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Antiallergic Activity of 2-Phenyl-8-azapurin-6-ones

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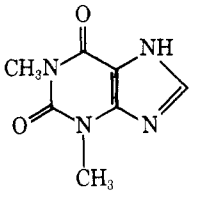
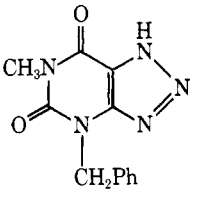
The synthesis and antiallergic activity in the rat passive cutaneous anaphylactic reaction of a series of 2-phenyl-8-azapurin-6-ones are described. Early in the investigation, a linear free-energy equation was established in which the activity was related to the size and hydrogen bonding capacity of the ortho substituent in the phenyl ring. This relationship was used to provide guidance and limits for subsequent work leading to 2-*o*-propoxyphenyl-8-azapurin-6-one which is 40 times more potent than disodium cromoglycate. It is suggested that good antiallergic activity in this series is associated with coplanarity of the phenyl group with the azapurin-6-one which would be favored by a high degree of hydrogen bonding.

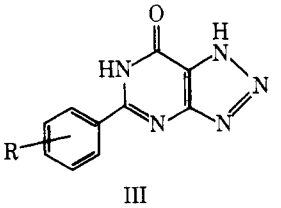
Methylxanthines, such as theophylline (I) and caffeine, inhibit the antigen-induced release of histamine and of a slow-reacting substance of anaphylaxis (SRS-A) from passively sensitized human lung and human basophilic leucocytes.[1,2] In this context the methylxanthines are much less potent than disodium cromoglycate and we have been engaged in progressive modification of the xanthine molecule in the hope of increasing potency and reducing side effects. We found that the introduction of a nitrogen atom into the 8 position, to give 8-azaxanthines, increased potency, particularly if the compounds contained a bulky substituent in the 3 position, e.g., II.[3] Further modifications have now been carried out and in the present paper we describe the synthesis and structure–activity relationships of a series of 2-phenyl-8-azapurin-6-ones (III).



I



II



III

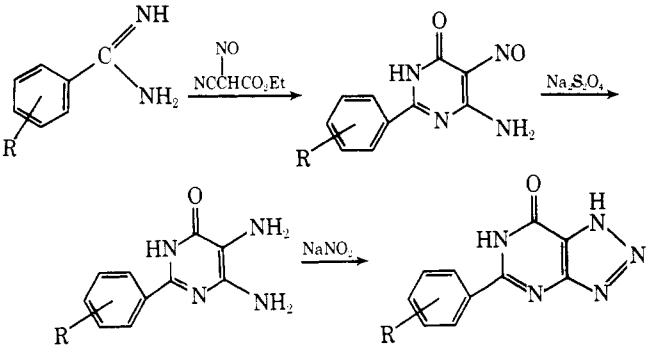
Chemistry. Most of the azapurinones were prepared from the appropriate benzamidine by the route indicated in Scheme I and are listed in Table I.

The hydroxy compound **6** was prepared by hydrogenolysis of the benzyloxy compound **19** and the amino derivative **24** by hydrolysis of the sulfonamide **29.**

The required amidines and their precursors were synthesized by standard procedures as indicated in the Experimental Section.

Many of the syntheses were carried out without purification of the intermediate, and only those compounds which have been characterized are included in the Experimental Section.

Scheme I



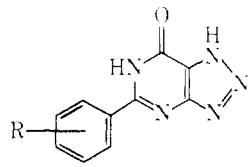
Biology. In screening this series, the determination of ID_{50}'s in the rat passive cutaneous anaphylactic (PCA) reaction was impracticable because the variability of response would have necessitated the use of large numbers of animals to achieve meaningful results. However, direct comparison with disodium cromoglycate (DSG) for their ability just to cause 100% inhibition of the rat PCA reaction following iv administration was satisfactory and reproducible to within ±25%.[3] The relative activities are given in Table I.

Discussion

When it was realized that the 2-aryl-8-azapurin-6-ones had interesting antiallergic properties, an extensive program of synthesis and biological screening was undertaken. We recognized that prompt application of extrathermodynamic correlation techniques,[4] if successful, could provide guidance to the direction of synthetic effort and reduce the time necessary to arrive at the most active members of the series.

Accordingly, when results were available on the first ten compounds (**1, 2, 4, 7, 14, 19, 30, 31, 38,** and **40**), correlations with partition (π), electronic (F, R), and steric parameters (MR, E_s) were sought but no significant relationships were revealed. Our work on the effect of substituents in the 8-azaxanthine system[3] led us to consider that bulky sub-

Table I. 2-Phenyl-8-azapurin-6-ones



Compd	R	Empirical formula	Mp, °C[a]	Yield, %	Rel act.[b]	Log P[c]	E_s[d]	$\Delta\bar{\nu}$[e]	Obsd log [MW × I][f]	Calcd log [MW × I][g]
1	H	$C_{10}H_7N_5O$	278–280[h,i]	62	4	1.27	1.24	0	2.931	2.441
2	2-CH_3	$C_{11}H_9N_5O$	263–265[i]	74	0.04	1.83	0	16	0.959	1.255
3	2-F	$C_{10}H_6FN_5O$	252–253[j]	67	0.5	1.41	0.78[k]	4	2.063	1.974
4	2-Cl	$C_{10}H_6ClN_5O$	268–270	72	0.2	1.98	0.27[k]	17	1.695	1.575
5	2-Br	$C_{10}H_6BrN_5O$	247–250	60	0.2	2.13	0.08[k]	30	1.767	1.540
6[l]	2-HO	$C_{10}H_7N_5O_2$	285–286[i]	70	4	0.60	0.69[k]	82	2.962	2.951
7	2-CH_3O	$C_{11}H_9N_5O_2$	252–253[i,j]	75	10	1.25	0.69[k]	108	3.386	3.311
8	2-C_2H_5O	$C_{12}H_{11}N_5O_2$	216–218[i]	54	10	1.65	0.69[k]	112	3.410	3.366
9	2-n-C_3H_7O	$C_{13}H_{13}N_5O_2$	241[i]	70	40	2.32	0.69[k]	118	4.035	3.449
10	2-n-C_4H_9O	$C_{14}H_{15}N_5O_2$	188–190	47	20	2.82[l]	0.69[k]	114	3.756	3.394
11	2-n-$C_5H_{11}O$	$C_{15}H_{17}N_5O_2$	175–176	39	10	2.32[l]	0.69[k]	116	3.476	3.421
12	2-n-$C_6H_{13}O$	$C_{16}H_{19}N_5O_2$	130–132	20	20	3.82[l]	0.69[k]	113	3.979	3.380
13	2-n-$C_{10}H_{21}O$	$C_{20}H_{27}N_5O_2$	114–115[m]	22	0.4	5.82[l]	0.69[k]	111	2.170	2.210[n]
14	2-i-C_3H_7O	$C_{13}H_{13}N_5O_2$	218–219[i]	45	5	2.12[l]	0.69[k]	128	3.132	3.587
15	2-i-C_4H_9O	$C_{14}H_{15}N_5O_2$	226–227[i]	66	10	2.62[l]	0.69[k]	114	3.455	3.394
16	2-s-C_4H_9O	$C_{14}H_{15}N_5O_2$	205–208[i]	11	10	2.62[l]	0.69[k]	129	3.455	3.601
17	2-i-$C_5H_{11}O$	$C_{15}H_{17}N_5O_2$	186–188[i]	71	4	3.12[l]	0.69[k]	116	3.078	3.421
18	2-$(CH_3)_3CCH_2CH_2O$	$C_{16}H_{19}N_5O_2$	226–227[i]	36	4	3.42[l]	0.69[k]	115	3.098	3.408
19	2-$C_6H_5CH_2O$	$C_{17}H_{13}N_5O_2$	240–242[i]	39	10	3.38[l]	0.69[k]	121	3.504	3.491
20	2-C_6H_5O	$C_{16}H_{11}N_5O_2$	227[i]	50	1	2.88[l]	0.69[k]	82	2.485	2.951
21	2-C_6H_5	$C_{16}H_{11}N_5O$	263–264[i]	46	<0.01			40		
22	2-CH_2=CH·CH_2O	$C_{13}H_{11}N_5O_2$	173–175	53	20			*o*		
23	2-CH≡C·CH_2O	$C_{13}H_9N_5O_2$	228–230[m]	33	4			*o*		
24[p]	2-NH_2	$C_{10}H_8N_6O$	284–286[i,j]	38	0.2			*o*		
25	2-$(CH_3)_2N$	$C_{12}H_{12}N_6O$	250–251[j]	41	0.2			*o*		
26	2-CH_3S	$C_{11}H_9N_5OS·H_2O$	223–226[j]	59	1			*o*		
27	2-CH_3SO_2	$C_{11}H_9N_5O_3S$	274–275[i]	61	0.01			*o*		
28	2-n-$C_4H_9SO_2$	$C_{14}H_{15}N_5O_3S$	282[i]	53	0.01			*o*		
29	2-TsN*H*	$C_{17}H_{14}N_6O_3S$	264–265[i,j]	72	0.1			*o*		
30	3-CH_3	$C_{11}H_{19}N_5O·0.25H_2O$	280–281	49	4	1.83	1.24	0	2.959	2.441
31	3-CH_3O	$C_{11}H_9N_5O_2$	272–273[i,j]	52	2	1.25	1.24	0	2.687	2.441
32	3-n-$C_6H_{13}O$	$C_{16}H_{19}N_5O_2$	220–221	67	2	3.82[l]	1.24	0	2.797	2.441
33	3-CH_3S	$C_{11}H_9N_5OS·0.75H_2O$	279–280	21	0.4	1.88	1.24	0	2.016	2.441
34	3-CF_3	$C_{11}H_6F_3N_5O$	268[i]	23	4	2.15	1.24	0	3.051	2.441
35	3-$(CH_3)_2N$	$C_{12}H_{12}N_6O$	273–275	58	0.5	1.45	1.24	0	2.108	2.441
36	3-$C_6H_5CH_2$	$C_{17}H_{13}N_5O$	249–251[i]	18	0.4	3.28[l]	1.24	0	2.084	2.441
37	4-CH_3	$C_{11}H_9N_5O$	287–289[i]	80	0.8	1.83	1.24	0	2.260	2.441
38	4-Cl	$C_{10}H_6ClN_5O$	298–299[i,j]	15	2	1.98	1.24	0	2.695	2.441
39	4-HO	$C_{10}H_7N_5O_2$	330[i]	48	2	0.60	1.24	0	2.661	2.441
40	4-CH_3O	$C_{11}H_9N_5O_2·0.25H_2O$	272[i,j]	46	1	1.25	1.24	0	2.386	2.441
41	4-n-C_3H_7O	$C_{13}H_{13}N_5O_2$	261–263[i]	67	2	2.32	1.24	0	2.734	2.441
42	4-n-$C_6H_{13}O$	$C_{16}H_{19}N_5O_2$	255[i]	51	0.2	3.82[l]	1.24	0	1.797	2.441
43	4-CH_3SO_2	$C_{11}H_9N_5O_3S$	310–312[i,j]	62	0.4	−0.36	1.24	0	2.066	2.441
44	4-$C_6H_5CH_2$	$C_{17}H_{13}N_5O$	272–274[i]	27	0.2	3.28[l]	1.24	0	1.783	2.441

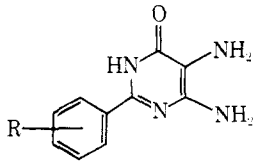
[a] Crystallized from EtOH or EtOH–H_2O unless otherwise stated. [b] Activity relative to DSG (=1) in the rat PCA test following iv administration. [c] Calculated by taking the log P of the parent compound as 1.270 (K. R. H. Wooldridge, unpublished results) and aromatic substituent values from C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 16, 1207 (1973). [d] Taft's steric factor for the substituent in the ortho position. Values taken from R. W. Taft, Jr., "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, p 598. [e] Difference (cm^{-1}) between the 1-NH stretching frequencies in the substituted compound compared with compound **1**. [f] Equation 3. [g] Melting point with decomposition. [h] Crystallized from DMF–H_2O. [i] Calculated from van der Waals radii: E. Kutter and C. Hansch, *J. Med. Chem.*, **12**, 647 (1969); *Arch. Biochem. Biophys.*, 135, 126 (1969); T. Fujita, *J. Med. Chem.*, 16, 923 (1973); M. Charton, *J. Am. Chem. Soc.*, **91**, 615 (1969). [j] By hydrogenation of compound **19** using 5% Pd/C at atmospheric pressure and room temperature. [k] Estimated value. [l] Substituent π values for higher alkoxy substituents were estimated from the propoxy value by additivity: C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, 33, 347 (1968). [m] Crystallized from AcOEt–petroleum ether (bp 40–60°). [n] Equation 4. [o] NH stretching maxima not clearly defined. [p] By hydrolysis of compound **29** by the method of G. W. H. Cheeseman, *J. Chem. Soc.*, 3308 (1955).

stituents might lead to increased activity and this was supported by the higher activity of the *o*-methoxy compound **7** as compared with that of the meta and para isomers **31** and **40**. However, the *o*-methyl compound **2** showed only 1/100 of the activity of the meta isomer **30**, so clearly other factors were involved. Intramolecular hydrogen bonding between

	n	r	s	F	p	
$\log[MW \times I] = 0.924 + 0.012\ \Delta\bar{\nu} + 1.467\ E_s$ (7.50) (7.72)	10	0.961	0.244	42.72	<0.0001	(1)
$\log[MW \times I] = 1.045 + 0.013\ \Delta\bar{\nu} + 1.125\ E_s$ (8.34) (4.64)	35	0.828	0.415	34.79	<0.0001	(2)
$\log[MW \times I] = 1.034 + 0.014\ \Delta\bar{\nu} + 1.135\ E_s$ (9.79) (5.28)	34	0.869	0.368	47.96	<0.0001	(3)
$\log[MW \times I] = 0.794 + 0.014\ \Delta\bar{\nu} + 1.227\ E_s + 0.256\ \log P - 0.074\ (\log P)^2$ (9.82) (5.75) (1.66) (2.69)	35	0.881	0.361	25.92	<0.0001	(4)
$\log[MW \times I] = 2.263 + 0.009\ \Delta\bar{\nu}$ (5.44)	35	0.688	0.528	29.64	<0.0001	(5)

the proton in the 1-N position and the ortho substituent might be implicated[5] and could be quantified by comparison of the position of the NH-stretching frequency in the substituted compound with that in the parent compound 1.[6] The ir shift, $\Delta\bar{\nu}$, may be regarded as an energy term and when this parameter was used in the multiparameter regression technique, the most significant relationship obtained was eq 1 where E_s represents Taft's steric factor of the ortho substituent in the phenyl ring, I represents the activity of a compound relative to disodium cromoglycate in the rat PCA test following iv administration, and MW is the molecular weight of the compound. The statistics for eq 1–4 are the standard error of estimate, s, the multiple correlation coefficient, r, and the F variance ratio. The value

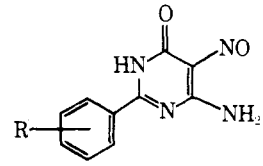
Table II



R	Mp, °C[a]	Formula	% yield
2-CH_3	133–135	$C_{11}H_{12}N_4O \cdot 0.5H_2O$	36[b]
2-F	240–242[c]	$C_{10}H_9FN_4O$	81[b]
2-Cl	126–130[c]	$C_{10}H_9ClN_4O \cdot 0.25H_2O$	27
2-Br	137–140	$C_{10}H_9BrN_4O$	12
2-CH_3O	223–224[c]	$C_{11}H_{12}N_4O_2$	51
2-C_2H_5O	139–143[c,d]	$C_{12}H_{14}N_4O_2 \cdot HCl \cdot 2H_2O$	36
2-n-C_3H_7O	162–164	$C_{13}H_{16}N_4O_2$	62[b]
2-n-$C_5H_{11}O$	144–145	$C_{15}H_{20}N_4O_2$	95[b]
2-n-$C_6H_{13}O$	150–152[c]	$C_{16}H_{22}N_4O_2$	42
2-i-C_3H_7O	192–193[c,e]	$C_{13}H_{16}N_4O_2 \cdot C_6H_3N_3O_7$	42[b]
2-i-C_4H_9O	165–167[c]	$C_{14}H_{18}N_4O_2$	78[b]
2-i-$C_5H_{11}O$	195–197[c,e]	$C_{15}H_{20}N_4O_2 \cdot C_6H_3N_3O_7$	52[b]
2-$C_6H_5CH_2O$	165–167[c]	$C_{17}H_{16}N_4O_2$	45[b]
2-CH_3S	227–229	$C_{11}H_{12}N_4OS$	88[b]
2-n-$C_4H_9SO_2$	236–237	$C_{14}H_{18}N_4O_3S$	55
3-CH_3	273–275[f]	$C_{11}H_{12}N_4O$	35[b]
3-CH_3O	225–227[c,f]	$C_{11}H_{12}N_4O_2$	47
3-n-$C_6H_{13}O$	156–157	$C_{16}H_{22}N_4O_2$	84[b]
4-CH_3	224–230	$C_{11}H_{12}N_4O \cdot 0.5H_2O$	19
4-HO	>300[f]	$C_{10}H_{10}N_4O_2$	91[b]
4-n-C_3H_7O	203–205	$C_{13}H_{16}N_4O_2$	65
4-n-$C_6H_{13}O$	175–176	$C_{16}H_{22}N_4O_2$	95[b]
4-n-CH_3SO_2	282–285[c]	$C_{11}H_{12}N_4O_3S$	93[b]

[a] Crystallized from EtOH or EtOH–H_2O unless otherwise stated. [b] Crude yield. [c] Melting point with decomposition. [d] Hydrochloride. [e] Picrate. [f] Crystallized from DMF–H_2O.

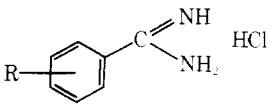
Table III



R	Mp, °C[a]	Formula	% yield
2-CH_3	249–251[b]	$C_{11}H_{10}N_4O_2 \cdot 0.2AcOH$	74[c]
2-F	258–259[d]	$C_{10}H_7FN_4O_2$	48[c]
2-CH_3O	216–217[b]	$C_{11}H_{10}N_4O_3$	84
2-C_2H_5O	221–222[b]	$C_{12}H_{12}N_4O_3$	66
2-n-C_3H_7O	215–216[b]	$C_{13}H_{14}N_4O_3$	76
2-n-$C_5H_{11}O$	223–224	$C_{15}H_{18}N_4O_3$	38
2-n-$C_6H_{13}O$	184–185	$C_{16}H_{20}N_4O_3$	60
2-n-$C_{10}H_{21}O$	144–146	$C_{20}H_{28}N_4O_3$	64
2-i-C_3H_7O	208–209[b]	$C_{13}H_{14}N_4O_3$	47
2-i-C_4H_9O	234–235[b]	$C_{14}H_{16}N_4O_3$	44
2-s-C_4H_9O	186–187	$C_{14}H_{16}N_4O_3$	70
2-i-$C_5H_{11}O$	212–214[b]	$C_{15}H_{18}N_4O_3$	60
2-$(CH_3)_3CCH_2CH_2O$	223–224[b]	$C_{16}H_{20}N_4O_3$	*e*
2-$C_6H_5CH_2O$	228–229[b]	$C_{17}H_{14}N_4O_3$	54
2-C_6H_5	240[b]	$C_{16}H_{12}N_4O_2$	55[c]
2-CH_2=$CHCH_2O$	217–220	$C_{13}H_{12}N_4O_3$	56[c]
2-$(CH_3)_2N$	212–213[b]	$C_{12}H_{13}N_5O_2$	20
2-CH_3S	233–234	$C_{11}H_{10}N_4O_2S$	70
2-CH_3SO_2	264–265[b]	$C_{11}H_{10}N_4O_4S$	42
2-n-$C_4H_9SO_2$	264[b]	$C_{14}H_{16}N_4O_4S$	36[c]
2-TsNH	245[b]	$C_{17}H_{15}N_5O_4S$	51
3-CH_3O	259[b]	$C_{11}H_{10}N_4O_3$	70
3-n-$C_6H_{13}O$	225[b]	$C_{16}H_{20}N_4O_3$	59
3-CH_3S	238[b]	$C_{11}H_{10}N_4O_2S$	74
3-CF_3	263[b]	$C_{11}H_7F_3N_4O_2$	68
4-HO	>300	$C_{10}H_8N_4O_3$	86
4-n-$C_6H_{13}O$	249–250[b]	$C_{16}H_{20}ON_4O_3 \cdot 0.5AcOH$	55
4-CH_3SO_2	295–296[b]	$C_{11}H_{10}N_4O_4S$	66

[a] Crystallized from AcOH or AcOH–H_2O unless otherwise stated. [b] Melting point with decomposition. [c] Crude yield. [d] Crystallized from DMF–H_2O. [e] Isolated as the crude sodium salt. A portion was acidified and crystallized.

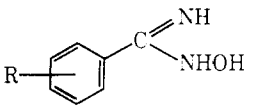
Table IV



R	Method	Mp, °C	Formula	% yield	Crystn solvent
2-F	B	168–171	$C_7H_7FN_2$·HCl	64[a]	EtOH–Et_2O
2-Br	B	303–305	$C_7H_7BrN_2$·HCl	58[a]	*b*
2-CH_3O	A	157–158	$C_8H_{10}N_2O$·HCl	77	EtOH–Et_2O
2-*n*-C_3H_7O	A	170–171	$C_{10}H_{14}N_2O$·HCl	42	*b*
2-*n*-$C_6H_{13}O$	B	156–158	$C_{13}H_{20}N_2O$·HCl	97[a]	2 *N* HCl
2-*n*-$C_{10}H_{21}O$	B	125–126[c]	$C_{17}H_{28}N_2O$·$C_6H_3N_3O_7$	97[a]	AcOH–H_2O
2-*i*-C_3H_7O	B	188–189[c]	$C_{10}H_{14}N_2O$·$C_6H_3N_3O_7$	95[a]	EtOH
2-*i*-C_4H_9O	B	187–188[c]	$C_{11}H_{16}N_2O$·$C_6H_3N_3O_7$	87[a]	Acetone
2-*s*-C_4H_9O	B	159–161[c]	$C_{11}H_{16}N_2O$·$C_6H_3N_3O_7$	95[a]	AcOH–H_2O
2-*i*-$C_5H_{11}O$	B	156–157	$C_{12}H_{18}N_2O$·HCl	86[a]	Acetone
2-$(CH_3)_3CCH_2CH_2O$	B	196–197	$C_{13}H_{20}N_2O$·HCl	96[a]	2 *N* HCl
2-$C_6H_5CH_2O$	B	184–185[c]	$C_{14}H_{14}N_2O$·$C_6H_3N_3O_7$	99[a]	EtOH
2-$CH{\equiv}CCH_2O$	B	91–93[d]	$C_{10}H_{10}N_2O$	83	C_6H_6
2-CH_3S	Text	290–291[e]	$C_8H_{10}N_2S$·HCl	15[a]	*b*
2-CH_3SO_2	A	173[b]	$C_8H_{10}N_2O_2S$	77[a]	EtOH
2-TsNH	A	258–260[d,e]	$C_{14}H_{15}N_3O_2S$	95[a]	DMF–H_2O
3-CH_3S	C	164–169	$C_8H_{10}N_2S$·HCl	64[a]	EtOH–Et_2O
3-$(CH_3)_2N$	C	200–210	$C_9H_{13}N_3$·HCl	55	2-Propanol
3-$C_6H_5CH_2$	C	185–187[c]	$C_{14}H_{14}N_2$·$C_6H_3N_3O_7$	37[a]	EtOH
4-CH_3	C	210–213	$C_8H_{10}N_2$·HCl	66	EtOH
4-$C_6H_5CH_2$	C	210–212[c]	$C_{14}H_{14}N_2$·HCl	44	H_2O

[a]Crude yield. [b]Not crystallized. [c]Picrate. [d]Free base. [e]Melting point with decomposition.

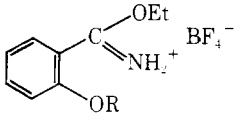
Table V



R	Mp, °C	Formula	% yield	Crystn solvent
2-$(CH_3)_2N$	134–136	$C_9H_{13}N_3O$	36	C_6H_6
2-CH_3S	170–172	$C_8H_{10}N_2OS$	35[a]	C_6H_6
2-CH_3SO_2	224–225	$C_8H_{10}N_2O_3S$	46	Acetone
2-*n*-$C_4H_9SO_2$	134–136	$C_{11}H_{16}N_2O_3S$	85[a]	EtOH
2-TsNH	138	$C_{14}H_{15}N_3O_3S$	72[a]	C_7H_8
2-CH_3O	101–103	$C_8H_{10}N_2O_2$	68	C_6H_6

[a]Crude yield.

Table VI



R	Mp, °C[a]	Formula	Crude yield, %
CH_3	141–143	$C_{10}H_{14}BF_4NO_2$	78
n-C_6H_{13}	73–74	$C_{15}H_{24}BF_4NO_2$	64
n-$C_{10}H_{21}$	97–99	$C_{19}H_{32}BF_4NO_2$	74
i-C_3H_7	130–132	$C_{12}H_{18}BF_4NO_2$	70
i-C_4H_9	108–110	$C_{13}H_{20}BF_4NO_2$	50
s-C_4H_9	78–80	$C_{13}H_{20}BF_4NO_2$	45
i-C_5H_{11}	121–123	$C_{14}H_{22}BF_4NO_2$	69
$(CH_3)_3CCH_2CH_2$	165–166	$C_{15}H_{24}BF_4NO_2$	86
$C_6H_5CH_2$	117–118	$C_{16}H_{18}BF_4NO_2$	75

[a]Crystallized from CH_2Cl_2–Et_2O.

in parentheses below the coefficients is the t test statistic.

Equation 1 is statistically highly significant and the probability that the relationship arose by chance is less than 1 in 10,000. As E_s decreases in numerical value with increasing size of the substituent group, the relationship suggests that biological activity is increased by high hydrogen bonding and reduced by large ortho substituents in the phenyl ring.

The knowledge of the factors associated with activity rapidly led us to synthesize the most active member of our series, the *o*-propoxy analog **9**, which is undergoing extensive biological evaluation.[7] The final group of compounds numbered 44, but for various reasons, the data on nine of these were unsuitable for quantitative treatment (see Table I). The activity of the 35 remaining compounds could be correlated by eq 2 (see Chart I).

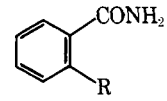
Chart I. Squared Correlations Matrix for Parameters Used in the Correlation Study (35 Compounds)

	log *P*	E_s	$\Delta\bar{\nu}$
log *P*	1.000	0.028	0.144
E_s		1.000	0.336
$\Delta\bar{\nu}$			1.000

Comparison of the figures of the activity calculated from eq 2 and the observed figures indicated that the largest deviations occurred with highly lipophilic compounds, particularly the decyloxy compound **13.** Elimination of this compound gave eq 3, while introduction of partition terms gave eq 4 where *P* represents the partition coefficient between octanol and water.

The inclusion of partition terms can hardly be justified statistically, and clearly the influence of partitions is much less important than the hydrogen bonding and steric effects except for highly lipophilic or hydrophilic compounds. However, eq 4 gives an optimum partition of log *P* = 2.00

Table VII



R	Mp, °C	Formula	% yield	Recrystn solvent
n-$C_{10}H_{21}O$	58–59	$C_{17}H_{27}NO_2$	73	Petroleum ether (bp 40–60°)
i-C_4H_9O	126–128	$C_{11}H_{15}NO_2$	34	Petroleum ether (bp 60–80°)
$(CH_3)_3CCH_2CH_2O$	87–88	$C_{13}H_{19}NO_2$	52	Cyclohexane
n-$C_4H_9SO_2$	102–103	$C_{11}H_{15}NO_3S$	83	H_2O

which is close to the value for the most active compound in the series (**9**). In fact, eq 3 (R^2 = 0.755) explains all the variance in activity which is not attributable to experimental error.

The observed activities of those compounds which could not be used to derive the regressions are in general agreement with the equations if reasonable suppositions are made as to the size and hydrogen bonding capabilities of the ortho substituents.

Equation 2 is a statistically significant improvement at the 99.9% confidence level (F test) over the best single parameter correlation, eq 5, which involves the wavelength shift, $\Delta\bar{\nu}$.

We interpret the relationships to mean that coplanarity of the phenyl substituent with the azahypoxanthine is a requirement for high antiallergic activity in the test system employed. Hydrogen bonding with a suitable ortho-substituted phenyl group would favor planarity while a bulky substituent would hinder planarity. Activity would be maximized by a high degree of hydrogen bonding coupled with small size, and simple ether substituents appear to be optimal in this respect. It is relevant that the low activity of 2-(2-pyridyl)-8-azapurin-6-one is increased 100-fold by formation of the corresponding pyridine N-oxide,[5] in which the hydrogen bonding would be expected to be substantially increased.

Experimental Section

Biological Methods. The backs of male Sprague–Dawley rats weighing 100–150 g were shaved with electric clippers and two skin sites diagonally opposite one another were sensitized by intradermal injection of 0.5 ml of a 1 to 20 dilution of *Nippostrongylus brasiliensis* antiserum. A further two diagonally opposite sites were sensitized with 0.05 ml of a 1 to 80 dilution of antiserum. After 48 hr each rat was injected intravenously with specific antigen (0.1–0.3 ml of *N. brasiliensis* worm extract, the required volume depending on the degree of sensitization of the rats and the potency of the antigen) and Evans Blue dye (0.2 ml of a 1.5% solution in saline). Each rat was killed 30 min after injection of antigen, the shaved area of skin was removed, and the responses were measured from the underside of the skin. The reactions were assessed subjectively by the amount of bluing, a score being allocated to each depending on its size and intensity.

Graded doses of the test compound in H_2O or a slight excess of NaOH solution were injected intravenously in groups of rats (at least two at each dose level) immediately before administration of the allergen and dye. The potency relative (I) to disodium cromoglycate was assessed by comparison with groups of rats treated with the graded doses of standard.

Statistics. Correlations were derived using a Wang 2200B computer with a multiple parameter regression analysis program written in BASIC.[8]

Syntheses. Melting points were determined on an "Electrothermal" instrument. Analytical results for compounds in the tables are within ±0.4% of the theoretical values (C, H, N).[9]

The 2-phenyl-8-azapurinones (Table I) were prepared from the appropriate amidines by the synthetic route outlined in Scheme I following standard procedures.[5] In many cases the intermediates were used in subsequent stages without purification. Novel, fully characterized, intermediates are listed in Tables II and III.

New amidines are listed in Table IV and were prepared by one of three methods as indicated in the table.

Method A. The appropriate amidoxime in ethanol was catalytically hydrogenated (Raney nickel) at 5 kg/cm^2 at 60°. New amidoximes prepared by the method of Miller[10] are listed in Table V.

Method B. Following the procedure of Weintraub et al.[11] the appropriate amides and triethyloxonium fluoroborate gave imidate ester fluoroborates which with ammonia afforded the amidines. New imidate esters are listed in Table VI.

A few of the benzamides were novel and are listed in Table VII. These were prepared by the method of Bavin et al.[12] or as described below.

***o*-Neohexyloxybenzamide.** Salicylamide (13.7 g, 0.1 mol), neohexyl chloride (13.2 g, 0.11 mol), and K_2CO_3 (15.2 g, 0.11 mol) in 2-ethoxyethanol (150 ml) were refluxed for 23 hr and then cooled in ice and filtered. The residue was washed with ether and the combined washings and filtrate were concentrated to an oil in vacuo and then poured onto water to give the benzamide (11.4 g, 52%): mp 87–88° (from cyclohexane).

***o*-Butylsulfonylbenzamide.** *o*-Butylsulfonylbenzoic acid (91%) was prepared by the method of Pain[13] and had mp 72.5–73.5°. Anal. ($C_{11}H_{14}O_4S$) C, H, S.

o-Butylsulfonylbenzoic acid (90 g) and $SOCl_2$ (30 ml) in C_6H_6 (300 ml) were refluxed for 1 hr and then evaporated in vacuo. The residue was treated at 0° with concentrated ammonia to give the benzamide (78 g, 83%): mp 102–103° (from H_2O).

Method C. The Pinner method[14] from a benzonitrile was used.

***o*-Butylsulfonylbenzonitrile.** *o*-Butylsulfonylbenzamide (23.5 g) and phosphorus oxychloride (100 ml) were heated on a steam bath for 2 hr. Excess of phosphorus oxychloride was removed under reduced pressure and the residue was treated with ice-cold water and extracted with ether. Fractional distillation of the extract afforded the benzonitrile (18.11 g, 84%): bp 225–227° (10 mm). Anal. ($C_{11}H_{13}NOS$) C, H, N, S.

***o*-(Methylthio)benzamidine Hydrochloride.** *o*-(Methylthio)benzamidoxime (1.75 g) in 3% HCl (100 ml) was electrolyzed in a divided cell using a carbon anode and a lead oxide cathode at 1.25 V for 1.5 hr. The reaction mixture was cooled to 0° and then brought to pH 11 with 50% NaOH and extracted with chloroform. Evaporation of the extract and treatment of the residue with methanolic HCl afforded the amidine hydrochloride (0.3 g, 15%). Anal. ($C_8H_{10}NO_2S$) C, H, N.

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Antimalarials. 7. 2,8-Bis(trifluoromethyl)-4-quinolinemethanols

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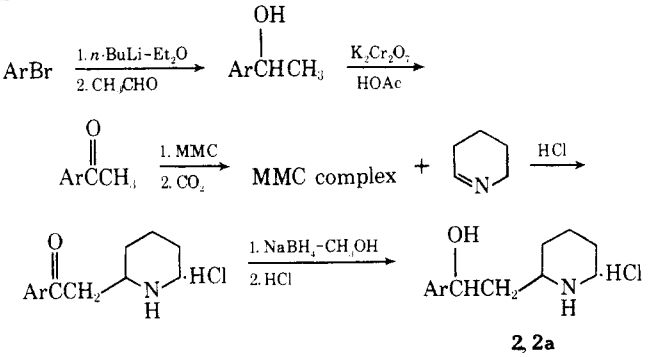
Based on the high antimalarial activity of α-(2-piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol, ten additional 2,8-bis(trifluoromethyl)-4-quinolinemethanols were prepared in which the amino alcohol side chain was structurally varied. Synthesis of the compounds is described and antimalarial activity data against *Plasmodium berghei* are presented and discussed in terms of the structure variations.

α-(2-Piperidyl)-2,8-bis(trifluoromethyl)-4-quinolinemethanol (**1**) was reported in 1971 by Ohnmacht et al.[1] to possess a high degree of antimalarial activity against *Plasmodium berghei* in mice.[2] This prompted the synthesis of ten additional analogs in which the amino alcohol group was variously altered. These included (a) variation in the alkyl group attached to nitrogen, (b) the preparation of homo analogs of the conventional α-alkylaminomethyl compound, and (c) the preparation of compounds bearing the α-alkylaminoisopropyl group. The homo analogs, i.e., ethanols as opposed to methanols, have been significantly more active in the case of certain quinoline, phenanthrene, and pyridinecarbinols.[3]

Chemistry. The target carbinolamines prepared in this work are tabulated in Table I. In all synthesis schemes, Ar is the 2,8-bis(trifluoromethyl)-4-quinolyl group. Compound **2**, the homo analog of **1**, was prepared from 2,8-bis(trifluoromethyl)-4-bromoquinoline according to Scheme I. The

Scheme I

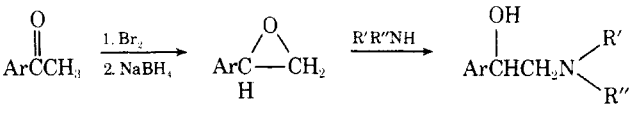


2, 2a

4-bromoquinoline was converted to the 4-lithioquinoline and condensed with acetaldehyde to form the 4-methylcarbinol (69–76%). The latter was oxidized with dichromate in acetic acid to yield the 4-acetylquinoline (87–88%). The acetyl compound was successfully converted to the required precursor, 2-piperidylmethyl 4-quinolyl ketone, using an interesting procedure reported recently by Claxton et al.[4] as follows. A standardized solution of magnesium methyl carbonate (MMC) in DMF was prepared by the method of Finkbeiner and Wagner.[5] 4-Acetylquinoline was added and the mixture was heated at 120° under N_2. After cooling, a separately prepared tripiperidine[6] was added to the MMC solution to give the 2-piperidylmethyl ketone in 50% yields based on acetylquinoline consumed. The conversions, however, were low, ranging from 33 to 43%. The 2-piperidylmethyl ketone was reduced with sodium borohydride to give the target carbinol, mp 257–261°, in 76% yield. The product was a mixture of two pairs of enantiomers (ca. 3:1). Recrystallization gave the predominant isomer, henceforth designated racemate A (**2**), mp 266–268°. Racemate B (**2a**), mp 261–263°, was isolated in low recovery from the mother liquors. A mixture of **2** and **2a** (1:1) melted at 248–255°. Initially, the preparation of **2** was attempted by more conventional routes without success. For example, 2,8-bis(trifluoromethyl)quinoline-4-carboxaldehyde (see below) was condensed with 2-picolyllithium. A four-component mixture (one major and three minor) was obtained with the desired intermediate 2-picolylcarbinol as a minor component (isolated in low yield).

Compounds **3, 5,** and **7** were prepared from the above intermediate, 2,8-bis(trifluoromethyl)quinolyl methyl ketone, by well-developed procedures as shown in Scheme II.[7]

Scheme II



3, R′ = *t*-Bu; R″ = H
5, R′ = *n*-Pr; R″ = H
7, R′ = R″ = *n*-Pr

Bromination yielded the bromo ketone as an oil which, without purification, was reduced with $NaBH_4$ to give the epoxide in 65–73% yield based on the starting methyl ketone. The epoxide was treated with the appropriate amine to yield compounds **3, 5,** and **7** in 74, 63, and 84% yields, respectively.