anism for the combination of a ligand-induced (represented by I, I′, and I″) with a pH-induced conformational change. Detailed measurements aiming at exact values for individual constants, are now in progress.

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Appendix

Equation 6 with $K_{II} = 0$ was previously derived.[19] Eq 6 presents thus an expression of the former derivations. More details on the derivation of eq 5 and 6 are also obtainable from a monograph on chemical relaxation[20] (see especially Tables 8.2 and 8.3, as well as Chapter 7). Expressions for apparent rate constants for the two-step scheme of Figure 1, heavy lines of part B (and K_H' defined as in part A) are easily obtained from eq 6 by setting $k_3 = k_4 = 0$ (as well as $K_{II} = 0$).

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Structure-Activity Correlations of Antimalarial Compounds. 1. Free-Wilson Analysis of 2-Phenylquinoline-4-carbinols

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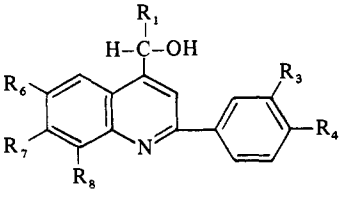
Sixty-nine 2-phenylquinoline-4-carbinols which had been tested in the mouse for antimalarial activity were studied by the Free-Wilson method for structure-activity correlation. The results for this study significantly support the additivity concept assumed by the Free-Wilson approach. The substituent constants for groups at the para position of the 2-Ph ring were found to correlate significantly with both Hammett's meta σ constants and Hansch's π values for those substituents. Substituents on the 7 position of the quinoline ring correlate well with para σ and π values. Substituent constants for groups at position 8 of the quinoline ring correlate with π values for these substituents. Substituent constants for groups at position 6 and on the meta position of the 2-Ph ring failed to correlate with σ or π values; the substituent constants for the 16 different aminoalkyl side chains failed to correlate with π, or π and π^2. The significance of these results is discussed.

The Free-Wilson method of structure-activity correlation[1] has been applied with varying degrees of success in recent years.[2-5] This paper reports a successful application of the technique to compare the antimalarial test results in mice for 69 substituted 2-phenylquinoline carbinols of general structure I.



I

The biological test reports, obtained from the Walter Reed computer record system, gave data obtained by Rane and coworkers by the reported method.[6] The dose in milligrams which cured 50% of the animals was obtained by extrapolation of the number of cures found for each of the doses tested, and was converted to the customary log $1/C$ value, where C = moles/kg test animal. For every compd, at least 3 graded doses were given to 5 animals per dose.

Results

Following the reported method[1] the matrix listed in Table II was used as input to be solved by a matrix inversion program developed by Free and coworkers.

The substituent constants (*sc*) which resulted from the regression analysis are listed in Table I. The correlation coefficient for the analysis is 0.905; the standard deviation is 0.359, and the overall "average" log $1/C$ value is 3.39.† The

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†This is the theoretical value for a hypothetical molecule in which none of the 6 substitutable positions contains any substituent group, including H. Substituent constants at R_3, R_4, R_6, R_7, and R_8 could be related to H as 0 by arbitrarily setting the matrix so that columns Q, U, AB, AF and AK in Table II are set equal to 0, rather than 1.

F statistic[17] for the correlation is 4.55; $F_{34,34}$ for the 1% level is 2.4; hence the correlation is highly significant. Thus the basic assumption of the Free-Wilson method (additivity of group effects) is confirmed for these biological data.

The same antimalarial data have been analyzed by the Hansch multiple parameter method;[18] the results will be compared with those obtained by the Free-Wilson method in paper 2 of this series.

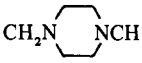
Discussion

Differences between the additive constants for groups at each position can be checked for statistical significance by T tests,[17] which are made between each *sc* value (other than the reference *sc*) and the *sc* value for the reference group at that position. The *sc* values are listed in Table I, and the reference *sc* for each position is in italics. This reference group is chosen as either the most frequently studied group, or as the hydrogen analog. The absence of a T test asterisk does *not* signify a lack of statistical significance for the particular *sc*; it only means that the distinction between that *sc* and the reference *sc* is not significant. If the two *sc* values are very close, it is unlikely that they will be significantly different. Also, unless the *sc* for a group, represented by only one or two examples, is very different from the reference *sc*, no significant difference should be expected.

These points are illustrated in Tables I and II. Groups E, I, and P (identified in Table II) gave *sc* values which are significantly different from that of group C (the reference group), even though they were represented by only one example each. Groups F and L were represented by two examples, but because their *sc* values were much closer to that for group C, they were not significantly different from C. Group A is especially interesting, in that it occurred in nine examples, but its *sc* was so close to that for group C that it, too, was not significantly different from it. It must be emphasized that this does not reflect upon the reliability of the *sc* value for group A; this can only be gauged by the overall F value and standard deviation for the entire regression.

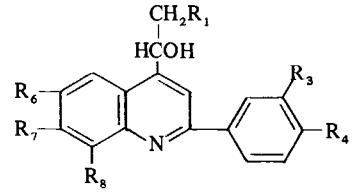
The most important information to be gained from a Free-Wilson analysis is the relative rank of substituent group constants at each position. This is summarized in Table I for

Table I. Substituent Constants[g]

	Substituent	Substituent constant (*sc*)[e]	n[a]	π[b]	$m-\sigma$[c]	$p-\sigma$[c]	E_R[d]
R_1	6-Methyl-2-piperidyl	0.397	1	0.88			
	2-Piperidyl	0.323	9	0.38			
	$CH_2N(C_4H_9)_2$	*0.262*	25	3.31			
	$CH_2N(CH_3)$ (i-C_3H_7)	−0.036	1	1.18			
	$CH_2N(C_6H_{13})_2$	−0.077*	14	5.31			
	CH_2N (i-C_5H_{11})$_2$	−0.174	2	4.18			
	CH_2NH-$CH_2C_6H_5$	−0.193	1	2.00			
	$CH_2N(C_8H_{17})_2$	−0.284	2	7.31			
		−0.431**	4	−0.17			
	$CH_2N(C_2H_5)_2$	−0.432**	3	1.31			
	CH_2-piperidyl	−0.451*	2	2.10			
	CH_2NH(cyclopropyl)	−0.573	1	0.02			
	$CH_2N(CH_2CH_2OCH_2CH_3)_2$	−0.574	1	1.37			
	$CH_2N(C_7H_{15})_2$	−0.697*	1	6.31			
	CH_2NH(1-adamantyl)	−0.906**	1	2.71			
	CH_2-morpholino	−0.973**	1	−0.58			
R_3	OCH_3	0.562	2	0.12	0.115	−0.270	0.11
	Cl	0.361	7	0.76	0.37	0.23	0.10
	H	*−0.0554*	58	0	0	0	0
	CF_3	−0.221	2	1.16	0.43	0.54	0.06[f]
R_4	I	0.445	1	1.26	0.35	0.28	0.12
	CF_3	0.145	1	1.16	0.43	0.54	0.06[f]
	Cl	0.123	34	0.70	0.37	0.23	0.10
	F	0.0437	5	0.15	0.34	0.06	0.19[f]
	H	*−0.150*	15	0	0	0	0
	OCH_3	−0.203	10	−0.04	0.115	−0.27	0.11
	CH_3	−0.240	3	0.52	−0.07	−0.17	0.03
R_6	CF_3	0.435*	6	1.16	−0.07	−0.17	1.16
	Cl	0.143	28	0.70	0.37	0.23	0.10
	OCH_3	−0.0641	10	−0.04	0.115	−0.27	0.11
	H	*−0.239*	25	0	0	0	0
R_7	CF_3	0.927**	2	1.16	0.43	0.54	0.06[f]
	Cl	0.487**	14	0.70	0.37	0.23	0.10
	F	0.209	4	0.14	0.34	0.06	0.19[f]
	H	*−0.168*	45	0	0	0	0
	OCH_3	−0.489	4	−0.04	0.115	−0.27	0.11
R_8	CF_3	0.774**	7	1.16	0.43	0.54	0.06[f]
	Cl	0.321**	19	0.70	0.37	0.23	0.10
	CH_3	−0.0785	8	0.52	−0.07	−0.17	0.03
	H	*−0.311*	35	0	0	0	0

[a] n = number of examples. [b] π constants for R_1 obtained from aliph series (ref 22); for arom substituents, π values obtd from ref 21. [c] σ constants (ref 17). [d] E_R values taken from ref 20, except where noted. [e] One asterisk indicates significance at the 5% level. Two asterisks indicate significance at the 1% level. [f] E_R values calculated by J. Rhee and C. Hansch, by CNDO/2 method, private communication. [g] For the overall regression, r = 0.905, s = 0.359, mμ = 3.39; F = 4.55, $F_{34,34}$ = 2.4 for 1%.

Table II.[a,b]



log 1/C	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	Ref
4.53	1																1						1					1				1								1		7
4.36			1															1					1						1				1						1			8
4.34			1														1							1					1				1						1			9
4.25	1																1				1							1					1							1		8
4.22			1														1						1							1				1				1				8
4.18			1														1						1					1							1			1				8
4.17			1														1						1						1			1							1			10
4.16			1														1						1						1			1						1				8
4.16	1																1				1								1			1						1				11
4.09				1													1						1					1						1						1		12
4.08			1														1						1							1		1								1		8
4.06			1														1						1								1	1								1		c
4.04			1														1								1				1			1							1			c
3.99			1																1		1								1			1							1			c
3.98							1											1					1						1			1							1			d
3.98			1														1					1						1			1							1			10
3.97			1														1						1						1			1					1				12
3.97	1																1						1						1			1							1			8
3.95				1													1						1							1		1								1		12
3.94	1																1									1		1				1								1		7
3.91			1														1						1					1						1			1				12
3.87			1														1										1				1			1			1				e
3.81														1			1						1						1			1							1			f
3.72								1									1						1						1			1							1			12
3.71			1														1					1						1					1				1				f
3.69			1														1						1					1				1							1		10
3.68				1													1						1					1							1		1				10
3.61	1																1					1							1			1								1	7
3.60										1								1					1						1			1						1			d
3.52											1						1				1							1						1			1				g
3.51			1														1										1		1					1			1				13
3.45			1														1									1				1		1								1	h
3.41				1														1					1								1	1					1				e
3.35				1													1				1								1			1							1			12
3.32				1													1						1					1				1							1			12
3.32				1																1							1		1			1						1			13
3.32				1													1										1		1					1				1			13
3.30			1															1					1								1	1						1			13
3.25				1													1						1						1			1							1			12
3.22				1													1										1				1			1			1				13
3.21			1														1				1										1	1					1				12
3.18												1					1						1					1						1						1		12
3.17															1		1				1								1			1							1			f

Table II *(Continued)*

log 1/*C*	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	Ref
3.15						1														1							1		1			1				1				13
3.14			1														1						1					1					1				1				10
3.13					1												1						1					1				1							1		*c*
3.12		1																1					1							1	1					1				13
3.07				1													1						1							1			1			1				13
3.02														1			1						1					1					1			1				14
2.83				1															1		1								1			1					1			10
2.82				1													1						1						1							1	1			13
2.82						1											1				1							1					1				1			12
2.80		1															1									1				1		1						1	*h*
2.76													1					1					1								1	1					1			13
2.76			1														1						1						1							1	1			13
2.71			1														1										1		1							1	1			13
2.71			1														1						1					1				1					1			12
2.65	1																1				1							1				1						1	7
2.65		1															1										1				1			1					*e*
2.64				1													1										1		1							1	1			13
2.49									1								1						1					1						1			1			14
2.58														1			1					1						1					1				1			14
2.57												1					1				1							1				1					1			12
2.54	1																1										1	1				1					1			15
2.54														1			1				1								1			1						1		14
2.54			1														1				1							1				1					1			12
2.51																1	1				1								1			1						1		14
2.50	1																1				1							1				1					1			16
2.45															1		1					1						1					1				1			14
Totals	9	3	25	14	1	2	1	1	1	1	1	2	1	4	2	1	58	7	2	2	15	5	34	1	1	3	10	25	28	6	10	45	4	14	2	4	35	19	7	8	
								(69)										(69)						(69)					(69)					(69)				(69)			

[a]For R_1 the substituents are: A, 2-piperidyl; B, *N*-Et_2; C, *N*-Bu_2; D, *N*-Hex_2; E, *N*-Hep_2; F, *N*-Oct_2; G, $NHCH_2C_6H_5$; H, *N*-Me-*i*-Pr; I, NH (adamantyl); J, NH (cyclopropyl); K, 6-methyl-2-piperidyl; L, *N*-*i*-amyl$_2$; M,N-$(CH_2CH_2OCH_2CH_3)_2$; N, *N*-methylpiperazine; O, *N*-piperidyl; P, morpholino; for R_2 the substituents are: Q, H; R, Cl; S, CF_3; T, OMe; for R_4: U, H; V, F; W, Cl; X, I; Y, CF_3; Z, CH_3; AA, OMe; for R_6: AB, H; AC, Cl; AD, CH_3; AE, OMe; for R_7: AF, H; AG, F; AH, Cl; AI, CF_3; AJ, OCH_3; for R_8: AK, H; AL, Cl; AM, CF_3; AN, CH_3. [b]Restrictions: 9A + 3B + 25C + 14D + E + 2F + G + H + I + J + K + 2L + M + 4N + 2O + P = 0; 58Q + 7R + 2S + 2T = 0; 15U + 5V + 34W + X + Y + 3Z + 10AA = 0; 25AB + 28AC + 6AD + 10AE = 0; 45AF + 4AG + 14AH + 2AI + 4AJ = 0; 35AK + 19AL + 7AM + 8AN = 0. Thus the 40 unknowns reduce to 34, with 69 compds; this leaves 34 degrees of freedom for error. [c]Obtd from A. J. Saggiomo, Germantown Laboratories, affiliated with the Franklin Institute, Philadelphia, Pa. [d]Obtd from J. Biel, Aldrich Chemical Co., Milwaukee, Wis. [e]Obtd from R. Rowlett, Virginia Institute for Scientific Research, Richmond, Va. [f]Obtd from E. Atkinson, Arthur D. Little Inc., Cambridge, Mass. [g]Obtd from J. Burkhalter, University of Michigan, Ann Arbor, Mich. [h]Obtd from R. E. Lutz, University of Virginia, Charlottesville, Va.

Table III. Correlations Obtained by Regression

Equation	r^a	s^a	$F^{a,b}$	Comments
Position 1				No significant correlations obtained between π or π^2 and π, and R_1 *sc*
Position 3				No significant correlations obtained
Position 4				
(1) sc^c = $-0.191(\pm0.236) + 0.978(\pm0.820)\sigma$-meta	0.808	0.157	9.39*	$F_{1,5} = 6.61$*
(2) *sc* = $-0.041(\pm0.174) + 0.676(\pm0.635)\sigma$-para	0.775	0.168	7.50*	$F_{1,5} = 6.61$*
(3) *sc* = $-0.170(\pm0.232) + 0.361(\pm0.318)\pi$	0.794	0.162	8.53*	$F_{1,5} = 6.61$*
(4) *sc* = $-0.127(\pm0.297) + 0.338(\pm1.136)\sigma$-para + $0.220(\pm0.592)\pi$	0.827	0.112	4.34	$F_{2,4} = 6.94$*
(5) *sc* = $-0.232(\pm0.232) + 0.626(\pm0.938)\sigma$-meta + $0.220(\pm0.353)$	0.895	0.133	8.06*	$F_{2,4} = 6.94$*
Position 6				No significant correlations obtained
Position 7				
(6) *sc* = $-0.010(\pm0.190) + 1.811(\pm0.654)\sigma$-para	0.981	0.123	77.7**	$F_{1,3} = 34.1$**
(7) *sc* = $-0.198(\pm0.397) + 0.998(\pm0.651)\pi$	0.942	0.213	23.8*	
(8) *sc* = $-0.457(\pm0.837) + 2.589(\pm2.787)\sigma$-meta	0.863	0.322	8.75	$F_{1,3} = 10.1$*
Position 8				
(9) *sc* = $-0.395(\pm0.566) + 0.959(\pm0.780)\pi$	0.966	0.151	27.9*	$F_{1,2} = 18.5$*

[a] Reference 17. [b] One asterisk indicates significance at the 5% level; two asterisks, at the 1% level. [c] *sc* = substituent constants obtd by the regression; see Table I.

all positions studied. However, in an attempt to gain more information from the analysis than just rank, correlations were sought by regression analysis for linear relationships between the *sc* values and the following parameters: Hammett σ constants (meta and para),[19] Otsu's E_T constants,[20] and Hansch's π values.[21,22] The results are presented in Table III.

These results point out possible linear relationships between polar effects of substituent constants in both benzenoid rings, and antimalarial activity. Also possible are relationships between the π values for some of the position substituents and antimalarial activity. The problem of differentiating between these possibilities when one is working with a limited set of substituents is discussed in a companion paper,[23] where the judicious selection of one or two additional substituents is discussed, to help resolve which parameter is really the important one.

It is noteworthy that no simple dependence of antimalarial activity was found for π values of the substituent groups at R_1. No correlation was found when the values for π and π^2 were studied; this was tried since the Hansch method has shown that such relationships are the rule, rather than the exception.

The larger coefficient for σ_p at R_7, 1.81, as compared to 0.98 for σ_m at R_4, gives a direct comparison of the relative effect upon antimalarial activity of changes in polar effects at these two substituent positions. Thus, polar effects of substituents at R_7 affect the antimalarial activity about 7 times more than do similar polar changes at R_4 on the 2-Ph ring (antilog of $0.83 \cong 7$). Of course it is not necessary to study the regression results in Table III to gain this information, since a similar conclusion is drawn from a comparison of the ranges of substituent constants at positions R_7 and R_4 (1.41 and 0.685, difference = 0.72, antilog ≅5.3), reported in Table I.

The results listed in Table III now allow one to predict maximum values of log $1/C$ which might be expected for compds bearing as yet unstudied substituents. More activity would be expected from increased electron withdrawal at R_7 than at any of the other aromatic ring positions. Thus, the preparation of the CF_3SO_2 analog at R_7 would be expected to result in an increased antimalarial activity of about 5-fold over the CF_3 analog (σ para for CF_3SO_2- = 0.93; for CF_3 = 0.55; difference = 0.38; from eq 5, Table III, $1.81 \times 0.38 = 0.68$; antilog ≅4.8).

The original presentation of the Free-Wilson method emphasized the relative ranking of substituent groups at each position. The present approach allows predictions to be made outside of the matrix of compounds employed in the Free-Wilson analysis, if significant correlations with standard parameters can be obtained for the *de novo sc* values. Of course it is possible that too great a change in σ could lead to a parabolic relationship;[18] hence, the prediction is to be considered as a maximum value, not necessarily fully achievable.

The application of eq 7, Table III, involving π instead of σ, would lead to a prediction that the CF_3SO_2 analog of a CF_3 member of structure I, should be approximately equivalent in activity. What is needed to resolve this problem is a substituent group such as CH_3SO_2, which is high in σ and very low in π.

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Synthesis of 1-*p*-Chlorobenzyl-7-azaindole-3-α-piperidylmethanol as a Potential Antimalarial Agent†

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A single diastereoisomer of 1-*p*-chlorobenzyl-7-azaindole-3-α-piperidylmethanol was found to have antimalarial activity about 0.5 that of quinine when tested in mice against *Plasmodium berghei*. This is the first example of any antimalarial activity in the 7-azaindole class. None of the substituted 7-azaindole intermediates synthesized in this study showed appreciable activity. Also, the low activity of the mixed diastereoisomers indicated that one of the isomers was inactive. An intermediate in the 4-step synthesis, 7-azaindole-3-carboxaldehyde, was prepared in good yield by a Duff reaction, which represents a new and facile method for introducing the 3-formyl group on an N-unsubstituted 7-azaindole.

Very little biological activity has been published for any of the azaindoles other than 3-azaindole (benzimidazole) derivatives.[1] The primary interest in azaindoles has been as potential antimetabolites to naturally occurring indole derivatives. A pharmacological profile of the unsubstituted azaindoles comparing the activities of these compounds with indole, diazaindoles, and purine was reported.[2] Antimalarial activity in plain indoles with antimalarial type and other miscellaneous side chains has not been observed.[3] Before this study none of the reported azaindoles would be considered as candidate antimalarial target compounds. The goal of this study was to explore the potential of 7-azaindole as a new antimalarial nucleus.

The basis for exploring the 7-azaindoles rests on the rationale that the structure of 1-*p*-chlorobenzyl-7-azaindole-3-α-piperidylmethanol is comparable to the quinoline-5-α-piperidylmethanols, and the latter compounds show antimalarial activity. In addition, 7-azaindole having a pK_a = 4.59 and log *P* = 1.82 is isolipophilic with respect to quinoline which has a pK_a = 4.95 and log *P* = 2.03‡

Chemistry. Unsubstituted 7-azaindole is not formylated under normal Vilsmeier reaction conditions and 7-azaindole-3-carboxaldehyde has been made from 7-azagramine.[4,5] A better method to prepare this aldehyde was discovered whereby 7-azaindole is 3-formylated with hexamethylenetetramine in refluxing aq AcOH. The yields in this reaction were consistently good and the product was pure enough for synthetic purposes. Following procedures for the plain indoles[6] 1-alkylation provided 1-*p*-chlorobenzyl-7-azaindole-3-carboxaldehyde plus some quaternary product.[7] The key aldehyde **3** was also prepared by first 1-alkylating[8] and then formylating under Vilsmeier reaction conditions. This experiment confirms earlier observations about Vilsmeier formylation of 7-azaindoles, *i.e.*, that this reaction is facilitated by 1-substitution.[9]

The condensation of **3** with 2-pyridyllithium gave 1-*p*-chlorobenzyl-7-azaindole-3-α-piperidylmethanol as a labile oil which tends to decompose back to its aldehyde and pyridyl components.[10] Low pressure hydrogenation of the side chain pyridyl in its pyridinium salt form provided 1-*p*-chlorobenzyl-7-azaindole-3-α-piperidylmethanol as mixed diastereoisomers. Fractional crystallization separated one of the diastereoisomers as stable microcrystals, and this isomer was tested for antimalarial activity. The second isomer was extremely hygroscopic and apparently inactive as an antimalarial agent.

Several other 3-substituted 7-azaindoles were prepared as possible intermediates with "handles" for the introduction of side chains. These included 3-bromo-7-azaindole,[11] 3-nitro-7-azaindole,[12] and 1-*p*-chlorobenzyl-7-azagramine. Mild MnO_4^- oxidation[13] of the aldehyde **3** gave 1-*p*-chlorobenzyl-3-carboxy-7-azaindole. Only starting material was recovered when the carboxylic acid **9** was treated with 2-PyLi in an attempt to prepare the ketone.[14] *n*-BuLi is known to metalate indoles on the 2 position[15] and the reactive 2-PyLi[16] may have formed a 2-lithio-7-azaindole in our reaction sys-

Table I. Antimalarial Activity and Toxicity of 7-Azaindoles in Mice[a]

Compd	Dose, mg/kg	IMST, days[b]	Toxic deaths[c]
1	640	0.8	0
2	640	0.7	0
3	640	0.5	0
4	640	0.5	0
5	640	0.3	0
6	640	0.3	0
8	10	0.3	0
	40	0.5	0
	160	0.7	0
	320	3.1	0
	640	3.9	2
8a	640	0.5	0
9	640	0.7	0
10	160	0.3	0
	320	0.9	3
	640	–	5
11	640	1.0	0
12	640	0.6	0

[a] Test data supplied by Walter Reed Army Institute of Research. [b] Increase in mean survival time between *Plasmodium berghei* infected mice administered the drug sc and controls. Non-drug-treated mice survived about 6 days following infection with *P. berghei*. Chemical therapy was initiated 3 days postinfection. For details of this test see T. S. Osdene, *et al.*[20] [c] Number of deaths/5 mice.

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‡The log *P* of 7-azaindole and this comparison with quinoline were provided by Professor Corwin Hansch, whose assistance is gratefully acknowledged.