Synthesis and Quantitative Structure–Activity Relationships of Antiallergic 2-Hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides and *N*-(2-Hydroxyphenyl)-1*H*-tetrazole-5-carboxamides

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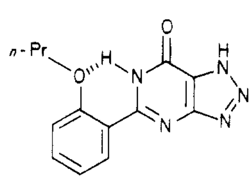
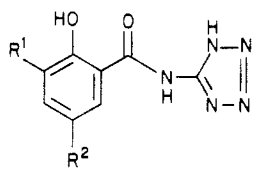
The synthesis and antiallergic activity of a series of 2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides and isomeric *N*-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamides is described. A relationship between structure and intravenous antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) test has been established using a Hansch/Free-Wilson model and used to direct studies toward potent derivatives. The contribution of physicochemical properties to activity is discussed. One member of this series, *N*-(3-acetyl-5-fluoro-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (**3f**), which was selected for further evaluation, has an ID_{50} value of 0.16 mg/kg po and is 130 times more potent than disodium cromoglycate (DSCG) on intravenous administration.

2-(*o*-Propoxyphenyl)-8-azapurin-6-one (Zaprinast; M&B 22,948) (**1**) is a potent inhibitor of reagin-mediated anaphylaxis and is superior to disodium cromoglycate (DSCG) in a number of test systems. Quantitative studies show that optimal antiallergic activity in 2-aryl-8-azapurin-6-ones (e.g., **1**) is associated with coplanarity between the heterocyclic and aryl rings and that coplanarity in M&B 22,948 (**1**) is particularly favored as a result of intramolecular hydrogen bonding.[1] The planar structure of compound **1** has been confirmed by an X-ray study.[2] Comparison of the azapurinones with other potent antiallergic molecules reveals common features, and these qualitative structure–activity relationships have been discussed by E.L. in a recent review.[3] Important requirements for antiallergic activity appear to be (i) an extended planar (or quasi-planar) aromatic system that is associated with (ii) an acidic function in close proximity to (iii) a carbonyl group. Inspection of structure **1** demonstrates that these features are present.[3]

The promotion of an extended planar system by intramolecular hydrogen bonding is a particularly interesting feature of the azapurinone (**1**). In our search for orally



1 (Zaprinast)



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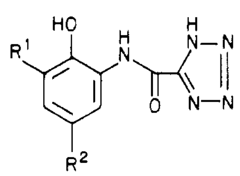

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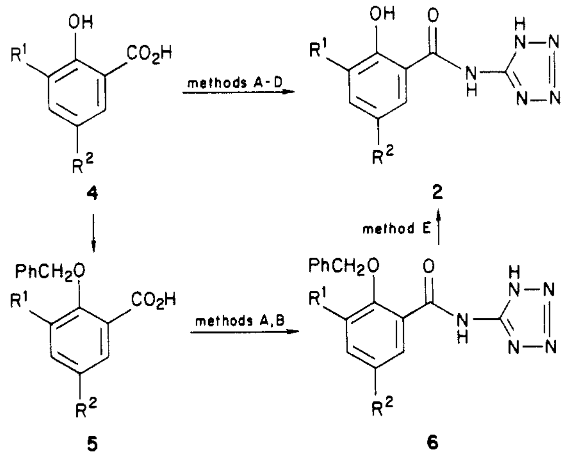
effective alternatives to DSCG we have been encouraged to investigate other molecules in which the requirement of extended planarity is facilitated by intramolecular hydrogen bonding. This paper describes how this approach led to the synthesis of two series of 5-substituted tetrazole derivatives, the 2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides (**2**)[4] and the *N*-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamides (**3**),[5] many of which possess outstanding antiallergic activity.

Scheme I[a]



[a] Reagents: (method A) 5-aminotetrazole–DCC in pyridine; (method B) 5-aminotetrazole–$SiCl_4$; (method C) (i) $SOCl_2$, (ii) 5-aminotetrazole; (method D) (i) PCl_3, (ii) 5-aminotetrazole; (method E) H_2–Pd–C.

Chemistry. *N*-1*H*-Tetrazol-5-ylbenzamides (**2** and **6**) are listed in Tables I and III and were prepared from the appropriate salicylic acid by methods summarized in Scheme I. The most convenient route involves condensation of a carboxylic acid (**4** or **5**) with anhydrous 5-aminotetrazole using dicyclohexylcarbodiimide (DCC) in pyridine (method A).[6] Alternatively, silicon tetrachloride was used as condensing agent (method B),[7] or the 5-aminotetrazole was reacted with the appropriate acid chloride generated in situ with either thionyl chloride

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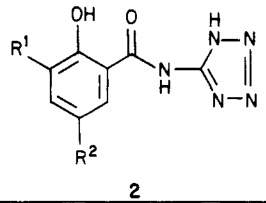
Table I. 2-Hydroxy-*N*-1*H*-tetrazol-5-ylbenzamides 2



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no.	R^1	R^2	method (% yield)	cryst solvent	mp, °C	formula	anal.[a]	rel act. $(I)^b$	log $[M_rI]$ obsd	log $[M_rI]$ calcd
2a	CH_3CO	H	A (49)	$DMF-H_2O$	291–292 dec	$C_{10}H_9N_5O_3$	C, H, N	1	2.393	2.596
2b	CH_3CO	CH_3	A (46), C(46)	$DMF-CH_3CO_2H$	279–281 dec	$C_{11}H_{11}N_5O_3$	C, H, N	1	2.417	2.240
2c	CH_3CO	C_2H_5	A (53)	$DMF-H_2O$	260–262 dec	$C_{12}H_{13}N_5O_3$	C, H, N	1	2.439	2.220
2d	CH_3CO	$n-C_3H_7$	A (40)	$DMF-H_2O$	257–258	$C_{13}H_{15}N_5O_3$	C, H, N	2	2.762	2.137
2e	CH_3CO	$i-C_4H_9$	A (35)	HCO_2H-H_2O	239–241 dec	$C_{14}H_{17}N_5O_3$	C, H, N	0.2	1.783	1.973
2f	CH_3CO	$t-C_4H_9$	A (51)	HCO_2H-H_2O	258–260 dec	$C_{14}H_{17}N_5O_3$	C, H, N	0.4	2.084	1.798
2g	CH_3CO	F	A (39)	$DMF-CH_3CO_2H$	268–270 dec	$C_{10}H_8FN_5O_3$	C, H, N	0.5	2.123	2.464
2h	CH_3CO	Cl	A (14)	$DMF-CH_3CO_2H$	269–271 dec	$C_{10}H_8ClN_5O_3$	C, H, Cl, N	0.05	1.149	2.318
2i	CH_3CO	Br	A (12)	$DMF-H_2O$	277–279 dec	$C_{10}H_8BrN_5O_3$	C, H, Br, N	0.05	1.212	2.263
2j	CH_3CO	CH_3O	A (60)	$DMF-H_2O$	288–290 dec	$C_{11}H_{11}N_5O_4$	C, H, N	2	2.743	2.438
2k	CH_3CO	NO_2	text (63)	HCO_2H	255–257 dec	$C_{10}H_8N_6O_5$	H, N; C[d]	1	2.465	1.873
2l	CH_3CO	SO_2NH_2	text (5)	$DMF-H_2O$	>310	$C_{10}H_{10}N_6O_5S$	C, H, N	0.2	1.814	1.844
2m	CH_3CO	$NHCOCH_3$	A (47)	HCO_2H	290	$C_{12}H_{12}N_6O_4$	C, H, N	0.2	1.784	1.741
2n	C_2H_5CO	CH_3	A (40)	HCO_2H	280–281	$C_{12}H_{13}N_5O_3$	C, H; N[e]	2	2.741	2.332
2o	C_2H_5CO	C_2H_5	A (40)	$DMF-H_2O$	262–263	$C_{13}H_{15}N_5O_3$	C, H, N	0.75	2.336	2.312
2p	CH_3O	H	A (69)	$DMF-CH_3CO_2H$	265–267 dec	$C_9H_9N_5O_3$	C, H, N	1	2.371	2.422
2q	CH_3O	CH_3	A (35)	$DMF-H_2O$	273–274 dec	$C_{10}H_{11}N_5O_3$	C, H, N	0.5	2.095	2.066
2r	CH_3O	C_2H_5	A (33)	$DMF-H_2O$	271–272 dec	$C_{11}H_{13}N_5O_3$	C, H, N	1	2.420	2.046
2s	CH_3O	$t-C_4H_9$	A (34)	$DMF-H_2O$	277 dec	$C_{13}H_{17}N_5O_3$	C, H, N	0.1	1.464	1.624
2t	CH_3O	Br	A (40)	$DMF-H_2O$	257	$C_9H_8BrN_5O_3$	C, H, Br, N	0.2	1.798	2.089
2u	CH_3O	CH_3O	A (27)	DMF	278–279	$C_{10}H_{11}N_5O_4$	C, H, N	0.5	2.122	2.264
2v	CH_3O	NO_2	A (34)	$DMF-H_2O$	257–258	$C_9H_8N_6O_5$	C, H, N	1	2.447	1.699
2w	CH_3O	CN	A (25)	DMF	264–265	$C_{10}H_8N_6O_3$	C, H, N	2	2.716	2.276
2x	CH_3O	$NHCOCH_3$	A (10)	$DMF-H_2O$	258–259 dec	$C_{11}H_{12}N_6O_4$	C, H, N	0.02	0.766	1.567
2y	H	H	E (87)	CH_3CO_2H	270–271 dec	$C_8H_7N_5O_2$	C, H, N	0.1	1.312	1.657
2z	H	CH_3	E (63)	$DMF-H_2O$	289–291 dec	$C_9H_9N_5O_2$	C, H, N	0.1	1.340	1.301
2aa	H	$t-C_4H_9$	B (20)	EtOH	252–253 dec	$C_{12}H_{15}N_5O_2$	C, H, N	0.01	0.417	0.859
2ab	H	F	A (46)	$DMF-CH_3CO_2H$	274 dec	$C_8H_6FN_5O_2$	C, H, N	0.1	1.348	1.525
2ac	H	Cl	E (77)	EtOH	266–269 dec	$C_8H_6ClN_5O_2$	C, H, N	0.1	1.380	1.378
2ad	H	Br	A (45)	CH_3CO_2H	272–274 dec	$C_8H_6BrN_5O_2$	C, H, Br, N	0.02	0.756	1.324
2ae	H	CH_3O	D (12.5)	$DMF-H_2O$	272–274 dec	$C_9H_9N_5O_3$	C, H, N	0.2	1.672	1.499
2af	H	CN	A (27)	CH_3CO_2H	310–312 dec	$C_8H_6N_6O_4$	C, H, N	0.5	2.061	1.510
2ag	H	NO_2	C (45)	CH_3CO_2H	271–272 dec	$C_8H_6N_6O_4$	C, H, N	0.5	2.097	0.933
2ah	H	CF_3	E (40)	i-PrOH	244–245 dec	$C_9H_6F_3N_5O_2$	C, H, F, N	0.02	0.737	0.968
2ai	H	CH_3S	A (24)	$DMF-CH_3CO_2H$	261–262 dec	$C_9H_9N_5O_2S$	C, H, N, S	0.2	1.701	1.350
2aj	H	CH_3SO_2	text (53)	CH_3CO_2H	291–292 dec	$C_9H_9N_5O_4S$	C, H, N, S	0.04	1.053	0.902
2ak	H	$(CH_3)_2NSO_2$	text (32)	EtOH	276–278 dec	$C_{10}H_{12}N_6O_4S$	C, H, N, S	0.05	1.193	0.905
2al	H	HO	E (66)	H_2O	299–300 dec	$C_8H_7N_5O_3$	C, H, N	0.1	1.345	1.499
2am	H	C_6H_5	A (45)	$DMF-CH_3CO_2H$	277–278 dec	$C_{14}H_{11}N_5O_2$	C, H, N	0.01	0.449	0.560
2an	H	CH_3CO	A (41)	$DMF-H_2O$	262–263 dec	$C_{10}H_9N_5O_3$	C, H, N	0.02	0.694	0.842
2ao	H	$NHCOCH_3$	A (35)	$DMF-H_2O$	222–224 dec	$C_{10}H_{10}N_6O_3$	H, N; C[f]	0.01	0.418	0.801
2ap	$HON{=}CCH_3$	C_2H_5	text (67)	$DMF-H_2O$	249–250 dec	$C_{12}H_{14}N_6O_3$	C, H, N	10	3.462	
2aq	$CH_3ON{=}CCH_3$	C_2H_5	text (87)	$DMF-H_2O$	272–275 dec	$C_{13}H_{16}N_6O_3$	C, H; N[g]	3.5	3.025	

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] Activity relative to M&B 22,948 (=1) in the rat PCA test following iv administration. The dose of M&B 22,948 required for 100% inhibition was 0.1 mg/kg. See ref 1b. [c] Calculated by eq 1. [d] C: calcd, 41.1; found, 41.7. [e] N: calcd, 25.4; found, 25.9. [f] C: calcd, 45.8; found, 45.2. [g] N: calcd, 27.6; found, 28.1.

(method C) or phosphorus trichloride (method D).[8] In some preparations the phenolic function was protected by a benzyl group that was subsequently removed by catalytic reduction (method E). In addition to preparation by the general methods A–E (Scheme I), chemical modification of some *N*-1*H*-tetrazol-5-ylbenzamides (**2**) gave additional derivatives, and details of these procedures are given in the Experimental Section, as indicated in Table I.

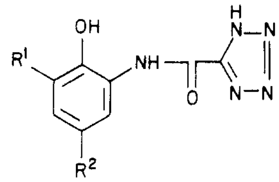
Novel salicylic acid derivatives (**4**) are listed in Table VI. 3-Acetyl-2-hydroxybenzoic acid (**4a**) was obtained using the following sequence: (i) isomerization of 3-allyl-2-hydroxyacetophenone using bis(benzonitrile)palladous chloride;[9] (ii) ozonolysis to give 3-formyl-2-hydroxyacetophenones; (iii) oxidation to the carboxylic acid using argentous oxide. Other novel carboxylic acids and their precursors were prepared by standard procedures as indicated in the Experimental Section.

Synthetic routes to the *N*-(2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamides (**3**) (Table II) are summarized in Scheme II. Six of the routes (methods F–K) are variations of an approach that requires protection of the tetrazole ring by a benzyl substituent that is removed in the final stage. The 1-benzyltetrazoles (**7**; Ar = Ph, R^3 = H) were deprotected by catalytic hydrogenation using 5% Pd on charcoal (method F), and this procedure was also successful using 2-benzyltetrazoles (**8**; Ar = Ph) (method G). In some

(8) Taborsky, R. G. (Ben Venue Laboratories, Inc.) U.S. Patent 3 278 372, 1966; *Chem. Abstr.* **1966**, *65*, 20068*d*.

(9) Golborn, P.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2870.

Table II. *N*-(2-Hydroxyphenyl)-1*H*-tetrazole-5-carboxamides 3



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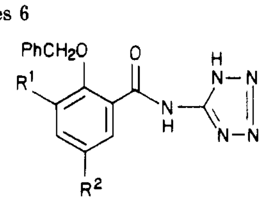
no.	R^1	R^2	method (% yield)	cryst solvent	mp, °C	formula	anal.[a]	rel act. (*I*)[b]	log [M_rI] obsd	log [M_rI] calcd[c]
3a	CH_3CO	H	J (84), L (41), N (48)	CH_3CO_2H	239–240	$C_{10}H_9N_5O_3$	C, H, N	20	3.694	3.497
3b	CH_3CO	CH_3	F (17), J (94), L (26)	DMF–H_2O	245–247 dec	$C_{11}H_{11}N_5O_3$	C, H, N	10	3.417	3.142
3c	CH_3CO	C_2H_5	F (82), G (13), J (70), K (93), L (53)	DMF–H_2O	239–241 dec	$C_{12}H_{13}N_5O_3$	C, H, N	20	3.740	3.121
3d	CH_3CO	*n*-C_3H_7	L (40)	DMF–H_2O	179–180	$C_{13}H_{15}N_5O_3$	C, H, N	10	3.461	3.038
3e	CH_3CO	*t*-C_4H_9	J (65)	*i*-PrOH	246–247 dec	$C_{14}H_{17}N_5O_3$	C, H, N	0.5	2.170	2.700
3f	CH_3CO	F	F (63), J (89), N (68)	MeCN	237–239 dec	$C_{10}H_8FN_5O_3$	C, H, F, N	20	3.724	3.365
3g	CH_3CO	Cl	J (67)	DMF–H_2O	242–244 dec	$C_{10}H_8ClN_5O_3$	C, H, Cl, N	7	3.295	3.219
3h	CH_3CO	Br	J (84)	DMF–H_2O	252–254 dec	$C_{10}H_8BrN_5O_3$	C, H, Br, N	2	2.814	3.165
3i	CH_3CO	CH_3O	J (86)	DMF–H_2O	251–253 dec	$C_{11}H_{11}N_5O_4$	C, H, N	10	3.443	3.340
3j	CH_3CO	CN	J (82), N (9)	DMF–H_2O	270–274 dec	$C_{11}H_8N_6O_3$	C, H, N	10	3.435	3.351
3k	CH_3CO	NO_2	J (62)	DMF–H_2O	239–240 dec	$C_{10}H_8N_6O_5$	C, H, N	5	3.164	2.774
3l	CH_3CO	CH_3SO_2	J (69)	DMF–H_2O	261–262 dec	$C_{11}H_{11}N_5O_5S$	C, H, N, S	2	2.813	2.743
3m	CH_3CO	CH_3CO	J (75)	DMF–H_2O	249–251 dec	$C_{12}H_{11}N_5O_4$	C, H, N	0.5	2.160	2.682
3n	CH_3CO	$NHCOCH_3$	J (64)	DMF–H_2O	270–271 dec	$C_{12}H_{12}N_6O_4$	C, H, N	0.5	2.189	2.642
3o	C_2H_5CO	CH_3	L (26)	EtOH	230–232 dec	$C_{12}H_{13}N_5O_3$	C, H, N	5	3.139	3.233
3p	C_2H_5CO	C_2H_5	L (26)	CH_3CO_2H	225–227 dec	$C_{13}H_{15}N_5O_3$	C, H, N	5	3.160	3.213
3q	C_2H_5CO	CN	J (80)	DMF–H_2O	257–259	$C_{12}H_{10}N_6O_3$	C, H, N	5	3.156	3.443
3r	CH_3O	H	I (47)	H_2O	218–220 dec	$C_9H_9N_5O_3$	C, H, N	5	3.070	3.323
3s	CH_3O	CH_3	I (22), M (17)	H_2O	222–223	$C_{10}H_{11}N_5O_3$	C, H, N[d]	2.5	2.794	2.967
3t	CH_3O	C_2H_5	I (43)	CH_3CO_2H	233–235	$C_{11}H_{13}N_5O_3$	C, H, N	10	3.420	2.947
3u	CH_3O	Br	M (20)	H_2O	217–219 dec	$C_9H_8BrN_5O_3$	C, H, N[e]	2	2.798	2.990
3v	H	H	I (42), M (9)	CH_3CO_2H	220–223	$C_8H_7N_5O_2$	C, H, N	1	2.312	2.558
3w	H	$(CH_3)_2NSO_2$	J (92)	EtOH–H_2O	240 dec	$C_{10}H_{12}N_6O_4S$	C, H, N	0.25	1.892	1.806
3x	*n*-C_3H_7CO	CH_3	H (37)	DMF–H_2O	231–233 dec	$C_{13}H_{15}N_5O_3$	C, H, N	4	3.063	
3y	*i*-C_3H_7CO	CH_3	J (66)	MeOH–H_2O	224–225 dec	$C_{13}H_{15}N_5O_3$	C, H, N	5	3.160	
3z	*c*-C_3H_5CO	CH_3	J (95)	DMF–H_2O	261–263 dec	$C_{13}H_{13}N_5O_3$	C, H, N	5	3.157	
3aa	$C_6H_5CH_2CO$	CH_3	J (50)	EtOH	202	$C_{17}H_{15}N_5O_3$	C, H, N	0.1	3.528	
3ab	CF_3CO	CH_3	J (81)	CH_3NO_2	248–249 dec	$C_{11}H_8F_3N_5O_3$	C, H, N	0.2	1.800	
3ac	NH_2CO	CH_3	text (60)	DMF	305–306	$C_{10}H_{10}N_6O_3$	C, H, N[f]	5	3.118	
3ad	$(CH_3)_2NCO$	CH_3	H (58)	CH_3NO_2	235	$C_{12}H_{14}N_6O_3$	C, H, N	1	2.463	
3ae	CH_3OCO	CH_3	H (18)	CH_3NO_2	238–240	$C_{11}H_{11}N_5O_4$	C, H, N	2	2.744	
3af	C_2H_5OCO	CH_3	H (13)	CH_3NO_2	252–254	$C_{12}H_{13}N_5O_4$	C, H, N	10	3.464	
3ag	HOCO	CH_3	text (90)	DMF–H_2O	264 dec	$C_{10}H_9N_5O_4$	C, H, N	0.2	1.721	
3ah	HN_4C	CH_3	J (33)	DMF–H_2O	264	$C_{10}H_7N_9O_2$	C, H, N	1	2.455	
3ai	HON=CCH_3	CH_3	text (38)	DMF–H_2O	245–247	$C_{11}H_{12}N_6O_3$	C, H, N	35	3.985	
3aj	CH_3ON=CCH_3	CH_3	text (63)	DMF–H_2O	271–273	$C_{12}H_{14}N_6O_3$	C, H, N	10	3.463	

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] Activity relative to M&B 22,948 (=1) in the rat PCA test following iv administration. The dose of M&B 22,948 required for 100% inhibition was 0.1 mg/kg. See ref 1b. [c] Calculated by eq 1. [d] N: calcd, 28.1; found, 27.5. [e] N: calcd, 22.3; found, 22.8. [f] N: calcd, 32.1; found, 31.4.

Table III. 2-(Benzyloxy)-*N*-1*H*-tetrazol-5-ylbenzamides 6

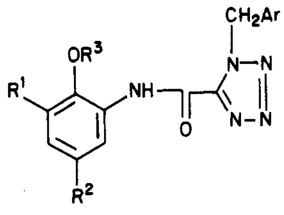


6

no.	R^1	R^2	method	% yield	mp, °C	cryst solvent	formula	anal.[a]
6a	H	H	D	47	265–266 dec	DMF	$C_{15}H_{13}N_5O_2$	H, N; C[b]
6b	H	CH_3	D	54	259–260	DMF–H_2O	$C_{15}H_{15}N_5O_2$	C, H, N
6c	H	Cl	D	20	256–257 dec	DMF–H_2O	$C_{15}H_{12}ClN_5O_2$	C, H, Cl, N
6d	H	CF_3	A	70	248–249	EtOH	$C_{16}H_{12}F_3N_5O_2$	C, H, N
6e	H	$PhCH_2O$	D	50	249–252	DMF	$C_{22}H_{19}N_5O_3$	C, H

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] C: calcd, 61.0; found, 60.0.

Table IV. *N*-Aryl-1-benzyltetrazole-5-carboxamides 7

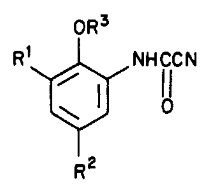


7

no.	R[1]	R[2]	R[3]	Ar	% yield	mp, °C	cryst solvent	formula	anal.[a]
7a	CH_3CO	H	H	p-$CH_3OC_6H_4$	80	155–157	MeCN	$C_{18}H_{17}N_5O_4$	C, H, N
7b	CH_3CO	CH_3	H	C_6H_5	93	183–184	MeCN	$C_{18}H_{17}N_5O_3$	C, H, N
7c	CH_3CO	CH_3	H	p-$CH_3OC_6H_4$	84	182–185	EtOH	$C_{19}H_{19}N_5O_4$	C, H, N
7d	CH_3CO	C_2H_5	H	C_6H_5	71	175–176	CH_3CO_2H	$C_{19}H_{19}N_5O_3$	C, H, N
7e	CH_3CO	C_2H_5	H	p-$CH_3OC_6H_4$	70	143–145	MeCN	$C_{20}H_{21}N_5O_4$	C, H, N
7f	CH_3CO	t-C_4H_9	H	p-$CH_3OC_6H_4$	44	107–109	MeOH	$C_{22}H_{25}N_5O_4$	H, N; C[b]
7g	CH_3CO	F	H	C_6H_5	80	205–208	MeCN	$C_{17}H_{14}FN_5O_3$	C, H, F, N
7h	CH_3CO	F	H	p-$CH_3OC_6H_4$	56	180–182	MeCN	$C_{18}H_{16}FN_5O_4$	C, H, F, N
7i	CH_3CO	Cl	H	p-$CH_3OC_6H_4$	36	201–203	MeCN	$C_{18}H_{16}ClN_5O_4$	C, H, Cl, N
7j	CH_3CO	Br	H	p-$CH_3OC_6H_4$	59	202–204	MeCN	$C_{18}H_{16}BrN_5O_4$	H, Br, N; C[c]
7k	CH_3CO	CH_3O	H	p-$CH_3OC_6H_4$	75	158–161	MeCN-Et_2O	$C_{19}H_{19}N_5O_5$	C, H, N
7l	CH_3CO	CN	H	p-$CH_3OC_6H_4$	42	240–242	MeCN	$C_{19}H_{16}N_6O_6$	C, H, N
7m	CH_3CO	NO_2	H	p-$CH_3OC_6H_4$	57	221–223	MeCN	$C_{18}H_{16}N_6O_6$	C, H, N
7n	CH_3CO	CH_3SO_2	H	p-$CH_3OC_6H_4$	39	234–237	MeCN	$C_{19}H_{19}N_5O_6S$	H, N; C[d]
7o	CH_3CO	CH_3CO	H	p-$CH_3OC_6H_4$	57	172–175	MeCN	$C_{20}H_{19}N_5O_5$	H; C; N[e]
7p	CH_3CO	$NHCOCH_3$	H	p-$CH_3OC_6H_4$	10	170		$C_{20}H_{20}N_6O_5$	H; C; N[f]
7q	C_2H_5CO	CN	H	p-$CH_3OC_6H_4$	72	214–216	MeCN	$C_{20}H_{18}N_6O_4$	H, N; C[g]
7r	CH_3O	H	$C_6H_5CH_2$	C_6H_5	72	145–147	EtOH	$C_{23}H_{21}N_5O_3$	C, H, N
7s	CH_3O	CH_3	$C_6H_5CH_2$	C_6H_5	4	179–181	EtOH	$C_{24}H_{23}N_5O_3$	C, H, N
7t	CH_3O	C_2H_5	$C_6H_5CH_2$	C_6H_5	50	150–151	$MeCO_2Et$	$C_{25}H_{25}N_5O_3$	H, N; C[h]
7u	H	H	$C_6H_5CH_2$	C_6H_5	50	140–142	EtOH	$C_{22}H_{19}N_5O_2$	C, H, N
7v	H	$(CH_3)_2NSO_2$	H	p-$CH_3OC_6H_4$	66	215 dec	EtOH-H_2O	$C_{18}H_{20}N_6O_5S$	C, H, N
7w	n-C_3H_7CO	CH_3	H	C_6H_5	78	166–169	$CHCl_3$-EtOH	$C_{20}H_{21}N_5O_3$	C, H, N
7x	i-C_3H_7CO	CH_3	H	p-$CH_3OC_6H_4$	79	144–145	$CHCl_3$-EtOH	$C_{21}H_{23}N_5O_3$	C, H, N
7y	c-C_3H_5CO	CH_3	H	p-$CH_3OC_6H_4$	64	180–182	C_6H_6	$C_{21}H_{21}N_5O_4$	H, N; C[i]
7z	$C_6H_5CH_2CO$	CH_3	H	p-$CH_3OC_6H_4$	62	202–205	$CHCl_3$-MeOH	$C_{25}H_{23}N_5O_4$	C, H, N
7aa	CF_3CO	CH_3	H	p-$CH_3OC_6H_4$	85	122–124	petroleum (100–120 °C)	$C_{19}H_{16}F_3N_5O_4$	H, F, N; C[j]
7ab	$(CH_3)_2NCO$	CH_3	H	C_6H_5	64	224–225	$CHCl_3$-MeOH	$C_{19}H_{20}N_6O_3$	C, H, N
7ac	CH_3OCO	CH_3	H	C_6H_5	70	168–170	$CHCl_3$-MeOH	$C_{18}H_{17}N_5O_4$	H, N; C[k]
7ad	C_2H_5OCO	CH_3	H	C_6H_5	66	189–191	$CHCl_3$-EtOH	$C_{19}H_{19}N_5O_4$	C, H, N
7ae	HN_4C	CH_3	H	p-$CH_3OC_6H_4$	24	220	DMF-H_2O	$C_{18}H_{17}N_9O_3$	C, H, N
7af	p-$CH_3OC_6H_4$-CH_2NHCO	CH_3	H	p-$CH_3OC_6H_4$	57	210	$CHCl_3$-MeOH	$C_{26}H_{26}N_6O_5$	C, H, N

[a] Analytical results were within ±0.4% of the theoretical value for all elements listed, except as shown in subsequent footnotes. [b] C: calcd, 62.4; found, 61.8. [c] C: calcd, 48.4; found 49.0. [d] C: calcd, 51.2; found, 50.4. [e] C: calcd, 58.7; found, 58.2. N: calcd, 17.1; found, 16.5. [f] C: calcd, 56.3; found, 55.4. N: calcd, 20.2; found, 19.5. [g] C: calcd, 59.1; found, 59.6. [h] C: calcd, 67.7; found, 67.0. [i] C: calcd, 61.9; found, 61.2. [j] C: calcd, 52.4; found, 51.9. [k] C: calcd, 58.9; found, 58.1.

Table V. Cyanoformanilides 9



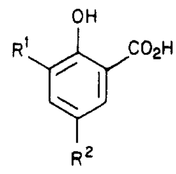
9

no.	R[1]	R[2]	R[3]	% yield	mp, °C	formula	anal.[a]
9a	CH_3CO	H	H	50	139–141	$C_{10}H_8N_2O_3$	na[b]
9b	CH_3CO	CH_3	H	48	155	$C_{11}H_{10}N_2O_3$	C, H, N
9c	CH_3CO	C_2H_5	H	56	125–127	$C_{12}H_{12}N_2O_3$	H, N; C[c]
9d	CH_3CO	n-C_3H_7	H	25	124–125	$C_{13}H_{14}N_2O_3$	H, N; C[d]
9e	C_2H_5CO	CH_3	H	37	145–150 dec	$C_{12}H_{12}N_2O_3$	na[b]
9f	C_2H_5CO	C_2H_5	H	40	138–140	$C_{13}H_{14}N_2O_3$	C, H, N
9g	CH_3O	CH_3	$C_6H_5CH_2$	45	94–95	$C_{17}H_{16}N_2O_3$	na[b]
9h	CH_3O	Br	$C_6H_5CH_2$	23	85 dec	$C_{16}H_{13}BrN_2O_3$	C, H, Br, N

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] The sample was pure by TLC and was used without analysis. [c] C: calcd, 62.1; found, 62.8. [d] C: calcd, 63.4; found, 62.9.

preparations the *N*-benzyl group was removed with aluminum chloride (method H). For some derivatives it was necessary to protect the phenolic function as a benzyl ether (7; Ar = Ph, R^3 = CH_2Ph) and subsequently both *O*- and *N*-benzyl groups were removed by catalytic reduction (method I). The *N*-(*p*-methoxybenzyl) group is an alternative protecting group that is conveniently removed by hot trifluoroacetic acid, and this method was successful for both 1-(*p*-methoxybenzyl) derivatives (7; Ar = 4-$CH_3OC_6H_4$, R^3 = H) (method J) and 2-(*p*-methoxybenzyl)

Table VI. 2-Hydroxybenzoic Acids 4

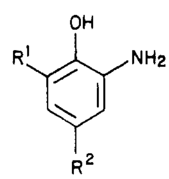


4

no.	R^1	R^2	% yield	cryst solvent	mp, °C	formula	anal.[a]
4a	CH_3CO	H	57	H_2O	135–136	$C_9H_8O_4$	C, H
4b	CH_3CO	C_2H_5	67	CCl_4	113–116	$C_{11}H_{12}O_4$	C, H
4c	CH_3CO	n-C_3H_7	56	CCl_4-petrol	95–96	$C_{12}H_{14}O_4$	C, H
4d	CH_3CO	i-C_4H_9	34	$MeCO_2Et$	131–133	$C_{13}H_{16}O_4$	na[b]
4e	CH_3CO	t-C_4H_9	39	$MeCO_2Et$	159–161	$C_{13}H_{16}O_4$	C, H
4f	CH_3CO	F	9	$EtOH-H_2O$	158–161	$C_9H_7FO_4$	C, H
4g	CH_3CO	NO_2	63	H_2O	208–209	$C_9H_7NO_6$	C, H, N
4h	CH_3CO	$NHCOCH_3$	44	CH_3CO_2H	256–258 dec	$C_{11}H_{11}NO_5$	C, H, N
4i	C_2H_5CO	C_2H_5	45	CCl_4	135–136	$C_{12}H_{14}O_4$	C, H
4j	CH_3O	C_2H_5	42	$CH_3CO_2H-H_2O$	141–142	$C_{10}H_{12}O_4$	C, H
4k	CH_3O	t-C_4H_9	74	HCO_2H	196–199	$C_{12}H_{16}O_4$	C, H
4l	CH_3O	CN	41	CH_3OH	228 dec	$C_9H_7NO_4$	na[b]
4m	CH_3O	CHO	37	$EtOH-H_2O$	252–256	$C_9H_8O_5$	na[b]
4n	HO	t-C_4H_9	38	$EtOH-H_2O$	217–219	$C_{11}H_{14}O_4$	C, H

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed. [b] The sample was not analyzed but was pure by TLC and NMR and was used immediately in the next stage.

Table VII. 2-Aminophenols 10



10

no.	R^1	R^2	% yield	mp, °C	formula	anal.[a]
10a	CH_3CO	CH_3	48	55–57	$C_9H_{11}NO_2$	C, H, N
10b	CH_3CO	C_2H_5	60	48–51	$C_{10}H_{13}NO_2$	C, H, N
10c	CH_3CO	n-C_3H_7	77	42–43	$C_{11}H_{15}NO_2$	C, H, N
10d	CH_3CO	F	99	113–114	$C_8H_8FNO_2$	C, H, F, N
10e	CH_3CO	Br	31	99–102	$C_8H_8BrNO_2$	C, H, Br, N
10f	CH_3CO	CN	65	152–156	$C_9H_8N_2O_2$	H, N; C[b]
10g	CH_3CO	NO_2	72	172–174	$C_8H_8N_2O_4$	C, H, N
10h	CH_3CO	CH_3CO	49	156–160 dec	$C_{10}H_{11}NO_3$	H, N; C[c]
10i	C_2H_5CO	CN	70	144–146	$C_{10}H_{10}N_2O_2$	H, N; C[d]
10j	H	$(CH_3)_2NSO_2$	68	156–160	$C_8H_{12}N_2O_3S$	C, H, N
10k	n-C_3H_7CO	CH_3	77	79–81	$C_{11}H_{15}NO_2$	C, H, N
10l	i-C_3H_7CO	CH_3	89	41–42	$C_{11}H_{15}NO_2$	C, H, N
10m	c-C_3H_5CO	CH_3	74	79–80	$C_{11}H_{13}NO_2$	C, H, N
10n	$C_6H_5CH_2CO$	CH_3	74	74–76	$C_{15}H_{15}NO_2$	H, N; C[e]
10o	CF_3CO	CH_3	57	87–88	$C_9H_8F_3NO_2$	C, H, F, N
10p	$(CH_3)_2NCO$	CH_3	51	108	$C_{10}H_{14}N_2O_2$	C, H, N
10q	CH_3OCO	CH_3	58	65–68	$C_9H_{11}NO_3$	H, N; C[f]
10r	C_2H_5OCO	CH_3	89	92–93	$C_{10}H_{13}NO_3$	C, H, N
10s	NH_4C	CH_3	79	195	$C_8H_9N_5O$	C, H, N
10t	p-$CH_3OC_6H_4CH_2NHCO$	CH_3	56	116–116.5	$C_{16}H_{18}N_2O_3$	C, H, N

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed except as shown in subsequent footnotes. [b] C: calcd, 61.4; found, 60.8. [c] C: calcd, 62.2; found, 61.1. [d] C: calcd, 63.2; found, 62.0. [e] C: calcd, 74.7; found, 73.9. [f] C: calcd, 59.7; found, 58.3.

derivatives (**8**; Ar = 4-$CH_3OC_6H_4$) (method K).

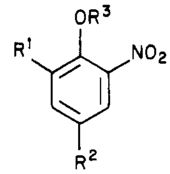
N-Aryl-1-benzyltetrazole-5-carboxamide intermediates (**7**) are shown in Table IV, and these, and also the *N*-aryl-2-benzyltetrazole-5-carboxamides (**8**), were prepared by reaction of an aromatic amine with the appropriately substituted benzyltetrazole-5-carbonyl chloride. These acid chlorides were formed by treatment of potassium 1- or 2-benzyltetrazole-5-carboxylates (**13** and **14**) with oxalyl chloride and were used immediately without characterization.

In the course of our studies we have found two preparative routes to the tetrazole-5-carboxamides (**3**) that do not require protection of the tetrazole ring (methods L–N). In one approach, a 2-aminophenol (**10**) was condensed with carbonyl dicyanide to give a cyanoformanilide (**9**; R^3 = H) (Table V), which upon treatment with aluminum azide ($AlCl_3$ + NaN_3) in tetrahydrofuran gave the desired product (**3**) (method L). A variation of this approach involved protection of the phenolic function as a benzyl ether (**9**; R^3 = CH_2Ph) and subsequent removal by catalytic hydrogenation (method M).

The most direct route to the 1*H*-tetrazole-5-carboxamides (**3**) involves activation of the dipotassium salt of tetrazole-5-carboxylic acid (**11**) using Vilsmeier's reagent ($Me_2N^+{=}CHOPOCl_2{\cdot}Cl^-$)[10] followed by reaction of the

(10) Meth-Cohn, O.; Tarnowski, B. *Adv. Heterecycl. Chem.* **1982**, *31*, 207.

Table VIII. 2-Nitrophenols and (2-Nitrophenyl)benzyl Ethers 14

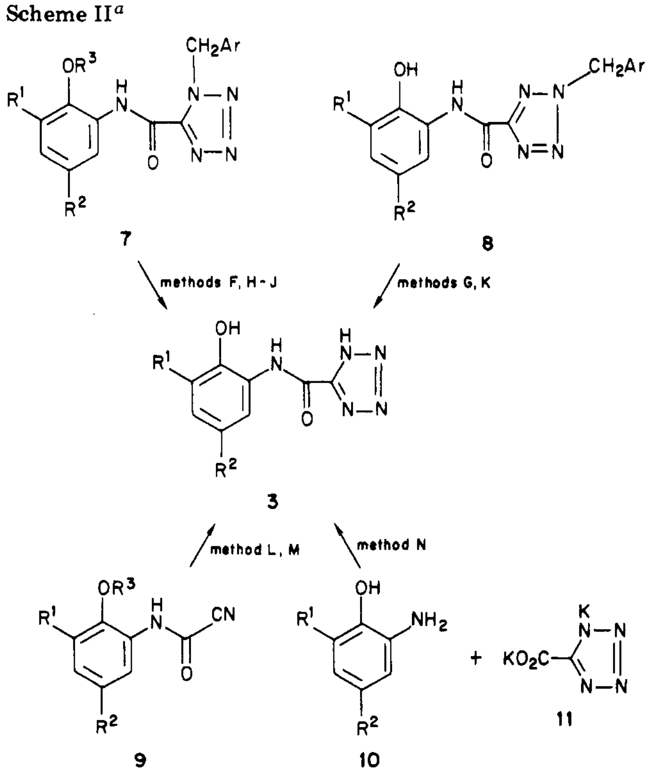


14

no.	R^1	R^2	R^3	% yield	mp or bp, °C	formula	anal.[a]
14a	CH_3CO	C_2H_5	H	44	118–120	$C_{10}H_{11}NO_4$	C, H, N
14b	CH_3CO	n-C_3H_7	H	42	67–68	$C_{11}H_{13}NO_4$	C, H, N
14c	CH_3CO	t-C_4H_9	H	2	80–81	$C_{12}H_{15}NO_4$	C, H, N
14d	CH_3CO	F	H	46	87–89	$C_8H_6FNO_4$	C, H, F, N
14e	CH_3CO	CN	H	59	142–143	$C_9H_6N_2O_4$	C, H, N
14f	CH_3CO	CH_3SO_2	H	50	189–191	$C_9H_9NO_6S$	C, H, N, S
14g	CH_3CO	CH_3CO	H	51	104–105	$C_{10}H_9NO_5$	H; C; N[b]
14h	C_2H_5CO	C_2H_5	H	25	86–87	$C_{11}H_{13}NO_4$	C, H, N
14i	C_2H_5CO	CN	H	40	90	$C_{10}H_8N_2O_4$	C, H, N
14j	CH_3O	C_2H_5	H	23	60	$C_9H_{11}NO_4$	C, H, N
14k	H	$(CH_3)_2NSO_2$	H	55	114–116	$C_8H_{10}N_2O_5S$	C, H, N
14l	n-C_3H_7CO	CH_3	H	55	72–74	$C_{11}H_{13}NO_4$	C, H, N
14m	i-C_3H_7CO	CH_3	H	76	75–77	$C_{11}H_{13}NO_4$	C, H, N
14n	c-C_3H_5CO	CH_3	H	68	122–125	$C_{11}H_{11}NO_4$	H, N; C[c]
14o	$C_6H_5CH_2CO$	CH_3	H	81	80–82	$C_{15}H_{13}NO_4$	C, H, N
14p	CF_3CO	CH_3	H	44	94–96	$C_9H_6F_3NO_4$	C, H, N
14q	$(CH_3)_2NCO$	CH_3	H	57	160–162	$C_{10}H_{12}N_2O_4$	C, H, N
14r	CH_3OCO	CH_3	H	24	145–147	$C_9H_9NO_5$	C, H, N
14s	C_2H_5OCO	CH_3	H	70	96–99	$C_{10}H_{11}NO_5$	C, H, N
14t	HN_4C	CH_3	H	42	243–245 dec	$C_8H_7N_5O_3$	C, H, N
14u	p-$CH_3OC_6H_4CH_2NHCO$	CH_3	H	16	170–173	$C_{16}H_{16}N_2O_5$	C, H, N
14v	CH_3O	H	$C_6H_5CH_2$	93	178–181 (0.2 mm)	$C_{14}H_{13}NO_4$	C, H, N
14w	CH_3O	CH_3	$C_6H_5CH_2$	70	173–175 (0.4 mm)	$C_{15}H_{15}NO_4$	C, H, N
14x	CH_3O	C_2H_5	$C_6H_5CH_2$	62	184–186 (0.1 mm)	$C_{16}H_{17}NO_4$	C, H, N
14y	CH_3O	Br	$C_6H_5CH_2$	81	74–76	$C_{14}H_{12}BrNO_4$	H, Br, N; C[d]

[a] Analytical results were within ±0.4% of the theoretical values for all elements listed, except as shown in subsequent footnotes. [b] C: calcd, 53.8; found, 52.5. N: calcd, 6.3; found, 7.2. [c] C: calcd, 59.7; found, 59.2. [d] C: calcd, 49.7; found, 49.0.

Scheme II[a]

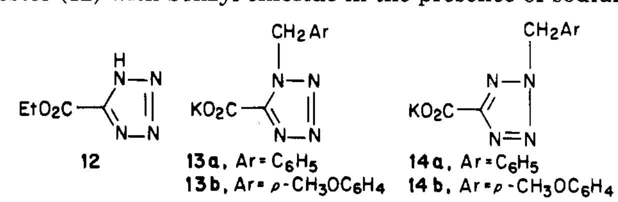


[a] Reagents: (methods F and G) H_2-Pd-C; (method H) $AlCl_3$; (method I) H_2-Pd-C; (methods J and K) CF_3CO_2H; (method L) $AlCl_3$-NaN_3; (method M) (i) $AlCl_3$-NaN_3, (ii) H_2-Pd-C; (method N) Me_2N^+=$CHCl^-OPOCl_2$.

active intermediate with an aromatic amine (**10**) (method N).

Aromatic amines (**10**) were obtained by reduction of the corresponding nitrobenzene; novel amines are listed in Table VII. Novel nitro derivatives, which were prepared by standard procedures, are listed in Table VIII.

Ethyl 1*H*-tetrazole-5-carboxylate (**12**),[11] which we have found convenient to prepare by treating a pyridine solution of ethyl cyanoformate with sodium azide and trifluoroacetic acid, is converted to the dipotassium salt (**11**) using aqueous ethanolic potassium hydroxide. Treatment of the ester (**12**) with benzyl chloride in the presence of sodium



hydride gives a mixture of the 1- and 2-benzyl esters, which were not isolated but were converted to the potassium salts (**13a** and **14a**) with aqueous ethanolic potassium hydroxide and separated by fractional crystallization. A similar procedure gave the 1- and 2-(p-methoxybenzyl) salts (**13b** and **14b**). Alternative routes to the 1-benzyl and 1-(p-methoxybenzyl) salts (**13a** and **13b**) have recently been described.[12]

Results

The role of hydrogen bonding in stabilizing a planar conformation of the azapurinone (**1**)[1,2] prompted us to

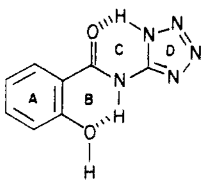
(11) Behringer, H.; Kohl, K. *Ber.* **1956**, *89*, 2648.
(12) (a) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Bell, S. C.; Capetola, R. J. *J. Med. Chem.* **1981**, *24*, 742. (b) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* **1981**, *24*, 748.

Table IX. Parameter Values[a] Used in the Derivation of Equations 1–3

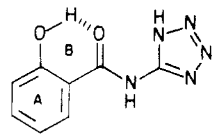
subst	ES	MR	π	subst	ES	MR	π
H	0.0	1.03	0.0	NO_2	−2.52	7.36	−0.28
CH_3	−1.24	5.65	0.56	CN	−0.51	6.33	−0.57
C_2H_5	−1.31	10.30	1.02	CF_3	−2.40	5.02	0.88
n-C_3H_7	−1.60	14.96	1.55	$NHCOCH_3$	−2.98[b]	14.93	−0.97
i-C_4H_9	−2.17	19.59	2.03	CH_3S	−1.07	13.82	0.61
t-C_4H_9	−2.78	19.62	1.98	CH_3SO_2	−2.63[b]	13.49	−1.63
F	−0.46	0.92	0.14	$(CH_3)_2NSO_2$	−2.62[b]	21.88	−0.78
Cl	−0.97	6.03	0.71	HO	−0.55	2.85	−0.67
Br	−1.16	8.88	0.86	C_6H_5	−3.82	25.36	1.96
CH_3O	−0.55	7.87	−0.02	CH_3CO	−2.84[b]	11.18	−0.55

[a] Unless otherwise stated, parameter values were taken from the Pomona College Medicinal Chemistry Parameter Files.[18] [b] Calculated by Wooldridge[16] following the method of Charton.[19]

consider some hydrogen-bonded analogues. In particular our interest was directed toward 2-hydroxy-N-1H-tetrazol-5-ylbenzamide (**15**), which in the hydrogen-bonded



15



16

form shown in structure **15** has important similarities with compound **1**. In addition to the desirable acidic proton on the tetrazole ring, coplanarity between the phenolic ring (ring A) and the amide function is favored by hydrogen bonding (ring B), and additional hydrogen bonding (ring C) of the tetrazole fragment could mimic the pyrimidine ring of the azapurinone (**1**). Alternative hydrogen-bonded forms of the molecule (e.g., **16**) are possible, and we do not wish to imply that structure **15** is necessarily the preferred geometry. However, the relationship between the hypothetical hydrogen-bonded structure (**15**) and the azapurinone (**1**) was the basis of the rationale that led to its synthesis and testing as a potential antiallergic compound.

The novel tetrazole derivative **15** (=**2y**) (Table I) was found to have one-tenth of the activity of the azapurinone (**1**) intravenously in the rat PCA test. This observation encouraged the examination of a series of derivatives, and the results of substitution at positions 3 and 5 are shown in Table I (compounds **2a–aq**). The 3-acetyl (**2a**) and 3-methoxy (**2p**) derivatives of compound **15** showed a significant improvement in potency being equiactive with the azapurinone (**1**).

The effect of modification of the amide and tetrazole fragments of structure **15** was also investigated. The N-methyltetrazole derivatives had less than one-tenth of the activity of the free tetrazole (**2y**), suggesting an important contribution by the acidic tetrazole proton. Furthermore, the v- and s-triazole analogues of compound **2y** had activity less than one-twentieth that of the tetrazole—a result that may be attributable to the weaker acidity of triazoles relative to tetrazoles.[13] These results suggested that manipulation of the tetrazole fragment was undesirable, and attention was directed toward the amide function. N-Methylation of the amido group of compound **2y** resulted in a reduction of activity to one-tenth of that of the parent system (**2y**), and replacement of the amide function by a number of other functions resulted in either loss or deterioration of activity. However, a significant improvement in activity was achieved when the amide group in compound **2y** was reversed to give N-(2-hydroxyphenyl)-1H-tetrazole-5-carboxamide (**3v**) (Table II). Compound **3v** is 10 times more potent than its isomer **2y**. On the basis of the enhancement of activity by a 3-acetyl substituent in the isomeric 2-hydroxy-N-1H-tetrazol-5-ylbenzamides (**2**) (Table I), the 3-acetyl derivative (**3a**) (Table II) was synthesized and found to have 10 times the potency of compound **3v**. In fact, compound **3a** is 100 times more active than the original lead (**2y**) and 10 times more active than the azapurinone (**1**). This result led to the synthesis of a series of analogues of compound **3v**. The results of modification at positions 3 and 5 are shown in Table II (compounds **3a–aj**).

The high potency of several N-(3-acetyl-2-hydroxyphenyl)-1H-tetrazole-5-carboxamides (**3**; $R^1 = CH_3CO$) made this series of special interest, and particular attention was paid to the preparation of a series of 5-substituted derivatives (compounds **3a–n**) (Table II) from which a short list of candidates for further evaluation as clinically useful antiallergic agents could be selected.

On the basis of broader pharmacological evaluation, compound **3f** was selected for further development. Compound **3f** has an ID_{50} value in the rat PCA test of 0.004 mg/kg, iv, and is approximately 13 times more potent than the azapurinone (**1**) (ID_{50} = 0.05 mg/kg, iv) and 130 times more potent that DSCG (ID_{50} = 0.5 mg/kg, iv). Upon oral administration compound **3f** has a very flat dose–response curve with an ID_{50} value of approximately 0.16 mg/kg.

Structure–Activity Relationships

Using data for 64 derivatives described in Tables I and II (compounds **2a–ao**, **3a–w**), we have derived eq 1 to

$$\log (M_r I) = 1.657 + 0.940\ (\pm 0.138)[3\text{-}CH_3CO] + 1.031\ (\pm 0.226)[3\text{-}C_2H_5CO] + 0.765\ (\pm 0.158)[3\text{-}CH_3O] + 0.901\ (\pm 0.122)[NHCOCN_4H] + 0.287\ (\pm 0.055)ES \quad (1)$$

$$n = 64,\ r = 0.889,\ s = 0.430,\ F = 43.65,\ p < 0.00001$$

describe the intravenous activity in the rat PCA test. Equation 1 is statistically highly significant: the figures in parentheses are for construction of 95% confidence limits, n is the number of data points, r is the correlation coefficient, s is the standard deviation from the regression equation, F is the F statistic, and p is the probability of the relationship arising by chance. The function $\log (M_r I)$, where M_r is the molecular weight of the test compound and I is its activity relative to the reference compound **1**, expresses the biological activity in molar terms. Equation 1 is a mixed Hansch/modified Free–Wilson linear multiple-regression model[14] and describes the effect of structural modification at three positions, each of which merits further discussion.

At position 3 of structures **2** and **3** (substituent R^1), a limited number of functional groups are of biological sig-

(13) Grimmett, M. R. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 4, p 365.

(14) Kubinyi, H. *J. Med. Chem.* **1976**, *19*, 587.

nificance, and this situation is suited to description by Free–Wilson group increments. In deriving eq 1, substituents at position 3 have been restricted to functional groups (R^1) that are represented by five or more test compounds (i.e., R^1 = H, CH_3CO, C_2H_5CO, CH_3O). Inspection of eq 1 shows that group increments for 3-CH_3CO, 3-C_2H_5CO, and 3-CH_3O substituents are large and highly significant. The ketone functions effectively increase potency (*I*) by a factor of 10, with a methoxy group making a slightly smaller contribution.

We believe that this high group activity may be attributable either to hydrogen bonding between the phenolic OH and the adjacent ketone or ether group or to chelation of a metal ion by the same substituents. This view is supported by the observation of even greater potency for acetoxime derivatives (compounds **2ap**, **2aq**, **3ai**, and **3aj**). The possible relationship between chelating activity and antiallergic potency has recently been discussed in a review.[3] A description of the chelating properties of some of these molecules will be the subject of a separate paper.[15]

Structural variation of the tetrazole fragment is limited to two groups. In eq 1 this difference is described by a Free–Wilson group increment for the tetrazole-5-carboxamide fragment [$NHCOCN_4H$] with the isomeric *N*-tetrazol-5-yl carbamoyl group [$CONHCN_4H$] taken as reference substituent. In eq 1 the relative contribution of the tetrazole-5-carboxamide group is highly significant. Reversal of the amide linkage (i.e., 2 → 3) makes a substantial contribution to activity although the reason for the enhancement is not clear. We have produced evidence in the previous section to suggest that the acidity of the tetrazole group may be related to its biological activity and the relatively greater acidity of the tetrazole-5-carboxamide function [$NHCOCN_4H$] may be significant. The pK_a values for the tetrazole groups in the isomers **2g** and **3f** are 4.20 ± 0.02 and 2.36 ± 0.06, respectively, at 25 °C. Both types of tetrazole function will be ionized at physiological pH. The difference in activity may well be associated with the significantly different charge distribution in the two types of tetrazole anion [$NHCOCN_4^-$ and $CONHCN_4^-$]. The charge distribution is, of course, closely related to the stability of the anions and, therefore, to the pK_a values. The pK_a values of the associated phenolic functions are 7.10 ± 0.02 (**2g**) and 8.69 ± 0.02 (**3f**). If phenolic acidity was related to the biological activity, then a variation of activity with the electronic structure of the substituents R^2 (**2** and **3**) would be expected but is not observed.

The *N*-phenyl-1*H*-tetrazole-5-carboxamides (**3**) are related to the *N*-phenyloxamic acids and esters, some derivatives of which are also potent antiallergic agents.[12] The electronic similarity between the carboxylate and tetrazole anions is clearly of significance in this context.[3]

A much wider range of substituents is significant at position 5 of structures **2** and **3** (substituent R^2), and this position is well suited to investigation by the Hansch method. In planning the synthesis of the derivatives in Tables I and II, substituents were selected to give a wide range of values of structural parameters (π, π^2, MR, *F*, *R*, ES) and to minimize interparameter correlation (see Chart I).[16] Note that ES is referenced to H = 0.[17] Equation 1 demonstrates a significant relationship between activity and the adjusted Taft steric parameter ES (t_{ES} = 5.215; $p < 0.0001$). As might be expected from the high negative correlation between ES and molar refractivity (MR) (Chart I), a significant relationship is also obtained using MR (eq 2; t_{MR} = 3.991; p = 0.0002). We interpret these relationships to mean that a small group is required at position 5. Bulky groups possibly inhibit binding of the planar molecules at the receptor. We have also explored the use of more sophisticated steric parameters, including Verloop's Sterimol parameters, but on balance we believe that a closer scrutiny of the shape of the substituents R^2 leads to overinterpretation of the results.

Chart I

Squared Correlation Matrix (r^2) for Parameters Investigated in the Correlation Study (64 Compounds)

	π^2	MR	ES	F	R
π	0.181	0.052	0.000	0.343	0.066
π^2		0.573	0.349	0.089	0.009
MR			0.629	0.013	0.013
ES				0.016	0.086
F					0.067

$$\log (M_rI) = 1.580 + 0.934\ (\pm 0.148)[3\text{-}CH_3CO] + 1.071\ (\pm 0.242)[3\text{-}C_2H_5CO] + 0.791\ (\pm 0.169)[3\text{-}CH_3O] + 0.928\ (\pm 0.131)[NHCOCN_4H] - 0.039\ (\pm 0.010)MR \quad (2)$$

$$n = 64,\ r = 0.871,\ s = 0.462,\ F = 36.34,\ p < 0.00001$$

Although there is no evidence of correlation with π, *F*, and *R*, a relationship between activity and π^2 has been found (eq 3; t_{π^2} = 3.466; p = 0.001). This probably arises from a chance correlation between π^2 and substituent size (see Chart I), but we cannot eliminate the possibility that the substituent R^2 has an optimum requirement of $\pi = 0$.

$$\log (M_rI) = 1.331 + 1.023\ (\pm 0.154)[3\text{-}CH_3CO] + 1.145\ (\pm 0.248)[3\text{-}C_2H_5CO] + 0.851\ (\pm 0.173)[3\text{-}CH_3O] + 0.896\ (\pm 0.136)[NHCOCN_4H] - 0.176\ (\pm 0.051)\pi^2 \quad (3)$$

$$n = 64,\ r = 0.863,\ s = 0.474,\ F = 33.80,\ p < 0.00001$$

It is important to note that although a consideration of possible modes of hydrogen bonding of the benzamidotetrazole (e.g., **15** or **16**) was the reason for undertaking the initial investigation of this class of molecules, we have been unable to obtain spectroscopic evidence to support or reject the original hypothesis and we do not claim that biological activity is necessarily associated with any particular mode of intramolecular hydrogen bonding. The general significance of hydrogen bonding in antiallergic molecule has been discussed elsewhere.[3]

Experimental Section

Biological Methods. In screening this series, the determination of ID_{50}'s in the rat passive cutaneous anaphylactic (PCA) reaction was less practicable because the variability of response would have necessitated the use of large numbers of animals to achieve meaningful results. Direct comparison with M&B 22,948 (Zaprinast) (**1**)[1] for ability to cause 100% inhibition of the rat PCA reaction following iv administration was more satisfactory and reproducible to within ±25%.[1] The relative activities (*I*) are given in Tables I and II.

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 1–20 dilution of *Nippostrongylus brasiliensis* antiserum. After 48 h 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

(15) Bowden, K.; Sharma, R. K., unpublished results. Sharma, R. K. Ph.D. Thesis, University of Essex, 1979.
(16) Wooldridge, K. R. H. *Eur. J. Med. Chem.* **1980**, *15*, 63.
(17) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91.
(18) Hansch, C.; Leo, A. J. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Wiley: New York, 1979.
(19) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615.

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 3% aqueous triethanolamine were injected intravenously in groups of rats (at least two at each dose level) immediately before administration of the allergen and dye. The potency (*I*) relative to M&B 22,948 (1) (Zaprinast) was assessed by comparison with groups of rats treated with the graded doses of standard.

Statistics. Correlations were derived on a Wang 2200 MVP computer with a multiple-parameter regression analysis program written in BASIC.[20]

Chemical Methods. Melting points were determined on an Electrothermal instrument and are uncorrected. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.[21] All structural assignments were consistent with IR and NMR spectra.

For each general synthetic procedure a representative example of the experimental details is given.

Preparation of *N*-1*H*-Tetrazol-5-ylbenzamides 2 and 6 (Tables I and III). Method A. 3-Acetyl-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide (2a). 3-Acetylsalicylic acid (**4a**) (3.0 g, 0.017 mol) and dicyclohexylcarbodiimide (3.8 g, 0.019 mol) were stirred in dry pyridine (30 mL) for 1 h. Anhydrous 5-aminotetrazole (1.6 g, 0.019 mol) was then added and the mixture stirred at 60 °C for 20 h. After cooling and filtration, the pyridine was removed under reduced pressure and the solid residue dissolved in 2 N ammonium solution with gentle heating. Undissolved solid was removed by filtration, and the cooled filtrate was acidified to pH 1 with concentrated HCl. The solid product was collected, boiled with 90% HCO_2H (5 min), and finally recrystallized from DMF–H_2O to give 2.0 g (49%) of **2a**.

Method B. 2-(Benzyloxy)-*N*-1*H*-tetrazol-5-ylbenzamide (6a). 2-(Benzyloxy)benzoic acid[22] (5.85 g, 0.025 mol) and anhydrous 5-aminotetrazole (2.18 g, 0.25 mol) were dissolved in dry pyridine (80 mL). Silicon tetrachloride (1.5 mL) was added dropwise, and stirring at room temperature was then continued (24 h). The mixture was poured onto iced water (300 mL) and stirred for 1 h. The solid product was collected, washed with water, and recrystallized from DMF to give 3.64 g (47%) of **6a**.

Method C. 3-Acetyl-2-hydroxy-5-methyl-*N*-1*H*-tetrazol-5-ylbenzamide (2b). 3-Acetyl-5-methylsalicylic acid[23] (1.94 g, 0.01 mol) was converted to the acid chloride by a standard procedure using $SOCl_2$. The acid chloride was dissolved in dry toluene (30 mL), anhydrous 5-aminotetrazole (1.7 g, 0.02 mol) was added, and the mixture was heated under reflux with stirring (18 h). After cooling, the mixture was diluted with light petroleum (bp 60–80 °C) (30 mL). The solid product was collected, stirred with 2 N HCl (30 mL) (30 min), washed with water, and recrystallized from DMF–CH_3CO_2H to give 1.2 g (46%) of **2b**.

Method D. 2-Hydroxy-5-methoxy-*N*-1*H*-tetrazol-5-ylbenzamide (2ae). A mixture of 5-methoxysalicylic acid[24] (12.0 g, 0.07 mol), anhydrous 5-aminotetrazole (13.6 g, 0.16 mol), dry toluene (200 mL), and PCl_3 (5.2 mL) was heated under reflux with stirring (18 h). After cooling, the solid product was collected, washed with 2 N HCl (200 mL), extracted with hot EtOH (200 mL), and recrystallized from DMF–H_2O to give 2.1 g (12.5%) of **2ae**.

Method E. 2-Hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide (2y). 2-(Benzyloxy)-*N*-1*H*-tetrazol-5-ylbenzamide (**6a**) (3.6 g, 0.012 mol) was added to *N*-methylpyrrolidin-2-one (130 mL), and 2 N NaOH was added dropwise with vigorous shaking until solution formed. The solution was then catalytically hydrogenated at 25 °C (70 psi) with 5% Pd on charcoal. The solvent was removed under reduced pressure and the residue treated with H_2O (175 mL). After adjustment to pH 4.5 (concentrated HCl), the solid product was collected, washed with H_2O and EtOH, and recrystallized from CH_3CO_2H to give 2.2 g (87%) of **2y**.

3-Acetyl-2-hydroxy-5-nitro-*N*-1*H*-tetrazol-5-ylbenzamide (2k). Compound **2a** (6.0 g, 0.024 mol) was nitrated with 70% HNO_3 (1.62 mL, 0.029 mol) in concentrated H_2SO_4 (30 mL) at 0 °C. Conventional workup and recrystallization from HCO_2H gave 5.0 g (63%) of **2k**.

3-Acetyl-2-hydroxy-5-sulfamoyl-*N*-1*H*-tetrazol-5-ylbenzamide (2l). Compound **2a** (3.0 g, 0.012 mol) was dissolved in chlorosulfonic acid (21 mL). After standing at room temperature (24 h), the mixture was added to iced water (150 mL). The precipitate was collected and added to concentrated ammonia solution (25 mL). Conventional workup and recrystallization from DMF–H_2O gave 0.2 g (5%) of **2l**.

2-Hydroxy-5-(methylsulfonyl)-*N*-1*H*-tetrazol-5-ylbenzamide (2aj). Compound **2ai** (1.26 g, 0.005 mol) in glacial CH_3CO_2H (10 mL) was stirred with 30% H_2O_2 (3 mL) at 100 °C (20 h). The cold mixture was poured onto water (70 mL), and the solid product was collected and recrystallized from glacial acetic acid to give 0.75 g (53%) of **2aj**.

5-(*N*,*N*-Dimethylsulfamoyl)-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide (2ak). Compound **2y** (2.05 g, 0.01 mol) was slowly added to chlorosulfonic acid (15 mL), and the mixture was allowed to stand at room temperature (19 h). The solution was then poured onto iced water (100 mL). The resulting precipitate was collected and washed, and the damp solid was added to a solution of dimethylamine in ethanol (33% w/v) (60 mL). After standing overnight, the mixture was diluted with water (100 mL). Acidification with concentrated HCl and cooling in ice gave a solid that was washed with water and recrystallized from ethanol to give 1.0 g (32%) of **2ak**.

3-Acetyl-5-ethyl-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide Oxime (2ap). A mixture of hydroxylamine hydrochloride (2.8 g, 0.04 mol) and anhydrous sodium carbonate (1.6 g, 0.02 mol) in *N*-methylpyrrolidin-2-one (40 mL) was stirred and heated at 80 °C (10 min). Compound **2c** (5.5 g, 0.02 mol) was then added, and heating (80 °C) and stirring were continued (15 h). After pouring into water (300 mL), the solution was adjusted to pH 1 (concentrated HCl), and the solid product was collected. Recrystallization from DMF–H_2O gave 3.9 g (67%) of **2ap**.

3-Acetyl-5-ethyl-2-hydroxy-*N*-1*H*-tetrazol-5-ylbenzamide Methoxime (2aq). This was prepared in a manner analogous to that for compound **2ap**, using compound **2c** (5.5 g, 0.02 mol), *O*-methylhydroxylamine hydrochloride (3.3 g, 0.04 mol), and sodium carbonate (1.6 g, 0.02 mol). Recrystallization from DMF–H_2O gave 5.3 g (87%) of **2aq**.

Preparation of 2-Hydroxybenzoic Acids 4 (Table VI). Novel benzoic acid derivatives are shown in Table VI. Unless otherwise stated, the precursors to the acids in Table VI are known or were prepared by standard methods using readily available materials.

The acids **4b**, **4f**, and **4i** were prepared by Fries rearrangement of the appropriate 2-(acyloxy)benzoic acid using the general procedure described by Amin, Patel, and Patel,[23] and the acids **4c**, **4d**, and **4e** were prepared by standard Friedel–Crafts acylation of the appropriate 2-hydroxybenzoic acid in CS_2 solution. Methylation of the appropriate 2,3-dihydroxybenzoic acids using dimethyl sulfate under standard conditions gave the acids **4j** and **4k**. Nitration of compound **4a** using concentrated H_2SO_4/concentrated HNO_3 at 0–5 °C gave compound **4g**, which upon catalytic reduction in the presence of acetic anhydride gave compound **4h**.

3-Acetyl-2-hydroxybenzoic Acid (4a). 3-Formyl-2-hydroxyacetophenone (15.0 g, 0.09 mol) was added over a period of 1 h to a stirred suspension of argentous oxide (23.2 g, 0.10 mol) in 0.9 M NaOH solution (300 mL) at 5–10 °C. After further stirring (1 h), the mixture was filtered. The filtrate was clarified with charcoal and acidified to give the benzoic acid, which was recrystallized from H_2O to give 9.4 g (57%) of **4a**.

5-Formyl-2-hydroxy-3-methoxybenzoic Acid (4m). 2-Hydroxy-3-methoxybenzoic acid[25] (21.0 g, 0.125 mol) was dissolved in CF_3CO_2H (200 mL), and hexamethylenetetramine (17.5 g, 0.125 mol) was added with stirring. After heating under reflux (3 h),

(20) Basil, B.; Loveless, A. H.; Wooldridge, K. R. H., unpublished results.
(21) Microanalyses were performed by the Microanalytical Laboratories, May & Baker Ltd.
(22) Cohen, J. B.; Dudley, H. W. *J. Chem. Soc.* **1910**, 1745.
(23) Amin, K. C.; Patel, G. S.; Patel, S. R. *J. Ind. Chem. Soc.* **1964**, *41*, 833.
(24) Tiemann, F.; Muller, W. H. M. *Ber.* **1881**, *14*, 1985.
(25) Perkin, W. H.; Stoyle, F. W. *J. Chem. Soc.* **1923**, 3171.

the CF_3CO_2H was removed under diminished pressure and the residue poured into a mixture of 2 N HCl (250 mL) and ether (125 mL). This mixture was stirred at room temperature (2 h), and after standing overnight, the solid product was collected and recrystallized from EtOH–H_2O to give 9.0 g (37%) of **4m**.

5-Cyano-2-hydroxy-3-methoxybenzoic Acid (41). Compound **4m** (1.96 g, 0.01 mol) was added to a solution of hydroxylamine hydrochloride (0.77 g, 0.011 mol) in DMF (10 mL), and the mixture was heated under reflux (15 min). After evaporation to dryness, the residue was triturated with 2 N HCl (6 mL), and the solid product was collected, washed with cold H_2O, and recrystallized from MeOH to give 0.8 g (41%) of **41**.

2-(Benzyloxy)-5-methylbenzoic Acid (5; R^1 = H, R^2 = CH_3). A mixture of methyl 5-methylsalicylate[26] (3.0 g, 0.018 mol), benzyl chloride (2.38 g, 0.019 mol), and anhydrous K_2CO_3 (2.5 g, 0.018 mol) in sulfolane (45 mL) was heated at 100 °C with stirring (21 h). The mixture was poured into ice water (300 mL) and adjusted to pH 6. The solid product was collected and heated under reflux with 2 N NaOH (100 mL) for 2 h. Upon cooling and acidification to pH 2, a colorless precipitate formed that was collected, washed with water (50 mL), and dried over P_4O_{10} to give 2-(benzyloxy)-5-methylbenzoic acid (3.65 g, 85%), mp 98–100 °C. Anal. ($C_{15}H_{14}O_3$) C, H.

3-Formyl-2-hydroxyacetophenone. A solution of 2-hydroxy-3-propenylacetophenone (40.9 g, 0.23 mol) in dry ethyl acetate (600 mL) at −70 °C was treated with ozonized oxygen (2% O_3) until ozone uptake ceased. Me_2S (60 mL) was added and the mixture allowed to warm to 25 °C (2 h). After standing at room temperature for a furthur 15 h, the volatile material was removed under diminished pressure and H_2O (200 mL) was added to the residue. The resulting precipitate was extracted into Et_2O (250 mL) and the ethereal solution washed (3 × 20 mL) and dried (Na_2SO_4). Evaporation gave a solid residue that was recrystallized from petroleum ether (bp 60–80 °C)–CCl_4 to give 3-formyl-2-hydroxyacetophenone (20.0 g, 54%), mp 67–69 °C. Anal. ($C_9H_8O_3$) C, H.

2-Hydroxy-3-propenylacetophenone. A solution of 3-allyl-2-hydroxyacetophenone[27] (100 g, 0.57 mol) and bis(benzonitrile)palladous chloride (5 g, 0.013 mol) in toluene (300 mL) was heated under reflux (20 h). After removal of the solvent, the resulting oil was distilled under reduced pressure to give 2-hydroxy-3-propenylacetophenone (90.0 g, 90%), bp 153–155 °C (18 mmHg). Anal. ($C_{11}H_{12}O_2$) C, H.

Preparation of *N*-(2-Hydroxyphenyl)-1*H*-tetrazole-5-carboxamides 3. Table II. Method F. *N*-(3-Acetyl-5-ethyl-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3c). Compound **7d** (65.0 g, 0.18 mol) in glacial acetic acid (1350 mL) was catalytically hydrogenated at 20 °C (60 psi) with 5% Pd on charcoal. The catalyst was thoroughly extracted with hot $CHCl_3$–CH_2Cl_2 (1:4) for 70 h. Evaporation of the mother liquor and extracts gave a solid product that was recrystallized from CH_3CO_2H to give 40.0 g (82%) of **3c**.

Method G. The procedure was the same as for method F except that a 2-benzyltetrazole (**8**; Ar = C_6H_5) was employed as starting material.

Method H. *N*-(3-Butanoyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide (3x). $AlCl_3$ (3.0 g, 0.02 mol) was slowly added to a solution of compound **7x** (2.5 g, 0.007 mol) in dry methylene chloride (50 mL) and the mixture stirred and heated under reflux for a further 30 min. After cooling, 2 N HCl (30 mL) was added and the mixture heated (10 min) to destroy the complex. Upon cooling, the solid product was collected and the organic layer evaporated to give a solid residue. The combined solids were recrystallized from DMF–water to give 0.7 g (37%) of **3x**.

Method I. *N*-(2-Hydroxy-3-methoxyphenyl)-1*H*-tetrazole-5-carboxamide (3r). Compound **7r** (3.0 g, 0.007 mol) in glacial acetic acid (150 mL) was catalytically hydrogenated at 50 °C (60 psi) with 5% Pd on charcoal. The hot mixture was filtered and the catalyst washed with additional hot glacial acetic acid. Evaporation of the combined acid filtrates give a residue that was dissolved in 2 N NH_4OH (50 mL) and acidified (concentrated HCl). The precipitate was recrystallized from water to give 0.8 g (47%) of **3r**.

Method J. *N*-(3-Acetyl-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3a). Compound **7a** (23.0 g, 0.063 mol) in CF_3CO_2H (400 mL) was heated under reflux (30 min). Evaporation under reduced pressure gave a solid that was recrystallized from glacial acetic acid (300 mL) to give 13.0 g (84%) of **3a**.

Method K. The procedure was the same as for method J except that a 2-(*p*-methoxybenzyl)tetrazole (**8**; Ar = *p*-$CH_3OC_6H_4$) was employed as starting material.

Method L. *N*-(3-Acetyl-2-hydroxy-5-*n*-propylphenyl)-1*H*-tetrazole-5-carboxamide (3d). Anhydrous $AlCl_3$ (2.84 g, 0.022 mol) was carefully added to cold, dry THF (35 mL). When all the material had dissolved, sodium azide (4.14 g, 0.064 mol) was added with vigorous stirring followed by 3-acetyl-2-hydroxy-5-*n*-propylcyanoformanilide (**9d**) (1.7 g, 0.007 mol). The mixture was then heated under reflux (24 h) and poured onto a mixture of ice (75 g) and concentrated HCl (20 mL). The solid product was collected, washed with water, and recrystallized from ethanol–water to give 0.8 g (40%) of **3d**.

Method M. *N*-(5-Bromo-2-hydroxy-3-methoxyphenyl)-1*H*-tetrazole-5-carboxamide (3u). 2-(Benzyloxy)-5-bromo-3-methoxycyanoformanilide (**9h**) (1.9 g, 0.005 mol) was treated with $AlCl_3$ (2.17 g, 0.016 mol) and sodium azide (3.08 g, 0.047 mol) in dry THF (30 mL) according to the procedure of method L. The oily product was dissolved in 2 N ammonia solution (100 mL), extracted with ether (2 × 50 mL) and the alkaline solution, and then acidified (concentrated HCl) to pH 1. The resulting oil was dissolved in ethanol and catalytically hydrogenated at 20 °C (atmospheric pressure) with 5% Pd on charcoal. Evaporation gave a brown solid that upon recrystallization from water gave 0.3 g (20%) of **3u**.

Method N. *N*-(3-Acetyl-5-fluoro-2-hydroxyphenyl)-1*H*-tetrazole-5-carboxamide (3f). Dry DMF (6.0 mL) in acetonitrile (13.8 mL) was stirred at −20 °C, and a solution of oxalyl chloride (2.1 mL) in acetonitrile (2.3 mL) was slowly added. After 15 min, compound **11** (4.56 g, 0.02 mol) was added, and after stirring for a further 20 min, a solution of the amine (**10d**) (2.04 g, 0.02 mol) and pyridine (8 mL) in acetonitrile (10 mL) was added dropwise (30 min). The stirred mixture was allowed to warm to room temperature (1 h) and finally heated under reflux (30 min). After cooling, the mixture was poured into water (100 mL) and the brown solution acidified to pH 1 (concentrated HCl). The solid product was recrystallized from acetonitrile to give 4.3 g (68%) of **3f**.

***N*-(3-Carbamoyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide (3ac).** Compound **7af** (4.8 g, 0.01 mol) and anisole (4.8 mL) in CF_3CO_2H (100 mL) were heated under reflux on a steam bath (1 h). The solvent was removed under diminished pressure, and ether (100 mL) was added to the residue. The solid product was collected and recrystallized from DMF to give 1.5 g (60%) of **3ac**.

***N*-(3-Carboxy-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide (3ag).** Compound **3ae** (3.5 g, 0.013 mol) in 2 N NaOH (500 mL) was stirred at room temperature (30 min). Acidification gave a solid product that was recrystallized from DMF–H_2O to give 3.0 g (90%) of **3ag**.

***N*-(3-Acetyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide Oxime (3ai).** A mixture of hydroxylamine hydrochloride (1.1 g, 0.016 mol), anhydrous sodium carbonate (0.6 g), H_2O (1 mL), and *N*-methylpyrrolidin-2-one (10.5 mL) was stirred and heated to 90 °C (15 min). Compound **3b** (1.0 g, 0.004 mol) was then added, and heating (95–100 °C) and stirring were continued (21 h). After pouring into 2 N HCl (50 mL), the solid product was collected, washed, and recrystallized from DMF–H_2O to give 0.4 g (38%) of **3ai**.

***N*-(3-Acetyl-2-hydroxy-5-methylphenyl)-1*H*-tetrazole-5-carboxamide Methoxime (3aj).** This was prepared in a manner analogous to that for compound **3ai** using compound **3b** (1.0 g, 0.004 mol), *O*-methyl hydroxylamine hydrochloride (0.96 g, 0.01 mol), H_2O (2 mL), and sodium carbonate (1.09 g). Recrystallization from DMF–H_2O gave 0.7 g (63%) of **3aj**.

Preparation of *N*-Aryl-1-benzyltetrazole-5-carboxamides 7 (Table IV). These derivatives were prepared from the appropriate aromatic amine (Table VII) and either potassium 1-benzyltetrazole-5-carboxylate (**13a**) or potassium 1-(4-methoxy-

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benzyl)tetrazole-5-carboxylate (**13b**). The following example gives typical conditions.

***N*-(3-Acetyl-2-hydroxyphenyl)-1-(4-methoxybenzyl)tetrazole-5-carboxamide (7a).** A mixture of potassium 1-(4-methoxybenzyl)tetrazole-5-carboxylate (**13b**) (24.5 g, 1.1 mol) and pyridine (4.5 mL) in dry toluene (500 mL) was stirred and cooled to 10 °C. $SOCl_2$ (75 mL) was then added rapidly and the mixture stirred at 20 °C (1 h). The solid KCl was removed by filtration under vacuum, and evaporation of the filtrate gave the crude acid chloride.

The acid chloride in dry CH_2Cl_2 (350 mL) was added dropwise to a stirred solution of 2-acetyl-6-aminophenol[28] (12.4 g, 0.08 mol) and pyridine (7.0 mL) in dry CH_2Cl_2 (450 mL) maintained at 10 °C. The total mixture was then stirred at 20 °C (1 h), and CH_2Cl_2 (1500 mL) was then added. The solution was washed (2 × 500 mL of H_2O), dried ($MgSO_4$), and evaporated to give a crude yellow-orange product. Recrystallization from CH_3CN (200 mL) gave 24.0 g (80%) of **7a**.

***N*-(3-Acetyl-5-ethyl-2-hydroxyphenyl)-2-benzyltetrazole-5-carboxamide (8; $R^1 = CH_3CO$, $R^2 = C_2H_5$, Ar = C_6H_5).** Using potassium 2-benzyltetrazole-5-carboxylate (**14a**) (0.9 g, 0.004 mol) and 2-acetyl-6-amino-4-ethylphenol (**10b**) (0.6 g, 0.003 mol) according to the procedure described for compound **7a**, after recrystallization of the product from EtOH, gave 0.77 g (57%) of **8** ($R^1 = CH_3O$, $R^2 = C_2H_5$, Ar = C_6H_5), mp 160–162 °C. Anal. ($C_{19}H_{19}N_5O_3$) C, H, N.

***N*-(3-Acetyl-5-ethyl-2-hydroxyphenyl)-2-(4-methoxybenzyl)tetrazole-5-carboxamide (8; $R^1 = CH_3CO$, $R^2 = C_2H_5$, Ar = *p*-$CH_3OC_6H_4$).** Using potassium 2-(*p*-methoxybenzyl)-tetrazole-5-carboxylate (**14b**) (1.5 g, 0.006 mol) and 2-acetyl-6-amino-4-ethylphenol (**10b**) (0.9 g, 0.005 mol) according to the procedure described for compound **7a** gave, after recrystallization from EtOH, 1.48 g (77%) of **8** ($R^1 = CH_3CO$, $R^2 = C_2H_5$, Ar = *p*-$CH_3OC_6H_4$), mp 159–161 °C. Anal. ($C_{20}H_{21}N_5O_4$) C, H, N.

Preparation of Cyanoformanilides 9 (Table V). The following example is representative of the method used to prepare the derivatives in Table V.

3-Acetyl-2-hydroxy-5-methylcyanoformanilide (9b). A solution of Me_2S (14 mL) in dry ether (35 mL) was stirred at 0 °C, and tetracyanoethylene oxide (3.66 g, 0.025 mol) was added. After 1 h the solid product [$Me_2SC(CN)_2$] was collected and washed with ether (50 mL), and the combined filtrates, containing carbonyldicyanide, were cooled to 0 °C.

A solution of 3-acetyl-2-hydroxy-5-methylaniline (**10a**) (4.2 g, 0.025 mol) in dry ether (50 mL) was added dropwise to the chilled carbonyl dicyanide solution over a period of 15 min. Stirring at 0 °C was continued (1 h), and the solid product was then collected. Recrystallization from toluene gave 2.6 g (48%) of **9b**.

Preparation of 2-Aminophenols 10 (Table VII). Novel fully characterized 2-aminophenols are shown in Table VII. In some cases the intermediate amines were used in subsequent stages without purification.

With the exception of compounds **10e** and **10g**, the amines were prepared by hydrogenation of the corresponding nitrophenol using 5% Pd/C catalyst in ethanol. Compound **10e** was prepared by reduction of 2-acetyl-4-bromo-6-nitrophenol[29] using 20% aqueous titanous chloride, and compound **10g** was prepared by reduction of 6-acetyl-2,4-dinitrophenol[30] using a mixture of ammonium chloride and sodium sulfide in hot MeOH.

Preparation of 2-Nitrophenols and (2-Nitrophenol)benzyl Ethers. Table VIII. Novel nitrobenzene derivatives are shown in Table VIII. These were prepared by nitration of the appropriate phenol at −20 °C using standard reagents and, where appropriate, alkylation using benzyl chloride. All precursors to the derivatives in Table VIII are known or were prepared by standard methods using readily available materials.

Preparation of Tetrazole Intermediates. Ethyl 1*H*-Tetrazole-5-carboxylate. A solution of ethyl cyanoformate (2.5 g, 0.025 mol) in dry pyridine (10 mL) was treated with a chilled mixture of CF_3CO_2H (4.4 mL) and dry pyridine (15 mL). Sodium azide (1.8 g, 0.027 mol) was then added to the stirred solution, and the mixture was stirred at 60 ± 5 °C (48 h). After cooling, the product was poured into a mixture of ice (50 g) and concentrated HCl (20 mL) and the aqueous mixture extracted with ether (3 × 50 mL). Evaporation of the dried ($MgSO_4$) ethereal extracts gave an oil that was passed down a silica gel column [petroleum ether (bp 40–60 °C)–ether (1:1) as eluant] to give 1.57 g (44%) of product, mp 88–93 °C (lit.[11] mp 87–88 °C).

Dipotassium 1*H*-Tetrazole-5-carboxylate (11). A solution of KOH (0.22 g) in water (0.7 mL) was added to a solution of ethyl 1*H*-tetrazole-5-carboxylate (0.36 g, 0.0025 mol) in hot EtOH (7.5 mL). The solid product that formed immediately was collected and washed with cold EtOH to give 0.16 g (42%) of **11**, mp >330 °C. Anal. ($C_2K_2N_4O_2$) C, N.

Potassium 1- and 2-Benzyltetrazole-5-carboxylates (13a and 14a). Sodium hydride (0.13 g, 0.006 mol) was added to dry sulfolane (10 mL), and after stirring (5 min), ethyl 1*H*-tetrazole-5-carboxylate (0.71 g, 0.005 mol) was added. After a further 20 min, benzyl chloride (0.7 g, 0.006 mol) was added and the mixture stirred at 60 °C (18 h). After pouring onto ice (25 g), the reaction product was extracted into ether (2 × 25 mL), washed with water (3 × 25 mL), dried ($MgSO_4$), and evaporated to give a pale yellow oil.

The oily product was dissolved in boiling EtOH (10 mL) and treated with a solution of KOH (0.27 g) in water (0.8 mL). The crystalline product was collected at 40–50 °C and washed with EtOH–ether to give 0.2 g (16%) of **14a**, mp 272–273 °C. Anal. ($C_9H_7KN_4O_2{\cdot}0.5H_2O$) C, H, N.

Upon cooling, the filtrate gave a second crop of crystals that were collected and washed with EtOH–ether to give 0.16 g (13%) of **13a**, mp 199–210 °C [lit.[12b] mp 200 °C dec]. Anal. ($C_9H_7KN_4O_2$) C, H, N.

Potassium 1- and 2-(*p*-Methoxybenzyl)tetrazole-5-carboxylates (13b and 14b). A procedure identical with that described above starting with ethyl 1*H*-tetrazole-5-carboxylate (0.71 g, 0.005 mol) and *p*-methoxybenzyl chloride (0.9 g, 0.006 mol) gave 0.3 g (40%) of (**14b**), mp 273–275 °C dec [Anal. ($C_{10}H_9KN_4O_3{\cdot}0.5H_2O$) C, H, N], and 0.26 g (34%) of **13b**, mp 192–194 °C dec (lit.[12b] mp 202–204 °C).

pK_a Measurements. The pK_a values of compound **2g** (4.20 ± 0.02; 7.10 ± 0.02) and compound **3f** (2.36 ± 0.06; 8.69 ± 0.02) in aqueous media at 25 °C were measured by using the spectroscopic method of Albert and Serjeant.[31] The values quoted are thermodynamic pK_a's corrected for the ionic strength of the buffer solutions.

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Registry No. **2a**, 67127-97-3; **2aa**, 100245-51-0; **2ab**, 67127-05-3; **2ac**, 67127-15-5; **2ad**, 67127-15-5; **2ae**, 67127-23-5; **2af**, 67127-11-1; **2ag**, 67127-27-9; **2ah**, 67127-41-7; **2ai**, 67127-07-5; **2aj**, 67127-35-9; **2ak**, 67127-30-4; **2al**, 67127-17-7; **2am**, 67127-10-0; **2an**, 67127-12-2; **2ao**, 67127-01-9; **2ap**, 70986-17-3; **2aq**, 70986-17-3; **2b**, 67127-28-0; **2c**, 67127-42-8; **2d**, 67127-47-3; **2e**, 100245-40-7; **2f**, 67127-45-1; **2g**, 67324-88-3; **2h**, 67126-96-9; **2i**, 67127-46-2; **2j**, 100245-41-8; **2k**, 67127-62-2; **2l**, 67127-40-6; **2m**, 100245-42-9; **2n**, 67127-48-4; **2o**, 67127-49-5; **2p**, 67126-94-7; **2q**, 100245-43-0; **2r**, 100245-44-1; **2s**, 100245-45-2; **2t**, 100245-46-3; **2u**, 100245-47-4; **2v**, 100245-48-5; **2w**, 100245-49-6; **2x**, 100245-50-9; **2y**, 61745-70-8; **2z**, 67127-18-8; **3a**, 70977-58-1; **3aa**, 70977-65-0; **3ab**, 70977-64-9; **3ac**, 100245-60-1; **3ad**, 70977-54-7; **3ae**, 70977-55-8; **3af**, 70977-56-9; **3ag**, 70977-54-7; **3ah**, 100245-59-8; **3ai**, 70977-61-6; **3aj**, 70977-62-7; **3b**, 70977-39-8; **3c**, 70977-41-2; **3d**, 70977-57-0; **3e**, 100245-54-3; **3f**, 70977-46-7; **3g**, 100245-55-4; **3h**, 70977-47-8; **3i**, 70977-48-9; **3j**, 70977-44-5; **3k**, 70977-42-3; **3l**, 70977-66-1; **3m**, 100245-56-5; **3n**, 70977-63-8; **3o**, 70977-59-2; **3p**, 70977-49-0; **3q**, 70977-51-4; **3r**, 70977-67-2; **3s**, 70977-52-5; **3t**, 70977-68-3; **3v**, 70977-38-7; **3w**, 100245-58-7; **3x**,

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70977-53-6; **3y**, 70977-43-4; **3z**, 70977-45-6; 4 (R^1 = CH_3CO, R^2 = Cl), 1760-85-6; 4 (R^1 = CH_3CO, R^2 = Br), 1760-84-5; [4] (R^1 = CH_3CO, R^2 = CH_3O), 55008-13-4; 4 (R^1 = C_2H_5CO, R^2 = CH_3), 1760-86-7; 4 (R^1 = R^2 = CH_3O), 61637-60-3; 4 (R^1 = CH_3O, R^2 = NO_2), 20718-78-9; 4 (R^1 = CH_3O, R^2 = $NHCOCH_3$), 100245-39-4; 4 (R^1 = H, R^2 = Br), 89-55-4; 4 (R^1 = H, R^2 = CN), 10435-57-1; 4 (R^1 = H, R^2 = CH_3S), 32318-42-6; 4 (R^1 = H, R^2 = C_6H_5), 323-87-5; 4 (R^1 = H, R^2 = CH_3CO), 13110-96-8; 4 (R^1 = H, R^2 = $NHCOCH_3$), 51-59-2; 4 (R^1 = CH_3CO, R^2 = CH_3), 1760-83-4; 4 (R^1 = CH_3CO, R^2 = CH_3) (acid chloride), 70986-26-4; 4 (R^1 = CH_3O, R^2 = CH_3), 4386-42-9; 4 (R^1 = H, R^2 = F), 345-16-4; 4 (R^1 = H, R^2 = t-C_4H_9), 16094-31-8; 4 (R^1 = H, R^2 = CH_3O), 2612-02-4; 4 (R^1 = H, R^2 = NO^2), 96-97-9; 4 (R^1 = H, R^2 = NO_2) (acid chloride), 3223-20-9; 4 (R^1 = CH_3O, R^2 = Br), 35090-76-7; **4a**, 67127-78-0; **4b**, 67127-75-7; **4c**, 67127-80-4; **4d**, 100245-30-5; **4e**, 67127-77-9; **4f**, 67127-79-1; **4g**, 100245-36-1; **4h**, 100245-37-2; **4i**, 67127-81-5; **4j**, 100245-34-9; **4k**, 100245-35-0; **4l**, 100297-40-3; **4m**, 3507-08-2; **4n**, 100245-33-8; 5 (R^1 = H, R^2 = CH_3), 67127-92-8; 5 (R^1 = R^2 = H), 14389-86-7; 5 (R^1 = H, R^2 = Cl), 52803-75-5; 5 (R^1 = H, R^2 = CF_3), 53985-54-9; 5 (R^1 = H, R^2 = $PhCH_2O$), 67127-91-7; **6a**, 100245-38-3; **6b**, 67127-71-3; **6c**, 67127-68-8; **6d**, 67127-74-6; **6e**, 67127-70-2; **7a**, 100245-22-5; **7aa**, 70977-95-6; **7ab**, 70978-13-1; **7ac**, 70978-11-9; **7ad**, 70978-12-0; **7ae**, 100245-28-1; **7af**, 100245-29-2; **7b**, 70977-74-1; **7c**, 70977-89-8; **7d**, 70978-15-3; **7e**, 70977-76-3; **7f**, 100245-23-6; **7g**, 100245-24-7; **7h**, 70977-96-7; **7i**, 100245-25-8; **7j**, 70977-97-8; **7k**, 70977-98-9; **7l**, 70977-93-4; **7m**, 70977-90-1; **7n**, 70978-01-7; **7o**, 100245-26-9; **7p**, 70977-91-2; **7q**, 70977-99-0; **7r**, 70978-02-8; **7s**, 70978-17-5; **7t**, 70978-03-9; **7u**, 70977-73-0; **7v**, 100245-27-0; **7w**, 70978-14-2; **7x**, 70977-92-3; **7y**, 70977-94-5; **7z**, 70978-00-6; 8 (R^1 = CH_3CO, R^2 = C_2H_5, Ar = C_6H_5), 70978-21-1; 8 (R^1 = CH_3CO, R^2 = C_{H5}, Ar = P-$CH_3OC_6H_4$), 70978-04-0; **9a**, 70978-25-5; **9b**, 100245-21-4; **9c**, 70978-26-6; **9d**, 70978-27-7; **9e**, 70978-18-6; **9f**, 70978-28-8; **9g**, 70978-30-2; **9h**, 70978-29-9; **10** (R^1 = CH_3CO, R^2 = Cl), 21312-85-6; **10** (R^1 = CH_3CO, R^2 = CH_3O), 55008-15-6; **10** (R^1 = CH_3oCO, R^2 = $NHCOCH_3$), 70978-63-1; **10** (R^1 = CH_oCO, R^2 = H), 70977-72-9; **10** (r^1 = CH_3CO, R^2 = t-C_{H9}), 100245-20-3; **10** (R^1 = C_2H_5CO, R^2 = C_2H_5), 70978-24-4; **10** (R^1 = C_2H_5CO, R^2 = CH_3), 70978-23-3; **10** (R^1 = CH_3CO, R^2 = CH_3SO_2), 70977-88-7; **10a**, 70977-71-8; **10b**, 70977-78-5; **10c**, 70978-22-2; **10d**, 70977-84-3; **10e**, 70977-85-4; **10f**, 70977-81-0; **10g**, 70977-79-6; **10h**, 100245-11-2; **10i**, 70977-86-5; **10j**, 24962-75-2; **10k**, 70978-64-2; **10l**, 70977-80-9; **10m**, 70977-82-1; **10n**, 70977-87-6; **10o**, 70977-83-2; **10p**, 70978-09-5; **10q**, 70978-07-3; **10r**, 70978-08-4; **10s**, 100245-12-3; **10t**, 100245-13-4; **11**, 70978-65-3; **12**, 55408-10-1; **13a**, 63005-72-1; **13a** (benzyl ester), 100245-14-5; **13a** (acid chloride), 64470-37-7; **13b**, 70977-77-4; **13b** (benzyl ester), 100245-16-7; **13b** (acid chloride), 66492-66-8; **14a**, 71002-71-6; **14b**, 70978-38-0; **14c**, 100245-06-5; **14d**, 70978-39-1; **14e**, 70978-59-5; **14f**, 70978-46-0; **14g**, 100245-07-6; **14h**, 70978-47-1; **14i**, 70978-55-1; **14j**, 70978-60-8; **14k**, 42247-91-6; **14l**, 70978-45-9; **14m**, 70978-42-6; **14n**, 70978-49-3; **14o**, 70978-50-6; **14p**, 70978-48-2; **14q**, 70978-44-8; **14r**, 67191-44-0; **14s**, 70978-43-7; **14t**, 100245-08-7; **14u**, 100245-09-8; **14**, 100245-10-1; **14w**, 70978-51-7; **14x**, 70978-52-8; **14y**, 70978-53-9; p-$CH_3OC_6H_4COCl$, 824-94-2; 2-acetyl-4-ethylphenol, 24539-92-2; 2-acetyl-4-propylphenol, 1990-24-5; 2-acetyl-4-*tert*-butylphenol, 57373-81-6; 2-acetyl-4-fluorophenol, 394-32-1; 2-acetyl-4-cyanophenol, 35794-84-4; 2-acetyl-4-(methylsulfonyl)-phenol, 20951-24-0; 2,4-diacetylphenol, 30186-16-4; 2-(1-oxopropyl)-4-ethylphenol, 63909-10-4; 2-(1-oxopropyl)-4-cyanophenol, 70978-58-4; 2-methoxy-4-ethylphenol, 2785-89-9; 4-(dimethylaminosulfonyl)phenol, 15020-57-2; 2-(1-oxobutyl)-4-methylphenol, 24323-47-5; 2-(1-oxoisobutyl)-4-methylphenol, 64207-03-0; 2-(cyclopropylcarbonyl)-4-methylphenol, 70978-56-2; 2-(benzylcarbonyl)-4-methylphenol, 24258-63-7; 2-(trifluoroacetyl)-4-methylphenol, 70978-57-3; 2-(dimethylaminocarbonyl)-4-methylphenol, 100245-03-2; methyl 2-hydroxy-5-methylbenzoate, 22717-57-3; ethyl 2-hydroxy-5-methylbenzoate, 34265-58-2; 2-(5-tetrazolyl)-4-methylphenol, 100245-04-3; 2-(4-methoxyphenylmethylaminocarbonyl)-4-methylphenol, 100245-05-4; 2-methoxy-6-nitrophenol, 15969-08-1; 2-methoxy-4-methyl-6-nitrophenol, 53411-80-6; 2-methoxy-4-bromo-6-nitrophenol, 70978-61-9; 2-methoxyphenol, 90-05-1; 4-methyl-2-methoxyphenol, 93-51-6; 4-bromo-2-methoxyphenol, 7368-78-7; 4-methyl-2-methoxy-6-nitrophenol, 66108-30-3; 4-bromo-2-methoxy-6-nitrophenol, 70978-54-0; 2-acetyl-4,6-dinitrophenol, 69027-37-8; ethyl cyanoformate, 623-49-4; potassium 2-benzyltetrazole-5-carboxylate, 70978-32-4; benzyl 2-benzyltetrazole-5-carboxylate, 100245-15-6; 2-benzyltetrazole-5-carbonylchloride, 100245-18-9; potassium 2-(p-methoxybenzyl)tetrazole-5-carboxylate, 70978-33-5; benzyl 2-(p-methoxybenzyl)tetrazole-5-carboxylate, 100245-17-8; 2-(p-methoxybenzyl)tetrazole-5-carbonyl chloride, 100245-19-0; tetracyanoethylene oxide, 3189-43-3; carbonyldicyanide, 1115-12-4; 3-methoxy-2-(benzyloxy)benzenamine, 70978-05-1; 5-methyl-3-methoxy-2-(benzyloxy)benzenamine, 70978-19-7; 5-ethyl-3-methoxy-2-(benzyloxy)benzenamine, 70978-06-2; 5-bromo-3-methoxy-2-(benzyloxy)benzenamine, 70978-31-3; 2-(benzyloxy)-benzenamine, 20012-63-9; 2-hydroxy-3-propenylacetophenone, 67127-96-2; 3-formyl-2-hydroxyacetophenone, 55108-29-7; 3-allyl-2-hydroxyacetophenone, 58621-39-9; 2-acetoxy-5-ethylbenzoic acid, 35421-90-0; 2-acetoxy-5-fluorobenzoic acid, 448-40-8; (1-oxopropyl)-5-ethylbenzoic acid, 67127-93-9; 5-propylsalicyclic acid, 28488-44-0; 5-isobutylsaslicyclic acid, 100245-31-6; 5-(*tert*-butyl)salicyclic acid, 16094-31-8; 5-ethyl-2,3-dihydroxybenzoic acid, 100245-32-7; 2-hydroxy-3-methoxybenzoic acid, 877-22-5; methyl 5-methylsalicylate, 22717-57-3; 5-tetrazolamine, 4418-61-5; 3-acetyl-2-hydroxy-5-(chlorosulfonyl)-n-(l*h*-tetrazol-5yl)benzamide, 100245-52-1; 5-(chlorosulfonyl)-2-hydroxy-n-(l*h*-tatrazol-5-yl)-benzamide, 100245-53-2; n-(cyanocarbonyl)-2-(benzyloxy)-benzenamine, 100297-41-4; n-(5-tetrazoylcarbonyl)-2-(benzyloxy)benzenamine, 100245-57-6.

Quantitative Evaluation of the β_2-Adrenoceptor Intrinsic Activity of *N-tert*-Butylphenylethanolamines†

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The extent of stimulation of the enzyme adenylate cyclase, and the concomitant production of cAMP, by a number of β-adrenoceptor agonists, all belonging to the class of the *N-tert*-butylphenylethanolamines, has been determined. The results have been used as direct measures for intrinsic sympathomimetic activity (ISA) and were correlated with various physicochemical parameters of the compounds. Significant correlations were established by means of the method of multiple regression analysis, and it was demonstrated that electronic effects only govern ISA. The use of ^{13}C NMR chemical shifts of the aromatic C atoms proved to be a valuable tool in this analysis.

In 1954, Ariëns[1] introduced the concept of intrinsic activity, as a necessary completion to the receptor-occupation theory, originally proposed by Clark.[2] Further refinements were made by Furchgott,[3] Nickerson,[4] and Stephenson,[5] and now it is generally believed that intrinsic activity does

† Dedicated to Jan van Dijk (Duphar, Weesp, The Netherlands) on the occasion of his retirement.

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