2-(Diethylamino)-6-nitrobenzonitrile (72). To a mixture of 3.82 g (0.02 mol) of 2-(ethylamino)-6-nitrobenzonitrile (73) and 3.2 g (0.02 mol) of ethyl iodide in 100 mL of DMF was added 0.96 g (0.02 mol) of 50% NaH (in oil) in portions. The mildly exothermic reaction was stirred for 10 min, poured into ice–water, and extracted into methylene chloride. Evaporation gave an oil that was passed through a short column of silica gel (20 g) with methylene chloride. The bright orange oil was collected and triturated with hexane to give 3.1 g of pure product, mp 39–41 °C.

2-Nitro-5-(dimethylamino)benzoic Acid (75). Sodium cyanoborohydride (57 g) was added to a mixture of 54.6 g (0.21 mol) of commercial (70%) 2-nitro-5-aminobenzoic acid and 240 mL of formalin in 1200 mL of acetonitrile. The reaction mixture was stirred overnight and evaporated to one-third volume. The product crystallized as the hemihydrate: mp 187–189 °C; yield 50 g (100%). Anal. ($C_9H_{10}N_2O_4 \cdot 0.5H_2O$) C, H, N.

5-(Dimethylamino)anthranilic Acid (76). A mixture of 10.5 g (0.05 mol) of the nitrobenzoic acid **75**, 5 g of 10% Pd on charcoal, and 25 g (0.3 mol) of cyclohexene in 200 mL of ethanol was heated at reflux for 3 h. The hot reaction mixture was filtered through Celite, the Celite pad was extracted three times with hot ethanol, and the combined ethanol filtrates were evaporated to one-third volume. Water was added to cloudiness, whereupon the pure product crystallized: yield 8.0 g (93%); mp 234–238 °C (lit.[28] 234–236 °C).

(28) R. A. Rossi and H. E. Bertorello, *An. Asoc. Quim. Argent.*, **55**, 227 (1967); *Chem. Abstr.*, **69**, 106 140*k*.

5-(Dimethylamino)isatoic Anhydride (77). A solution of 10.9 g (0.06 mol) of the anthranilic acid **76** in 300 mL of dioxane was treated with 18.4 g (0.19 mol) of liquid phosgene. The reaction mixture was warmed to 40 °C and left overnight at room temperature. The title compound (13.8 g, 95%) was filtered off as the hydrochloride, mp 256–258 °C dec. Anal. ($C_{10}H_{10}N_2O_3 \cdot HCl$) C, H, N, Cl.

5-(Dimethylamino)anthranilamide (78). The isatoic anhydride **77** (4.85 g, 0.02 mol) was added to 70 mL of 1 N NH_4OH. After 30 min the product was extracted into methylene chloride. Recrystallization from ethyl acetate–hexane gave the desired amide (1.4 g, 39%), mp 149–151 °C. Anal. ($C_9H_{13}N_3O$) C, H, N.

[[2-Carbamoyl-4-(dimethylamino)phenyl]amino]oxoacetic Acid Ethyl Ester (79). 5-(Dimethylamino)anthranilamide (**78**) was acylated in the usual manner with ethyloxalyl chloride. The product was obtained in 72% yield after recrystallization from ethanol, mp 203–205 °C. Anal. ($C_{13}H_{17}N_3O_4$) C, H, N.

2-Acetamido-6-nitrobenzonitrile (92). To 6 g (0.037 mol) of 2-amino-6-nitrobenzonitrile (**40**) in 100 mL of pyridine was added 3.5 g (0.044 mol) of acetyl chloride. After 1 h, the mixture was poured into diluted HCl, the aqueous portion was extracted with CH_2Cl_2, and the combined extracts were dried and evaporated. The solid was recrystallized.

Acknowledgment. We thank Bruce Hofmann and his staff for the analytical and spectral data, Drs. A. Lewis and R. Carlson for invaluable additional biological testing, and Gwen Rivnak and L. D. Lofton for the initial biological test data. A very special thanks to Ms. Barbara Smalley for the preparation of this manuscript.

5-Tetrazolecarboxamides and Their Salts: New Orally Active Antiallergy Agents

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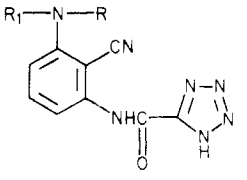
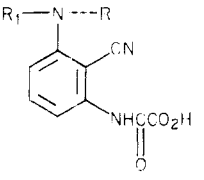
Research Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania. *Received September 12, 1980*

A new series of orally active antiallergy agents, tetrazole-5-carboxamides, has been prepared by acylation of substituted anilines or aminopyridines with 1-benzyl- or 4-(methoxybenzyl)-5-tetrazolecarbonyl chloride and subsequent removal of the benzyl substituent. Compounds **16**, **18**, and **28** showed very good oral activity.

Many of the antiallergy agents of the disodium cromoglycate type appear to be short-lived in vivo,[2,3] and the search for compounds with a longer plasma half-life, and hence duration of action, is continuing.[4] There are numerous examples in which the tetrazole moiety has been used to replace a carboxylic acid function[5,6] and in some cases, such as the tetrazole analogue of nicotinic acid,[7] the duration of activity is enhanced. In addition, the use of a tetrazole ring in antiallergic compounds is not new.[8] With these ideas in mind we felt that the tetrazole analogues (**1**) of our previously disclosed[9] oxanilic acids (**2**) should be prepared.



1



2

Chemistry. Various 5-aminotetrazolecarboxamides are known antiallergy agents,[10] but the 5-carboxamidotetrazoles (such as **1**) have not been extensively studied.[11] Since we had at our disposal a ready access to substituted anthranilonitriles,[9] we felt that the easiest route to the desired compounds was via the acid chloride **3**. This acid chloride is not known, and the synthesis of the corresponding ester **4** has suffered from very poor yields.[12,13] In addition, hydrolysis of the ester results in decarboxylation.

(1) Ortho Pharmaceutical Corp., Raritan, NJ 08869.
(2) H. G. Johnson, C. A. van Hout, and J. B. Wright, *Int. Arch. Allergy Appl. Immunol.*, **56**, 416 (1978).
(3) M. K. Church, *Med. Actual.*, **14**, 281 (1978).
(4) J. B. Wright, C. M. Hall, and H. G. Johnson, *J. Med. Chem.*, **21**, 930 (1978).
(5) For a list of references describing substitution of an acid by a tetrazole, see R. N. Butler, *Adv. Heterocycl. Chem.*, **21**, 355 (1977).
(6) J. M. McManus and R. M. Herbst, *J. Org. Chem.*, **24**, 1643 (1959).
(7) G. F. Holland and J. N. Pereira, *J. Med. Chem.*, **10**, 149 (1967).
(8) J. F. Batchelor, L. G. Garland, A. F. Green, D. T. D. Hughes, M. J. Follenfant, J. H. Gorvin, H. F. Hodson, and J. E. Tateson, *Lancet*, 1169 (1975).
(9) The biological methods used and the statistical significance of the data are identical with that of D. H. Klaubert, J. H. Sellstedt, C. J. Guinosso, R. J. Capetola, and S. C. Bell, *J. Med. Chem.*, preceding paper in this issue.
(10) G. P. Ellis, G. J. P. Becket, D. Shaw, H. K. Wilson, C. J. Vardey, and I. F. Skidmore, *J. Med. Chem.*, **21**, 1120 (1978).
(11) B. E. Fisher, A. J. Tomson, and J. P. Horwitz, *J. Org. Chem.*, **24**, 1650 (1959).
(12) E. Oliveri-Mandalà, *Gazz. Chim. Ital.*, **41**, 59 (1911).

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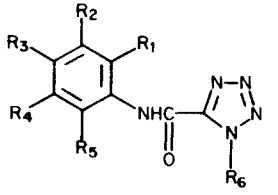
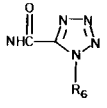
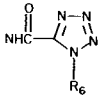
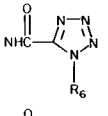
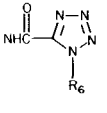
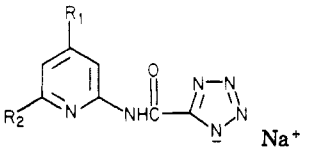
Table I. Tetrazole-5-carboxanilides

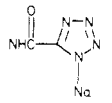
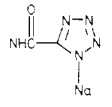


compd	R_1	R_2	R_3	R_4	R_5	R_6	mp, °C	% yield[a]	formula	solvate	anal.	rat PCA ED_{50}, mg/kg ip	rat PCA ED_{50}, mg/kg po
11	CN	H	H	H	H	Na^+	>300	74	$C_9H_5N_6NaO$	H_2O	C, H, N	0.5	10
12	CN	NHEt	H	H	H	Na^+	165–170	94	$C_{11}H_{10}N_7NaO$	$1.1H_2O$	C, H, N	1.1	2.6
13	CN	NMe_2	H	H	H	Na^+	155–158	70	$C_{11}H_{10}N_7NaO$	$0.125F_3AcOH$	C, H, N	2.0	1.7
14	CN	c-NC_5H_{10}	H	H	H	Na^+	164–167	82	$C_{14}H_{14}N_7NaO$	$0.52H_2O$	C, H, N	0.4	7.0
15	CN	c-$N(CH_2CH_2)_2O$	H	H	H	H	253–256	71	$C_{13}H_{13}N_7O_2$		C, H, N	0.5	10.0
16	CN	c-$N(CH_2CH_2)_2N$-CH_3	H	H	H	H	290 dec	57	$C_{14}H_{16}N_8O$	$0.44H_2O$	C, H, N	0.02	0.2
17	$CONH_2$	NMe_2	H	H	H	Na^+	193 dec	84	$C_{11}H_{12}N_7NaO_2$		C, H, N	0.9	34
18	$CONH_2$	OMe	H	H	H	H	249 dec	79	$C_{10}H_{10}N_6O_3$		C, H, N	0.1	0.2
19	$CONH_2$	c-NC_5H_{10}	H	H	H	Na^+	291 dec	71	$C_{14}H_{16}N_7NaO_2$	$0.7H_2O$, 0.4EtOH	C, H, N	0.8	46.0
20	$CONH_2$	c-$N(CH_2CH_2)_2O$	H	H	H	Na^+	293 dec	92	$C_{13}H_{14}N_7NaO_3$	$0.6H_2O$	C, H, N	0.2	*b*
21	$CONH_2$	c-$N(CH_2CH_2)_2N$-CH_3	H	H	H	H	>300	68	$C_{14}H_{18}N_8O_2$	$0.15H_2O$	C, H, N	0.01	2.3
22	H	CN	H	$NHCOCO_2Et$	H	H	250 dec	87	$C_{13}H_{11}N_7O_4$	$0.15H_2O$	C, H, N	0.2	*b*
23	H	CN	H		H	Na^+	>300	92	$C_{11}H_5N_{11}Na_2O_2$	$1.5H_2O$	C, H, N	0.04	1.0
24	H	CN	H		Cl	Na^+	>300	73	$C_{11}H_4N_{11}ClNa_2O_2$	$0.75H_2O$	C, N; H[c]	0.3	*b*
25	H	$CONH_2$	H		H	Na^+	>300	68	$C_{11}H_7N_{11}Na_2O_3$	$1.35H_2O$	C, H, N	0.02	>10
26	H	CF_3	H		Cl	Na^+	295 dec	75	$C_{11}H_4N_{10}ClF_3Na_2O_2$	$2.65H_2O$	C, H, N	1.6	*b*
cromolyn sodium												8	NA[d]

[a] Method D. [b] Not tested. [c] H: calcd, 1.33; found, 0.87. [d] Not active.

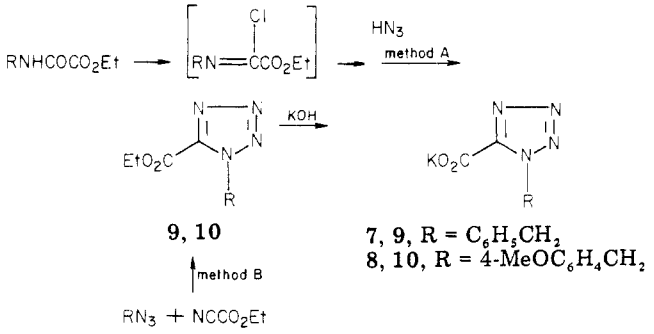
Table II. Pyridinyl-5-tetrazolecarboxamides



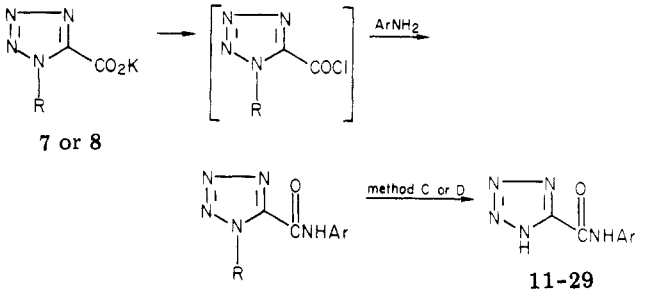
no.	R_1	R_2	mp, °C	formula	% yield[a]	solvate	anal.	rat PCA ED_{50}, mg/kg ip	rat PCA ED_{50}, mg/kg po
27	H	H	154	$C_7H_5N_6NaO$	71	H_2O	C, H, N	0.31	0.68
28	H		>300	$C_9H_5N_{11}Na_2O_2$	60	$3H_2O$	C, N; H[b]	0.02	0.1
29	Cl		>300	$C_9H_4ClN_{11}Na_2O_2$	69	$0.42H_2O$	C, H, N	0.2	2.0

[a] Method D. [b] H: calcd, 2.77; found, 2.32.

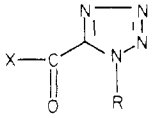
Scheme I



Scheme II



Substitution on nitrogen-1 is reported to give much greater stability to the acid upon hydrolysis,[14] although Amstutz[15] reports no increased stability with position 1 substitution. In any case, our choice for a tetrazole synthon was 1-benzyl-5-tetrazolecarbonyl chloride (**5**). However, since the subsequent deprotection step (Scheme II, method C) was a low yield reaction, we usually favored the use of 1-(4-methoxybenzyl)-5-tetrazolecarbonyl chloride (**6**, method D). Neither of the acid chlorides (**5** or **6**) were ever isolated or purified but were always used directly in the next step after preparation from the easily purified and stored potassium salts **7** and **8**. We found two equally



3, R = H; X = Cl
4, R = H; X = OEt
5, R = $CH_2C_6H_5$; X = Cl
6, R = $CH_2C_6H_4$(4-OMe); X = Cl
7, R = $CH_2C_6H_5$; X = $-O^-K^+$
8, R = $CH_2C_6H_4$(4-OMe); X = $-O^-K^+$

effective methods for the preparation of the necessary intermediate esters **9** and **10** (Scheme I).

Method A consists of treating the appropriate benzylamine with ethyloxalyl chloride,[9] converting the resultant oxamide to the imidoyl halide, and conversion of this material in situ with hydrazoic acid to the desired ester **9** or **10**.

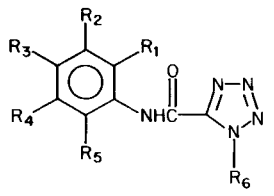
Method B consists of the direct reaction[16,17] of ethyl cyanoformate with benzyl azide or 4-methoxybenzyl azide[18] in a Teflon-lined bomb at 130 °C[19], resulting in an excellent yield of the ester **9** or **10**. Hydrolysis of the ester in ethanol with 1 equiv of potassium hydroxide yields the crystalline potassium salt **7** or **8**.

The tetrazoles **11–29** were prepared via the sequence of Scheme II. The potassium salt was converted to the acid chloride with oxalyl chloride–pyridine and was used directly.

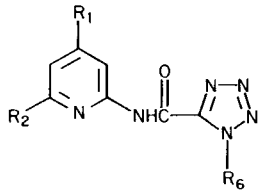
The benzyl-protected tetrazoles could be converted to the tetrazoles by hydrogenolysis with palladium on charcoal (method C); however, by using the 4-methoxybenzyl

(13) M. H. Poonian, E. F. Nowoswiat, J. F. Blount, T. H. Williams, R. G. Pitcher, and M. J. Kramer, *J. Med. Chem.*, **19**, 286 (1976). After we had started this work, a high-yield synthesis of this ester appeared: D. Moderhack, *Chem. Ber.*, **108**, 887 (1975).
(14) E. Oliveri-Mandalá and T. Passalacqua, *Gazz. Chim. Ital.*, **41**, 431 (1911).
(15) C. R. Jacobson, A. B. Kerr, Jr., and E. D. Amstutz, *J. Org. Chem.*, **19**, 1909 (1954).
(16) W. R. Carpenter, *J. Org. Chem.*, **27**, 2085 (1962), and references cited therein.
(17) A. S. Katner, U.S. Patent 3962272, 1976.
(18) Fr. Moulin, *Helv Chim. Acta*, **35**, 167 (1952).
(19) **Caution**! We have had one detonation in this procedure while attempting the condensation of 2.5 mol of each component in a regular unlined steel bomb. The temperature control of the oil bath had failed and the last recorded external temperature was 170 °C. A thermal stability study of 4-methoxybenzyl azide indicates a tendency for exothermic decomposition with evolution of a gas (nitrogen?) beginning at 170–180 °C, not becoming vigorous until approximately 210 °C.

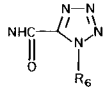
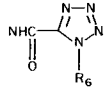
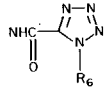
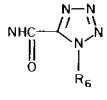
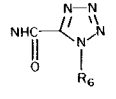
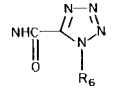
Table III. Intermediate 1-Protected Tetrazoles



30–45



46–48

no.	R_1	R_2	R_3	R_4	R_5	R_6[a]	mp, °C	% yield[b]	formula	anal.	recrystn solvent[c]
30	CN	H	H	H	H	4-MeO-Bzl	137–139	58	$C_{17}H_{14}N_6O_2$	C, H, N	A
31	CN	NHEt	H	H	H	4-MeO-Bzl	152–154	66	$C_{19}H_{19}N_7O_2$	C, H, N	A
32	CN	NMe_2	H	H	H	4-MeO-Bzl	171–173	56	$C_{19}H_{19}N_7O_2$	C, H, N	A
33	CN	c-NC_5H_{10}	H	H	H	4-MeO-Bzl	166–168	61	$C_{22}H_{23}N_7O_2$	C, H, N	A
34	CN	c-$N(CH_2CH_2)_2O$	H	H	H	Bzl	184–187	60	$C_{20}H_{19}N_7O_2$	C, H, N	A
35	CN	c-$N(CH_2CH_2)_2N$-CH_3	H	H	H	4-MeO-Bzl	177–179	65	$C_{22}H_{24}N_8O_2$	C, H, N	A
36	$CONH_2$	NMe_2	H	H	H	4-MeO-Bzl	130–132	60	$C_{19}H_{21}N_7O_3$	C, H, N	B
37	$CONH_2$	OMe	H	H	H	Bzl	190–192	58	$C_{17}H_{16}N_6O_3$	C, H, N	A
38	$CONH_2$	c-NC_5H_{10}	H	H	H	Bzl	175–177	64	$C_{22}H_{25}N_7O_3$	C, H, N	B
39	$CONH_2$	c-$N(CH_2CH_2)_2O$	H	H	H	Bzl	181–184	64	$C_{21}H_{23}N_7O_4$	C, H, N	C
40	$CONH_2$	c-$N(CH_2CH_2)_2N$-CH_3	H	H	H	Bzl	183–184	69	$C_{22}H_{26}N_8O_3$	C, H, N	A
41	H	CN	H	$HNCOCO_2Et$	H	Bzl	159–162	67	$C_{21}H_{19}N_7O_5$	C, H, N	C
42	H	CN	H		H	Bzl	206–209	52	$C_{27}H_{23}N_{11}O_4$	C, H, N	A
43	H	CN	H		Cl	Bzl	223–225	55	$C_{27}H_{22}N_{11}O_4Cl$	C, H, N; Cl[d]	C
44	H	$CONH_2$	H		H	4-MeO-Bzl	163–166	52	$C_{27}H_{25}N_{11}O_5$	C, H, N	D
45	H	CF_3	H		Cl	4-MeO-Bzl	185–186	56	$C_{27}H_{22}N_{10}ClF_3O$	C, H; N[e]	A
46	H	H				4-MeO-Bzl	111–112	61	$C_{15}H_{14}N_6O_2$	C, H, N	A
47	H					4-MeO-Bzl	188–191	74	$C_{25}H_{23}N_{11}O_4$	C, H; N[f]	A
48	Cl					4-MeO-Bzl	201–203	51	$C_{25}H_{22}ClN_{11}O_4$	C, H, N	B

[a] 4-MeO-Bzl = 4-methoxybenzyl; Bzl = benzyl. [b] Acylation step. [c] Solvents: A, acetonitrile; B, ethyl acetate–hexane; C, ethanol; D, DMF–ethanol. [d] Cl: calcd, 5.91; found, 6.57. [e] N: calcd, 21.78; found, 21.30. [f] N: calcd, 28.45; found, 29.39.

group, a standard trifluoroacetic acid–anisole deprotection procedure (method D) could be employed in better yield.

Results and Discussion

Tables I and II give the pharmacological data in the rat PCA test[9] of this class of compounds. It is obvious that they represent a potent orally active series of antiallergy agents. It is also clear that the most potent of these compounds has an ED_{50} very similar to that of the most potent of our oxanilic acids.[9] However, it is interesting to note that compound **18**, which is the tetrazole analogue of [[2-(aminocarbonyl)-3-methoxyphenyl]amino]oxoacetic acid ethyl ester,[9,20] shows a remarkable enhancement of potency (50–100 times), whereas the amino-substituted analogue **12** is at least 10 times less potent than the corresponding oxanilate. Similarly, the *N*-methylpiperazinyl derivative **16**, which was not very impressive as an oxanilate, is one of the most potent of the tetrazole compounds.

In terms of duration of activity, we found no appreciable increase with these tetrazoles over the corresponding carboxylates. For example, when compound **23** was administered (5 mg/kg) 15 min before challenge, no significant inhibition of the PCA response was found ip or po. Thus, although it was possible to prepare a tetrazole analogue of a carboxylic acid compound and retain the antiallergy activity, we were not able to prepare an analogue which increased the duration of activity in the rat PCA test. The benzyl-substituted tetrazole intermediates had little activity in the rat PCA assay.

Experimental Section

Melting points were taken on a Thomas-Hoover oil bath melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 21 spectrometer, and the NMR spectra were measured on a Varian A-60 or a JEOL Model C-60 HL spectrometer. All spectra were consistent with the assigned structures. Combustion analyses were performed on a Perkin-Elmer Model 240 elemental analyzer and were within ±0.4% of the theoretical values except as noted.

Potassium 1-Benzyltetrazole-5-carboxylate (7). To a solution of 11.6 g (0.05 mol) of the ethyl ester **9** in 60 mL of warm ethanol was added 3.96 g (0.06 mol) of KOH in 7 mL of H_2O. The salt precipitated immediately; however, the mixture was kept at room temperature overnight and filtered, and the product was washed with ethanol and then with ether: yield 11 g (90%); mp 200 °C dec. Anal. ($C_9H_7N_4O_2K$) C, H, N.

Potassium 1-(4-Methoxybenzyl)tetrazole-5-carboxylate (8). This was prepared from the corresponding ester **10** as above, mp 202–204 °C.

Ethyl 1-Benzyltetrazole-5-carboxylate (9). Method A. To a solution of 20.7 g (0.1 mol) of ethyl *N*-benzyloxamate and 9.7 g (0.125 mol) of pyridine in 100 mL of methylene chloride at 25 °C was slowly added 26 g (0.125 mol) of PCl_5 through a Gooch tube. After 1 h at room temperature, 112 mL of 1.8 M hydrazoic acid in benzene was added, and the resultant solution was stirred an additional 1 h at room temperature and then heated at reflux for 5 h. The reaction mixture was cooled overnight, poured into cold $NaHCO_3$ solution, and ether was added, and the organic layer was separated and then washed successively with $NaHCO_3$ solution, 1 N HCl solution, and brine. Evaporation of the dried solvent gave 22.5 g of an oil, which was distilled on a falling film molecular still at 135 °C and 0.15 mm, giving 11 g (48%) of product, mp 58–60 °C. Anal. ($C_{11}H_{12}N_4O_2$) C, H, N.

Method B. A mixture of 2.66 g (0.02 mol) of benzyl azide[18] and 2.2 g (0.022 mol) of ethyl cyanoformate was heated in a Teflon-lined steel bomb at 130 °C for 6 h. The resultant mixture was passed through 100 g of silica gel with methylene chloride, and the desired product was collected and recrystallized from ether–pentane: yield 2.9 g (62%).

Ethyl 1-(4-Methoxybenzyl)tetrazole-5-carboxylate (10). This material was prepared in the same way as ester **9**, substituting ethyl *N*-(4-methoxybenzyl)oxamate in method A and using 4-methoxybenzyl azide in method B: yield 67%; mp 50–52 °C.

General Acylation Procedure. 1-Benzyl-*N*-[2-cyano-3-(4-morpholinyl)phenyl]-1*H*-tetrazole-5-carboxamide (34). To a mixture of 7.3 g (0.03 mol) of the potassium salt (**7**) and 1.5 mL (0.019 mol) of pyridine in 135 mL of benzene at 0 °C was rapidly added 25 mL (0.03 mol) of oxalyl chloride. The mixture is stirred at 15 °C for 0.5 h and then evaporated to dryness at 15 °C. To the residue was added 100 mL of benzene, which was evaporated again. This washing was repeated. The resulting crude 1-benzyl-5-tetrazolecarbonyl chloride was dissolved in 130 mL of CH_2Cl_2 and was added to a solution of 2-amino-6-(4-morpholinyl)benzonitrile[9] (6.1 g, 0.03 mol) and 2.7 mL (0.034 mol) of pyridine in 130 mL of CH_2Cl_2 at 5 °C. After stirring for 2 h at room temperature, the reaction mixture was washed successively with water (twice) and brine and then dried and evaporated. The residue was recrystallized from acetonitrile: yield 7 g (60%).

Deprotection Procedures. Method C. *N*-[2-Cyano-3-(4-morpholinyl)phenyl]-1*H*-tetrazole-5-carboxamide (15). The 1-benzyl derivative **34** (2 g) was hydrogenated in acetic acid with 10% Pd/C (1 g) overnight. The mixture was filtered through Celite, and the filter cake was thoroughly washed with hot acetic acid. The combined filtrates were evaporated to dryness, triturated with 10 mL of concentrated NH_4OH in 60 mL of water, and filtered. The filtrate was acidified with 1 N HCl to pH 2, and the product was collected and recrystallized from acetonitrile: yield 0.5 g (33%).

Method D. *N,N'*-(2,6-Pyridinediyl)bis[1*H*-tetrazole-5-carboxamide] Sodium Derivative (28). A mixture of 13.3 g (0.025 mol) of the protected tetrazole **47** and 27 mL of anisole in 270 mL of F_3AcOH was heated at reflux for 30 min. Evaporation of the solvent and trituration with ether gave 4.5 g (60%) of the deprotected tetrazole, which was converted to the sodium salt by the method below.

Sodium Salts of Tetrazoles. A suspension of the tetrazole in water was treated with the necessary amount of 1.00 N NaOH. The resultant solution was lyophilized to give the desired sodium salts, frequently as a multiple hydrate.

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