRS-A in the absence of drugs amounted to 212 ± 49 units/g $\bar{x}$ ± SE (n = 30). All measurements were made on a minimum of three samples of tissue for each experiment, and the results of several experiments were statistically evaluated using a one-sided Student's t test.

Examples of Scheme I. Synthetic Route Ia. 5-Acetyl-4-hydroxy-3-[1-[(4-hydroxyphenyl)amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione (25). A mixture of 4.24 g (0.02 mol) of **6a**,[14] 2.18 g (0.02 mol) of 4-hydroxyaniline, and 200 mL of MeOH was heated to reflux for 18 h, cooled, and filtered to give 3.2 g (53%) of **25**: mp 223–225 °C. Compound **25** was recrystallized from MeOH with no improvement in melting point. Anal. ($C_{15}H_{13}NO_6$) C, H, N.

Synthetic Route Ib. 5-Acetyl-4-hydroxy-3-[1-[[3-[(methylsulfonyl)amino]phenyl]amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione (62). To a solution of 1.08 g (0.005 mol) of 3-[(methylsulfonyl)amino]nitrobenzene in 100 mL of ethanol was added 300 mg of 10% palladium on carbon catalyst, and the mixture hydrogenated at 3.4 atm in a Parr shaker until hydrogen absorption was complete. The catalyst was removed by filtration; 1.08 g (0.005 mol) of **6a**[14] was added to the filtrate; the resulting solution was heated under reflux for 1 h, concentrated to half the original volume, and cooled; and the resulting crystals were filtered and washed with methanol to give 1.7 g (90%) of **62**, mp 196 °C. Anal. ($C_{16}H_{16}N_2O_7S$) C, H, N, S.

Example of Scheme II. 5-Acetyl-4-hydroxy-3-[1-[(3-aminophenyl)amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione (41). A mixture of 1.0 g (0.007 mol) of 3-nitroaniline and 1.5 g (0.007 mol) of **6a**[14] in 50 mL of methanol was heated at reflux temperature for 2 h and cooled, and the crystalline solid was filtered to give 1.9 g (83%) of 5-acetyl-4-hydroxy-3-[1-[(3-nitrophenyl)amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione, which was dissolved in 100 mL of ethanol, treated with 300 mg of 10% palladium on carbon catayst, and hydrogenated at 3.4 atm in a Parr shaker until hydrogen absorption was complete. The mixture was heated to boiling; the catalyst was filtered; and the filtrate was concentrated until crystallization began, then chilled, and filtered to give 0.5 g (25%) of **41**, mp 165–167 °C. Anal. ($C_{15}H_{14}N_2O_5$) C, H, N.

***N*-(3-Nitrophenyl)-*N'*-[(4-methylphenyl)sulfonyl]thiourea (114).** A solution of 10.6 g (0.05 mol) of p-toluenesulfonyl isothiocyanate[15] and 6.36 g (0.05 mol) of 3-nitroaniline in 20 mL of diethyl ether was stirred for 2 h at 0 °C and then for 18 h at room temperature. Filtration gave 7.5 g (43%) of **114**, which was recrystallized from benzene–hexane, mp 128–129 °C. Anal. ($C_{14}H_{13}N_3O_4S_2$) C, H, N, S.

***N*-(3-Nitrophenyl)-*N'*-[(4-methylphenyl)sulfonyl]guanidine (115).** A solution of 2.10 g (0.006 mol) of **114**, 1.0 g (0.008 mol) of dimethyl sulfate, and 0.70 g (0.007 mol) of triethylamine in 20 mL of methanol was refluxed for 90 min and cooled, and the white solid was filtered and washed with cold methanol to give 1.10 g (50%) of *S*-methyl-*N*-(3-nitrophenyl)-*N'*-tosylthiourea, mp 138 °C. The whole (0.003 mol) was dissolved in 15 mL of glacial acetic acid and was cooled in an ice bath while a slow stream of chlorine was passed through it for 30 min. The mixture was allowed to stand at room temperature for 18 h and then filtered to give 0.9 g (85%) of solid, mp 166–167 °C, which was dissolved in 15 mL of acetonitrile, and the solution was saturated with ammonia with cooling over 20 min. The resulting white solid was removed and the filtrate was concentrated until crystallization began when it was chilled and filtered to give 0.75 g (88%) of **115**, mp 201 °C. **115** was recrystallized from acetonitrile with no improvement of melting point. Anal. ($C_{14}H_{14}N_4O_4S$) C, H, N, S.

5-Acetyl-4-hydroxy-3-[1-[(3-sulfamidophenyl)amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione (66). To a solution of 1.3 g (0.011 mol) of sulfamyl chloride[16] in 20 mL of benzene was added 2.8 g (0.02 mol) of 3-nitroaniline in 50 mL of diethyl ether, and the mixture was stirred at 4 °C for 1 h. The solvent was removed in vacuo and the residue was treated with 50 mL of ice–water and filtered. The solid was resuspended in 10% HCl and filtered to give 1.5 g of crude 3-sulfamidonitrobenzene, mp 180 °C, which was an equal mixture of **118** and **119** (based on μ-styragel chromatography). The whole was dissolved in 100 mL of ethanol and hydrogenated over 300 mg of 10% palladium on carbon at 3.4 atm in a Parr shaker. The catalyst was filtered, and the solvent was removed in vacuo and replaced with 30 mL of MeOH containing 1.01 g (0.005 mol) of **6a**. The solution was refluxed for 1 h, cooled, and filtered to give 280 mg (15%) of crude **66**, mp 151 °C. The whole was dissolved in 9 mL of THF and chromatographed in 3 × 90 mg portions on microstyragel (Waters 10Å, 25 × 1000 mm) at a flow rate of 0.5 mL/min. Two fractions were collected based on UV absorption at 254 nm and evaporated under N_2 flow to give 151 mg of disulfamide, mp 170–171 °C, and 126 mg (5% based on crude **118** and **119**) of **66**: mp 153–155 °C. Anal. ($C_{15}H_{15}N_3O_7S$) C, H, N, S.

5-Acetyl-4-hydroxy-3-[1-[(4-sulfamidophenyl)amino]ethylidene]-2*H*-pyran-2,6(3*H*)-dione (67). The reaction sequences were run in the same manner as for **66** on 8.0 g (0.058 mol) of 4-nitroaniline and 6.7 g (0.038 mol) of sulfamyl chloride[16] to give 2.0 g (24%) of 4-nitrophenylsulfamide, mp 168 °C, which was carried through to give 1.1 g of crude **67** which was recrystallized from THF to give 0.95 g (50%) of **67**, mp 221 °C. Anal. ($C_{15}H_{15}N_3O_7S$) C, H, N.

3-(Propenoylamido)nitrobenzene (120). To a solution of 13.8 g (0.1 mol) of 3-nitroaniline in 100 mL of diethyl ether and 30 mL of ethyl acetate was added 9.0 g (0.1 mol) of acryloyl chloride followed by 4.0 g (0.1 mol) of NaOH in 20 mL of H_2O, and the mixture was stirred for 18 h at room temperature. The solid was filtered and recrystallized from EtOH/H_2O to give 19.0 g (97%) of **120**, mp 150 °C. Anal. ($C_9H_8N_2O_3$) C, H, N.

3-(α-Ketomalonamoyl)nitrobenzene (121) and 3-Glyceramidonitrobenzene (122). To a mixture of 10.0 g (0.055 mol) of **120** in 500 mL of t-BuOH, 400 mL of H_2O and 250 g of ice at 5 °C was added a solution of 12 g (0.075 mol) of $KMnO_4$ and 5.0 g (0.125 mol) of NaOH in 400 mL of H_2O. After 5 min, the reaction was quenched by passing SO_2 through the mixture until the solution turned pale yellow. The solution was cooled and filtered, the solid was saved, and the aqueous layer was extracted with 3 × 250 mL of EtOAc. The organic extract was washed with H_2O, dried over $MgSO_4$, and evaporated in vacuo to give 2.6 g of crude product, which was recrystallized from i-PrOH to give 2.1 g (20%) of **122**: mp 143–144 °C. Anal. ($C_9H_{10}N_2O_5$) C, H, N.

The insoluble solid from filtration was treated with 3 × 100 mL of ethereal HCl and filtered, and the solvent was removed in vacuo to give crude **121**, which was triturated with cold i-PrOH and cold 1 N HCl to give 1.7 g (14%) of **121**, mp 110 °C. Anal. ($C_9H_6N_2O_6$) C, H, N.

3,5-Diaminonitrobenzene (124). In a 2-L flask equipped with mechanical stirrer, thermometer, and reflux condenser was placed 125 mL of 30% fuming sulfuric acid, 30 mL of concentrated sulfuric acid, 35 g (0.165 mol) of 5-nitroisophthalic acid, and 200 mL of chloroform. The mixture was stirred vigorously, and the addition of 35 g (0.54 mol) of powdered sodium azide was begun. The temperature of the reaction was carefully maintained at 32–35 °C by external ice-bath cooling and rate of addition of sodium azide. When the addition was complete (20 min), the mixture was stirred for 18 h at room temperature, then heated to reflux for 1 h, and finally poured into 2 L of crushed ice. The $CHCl_3$ layer was separated and the aqueous layer made basic (pH 10) with concentrated ammonium hydroxide, which gave an orange solid that was filtered and washed with water to give 25.0 g (97%)

of **124**, mp 146–148 °C (lit. mp 140–141 °C[17]). **124** was recrystallized from water with no improvement of melting point.

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Application of Quantitative Structure–Activity Relationships in the Development of the Antiallergic Pyranenamines[1]

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QSAR techniques played a major role in development of the antiallergic pyranenamines (I). Graphical analysis of data resulting from an unsuccessful Topliss approach suggested that increased substituent hydrophilicity might enhance potency. The 3-NHAc-4-OH derivative which first resulted was an order of magnitude more potent than any preceding series member, and its deacylated congener is clinical candidate SK&F 78729 (R_1 = $-NH_2$, R_2 = OH, R_3 = H). Further pursuit of hydrophilicity and other strategies suggested by multiple regression yielded 98 pyranenamines, the most active [R_1 = R_3 = $NHCO(CHOH)_2H$, R_2 = H] being 1000 times more potent than any original series member.

Quantitative structure–activity relationships (QSAR) are equations which express the biological potencies of a series of related compounds as a linear function of their physiochemical properties. A major reason for deriving a QSAR hypothesis is the hope that some aspect of the QSAR can be extrapolated to produce compounds of higher potency. Unfortunately, most of the few examples of successful extrapolation, or "predictive successes",[2] are vulnerable to the following general criticisms: (1) The successful extrapolations are relatively small in magnitude, the potency enhancement in only one instance[3a] being appreciably more than twofold. Most predictions are interpolative. (2) The number of superior compounds associated with any individual successful extrapolation is small. Since an energetic synthesis program is expected to produce compounds of higher potency eventually, regardless of the correctness of any guiding hypothesis, it could be argued that the QSAR success rate is not greater than that produced by chance—or "seat of the pants"—methods alone. (3) The elaborate statistical and computer technologies used to derive QSAR might not be necessary. Alternative but simpler physicochemically based strategies, in particular the "Topliss tree",[3b] seem to point to superior compounds with far less work. (4) "Sooner or later" the compounds embodying the successful extrapolations would have been stumbled upon in any case.

The directed development of the pyranenamine series constitutes a use of QSAR techniques which convincingly counters these criticisms. In retrospect, this development process passed through four sequential phases: (1) progress prior to the use of specialized QSAR techniques; (2) an initial "breakthrough" QSAR prediction using a graphical technique to identify a critical structural property; (3) exploitation of the breakthrough by synthesis of a wide variety of compounds having the desirable property, regression procedures being used in order to explore other structural trends; (4) refinement and confirmation of the SAR understanding embodied in the regression model by synthesis of some less accessible pyranenamines expected to have maximal potency. After an introductory characterization of the biological test system and of the parameters and techniques employed in regression work, the bulk of this paper discusses each of these sequential phases.

Overall Considerations. As discussed within the preceding article,[4] 3-[(arylamino)ethylidene]-5-acyl-

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