dichloromethane (25 mL). The tan solid was filtered off and suspended in cold (0 °C) DMF (50 mL). Anhydrous ammonia was bubbled through for 10 min, and the resulting solution was allowed to stand at room temperature overnight. The DMF solution was evaporated to dryness under reduced pressure, and the residue was washed with CH_2Cl_2 and ether and dried: yield 3.0 g; mp 340–345 °C dec.

Method M. 7-Chloro-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carbonitrile. 7-Chloro-4,9-dihydro-4-methyl-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamide (3 g, 0.011 mol) was heated at 56 °C with thionyl chloride (1.6 mL, 0.022 mol) and DMF (35 mL) for 18 h. The resulting clear solution was evaporated to dryness, and the residue was treated with water (600 mL). After the solution was left standing for 1 h, the crude nitrile was filtered off, washed with water, and recrystallized from a DMF–EtOH mixture: yield 2.4 g (84%); mp 350 °C; IR (Nujol) 2240, 1705, 1695, 1600 cm^{-1}; UV (EtOH) λ_{max} 222 nm (ϵ 26 500), 239 (43 500), 252 (24 250), 288 (8250), 297 (11 500), 375 (6250); NMR (F_3AcOH) δ 4.1 (s, 3), 6.9 (s, 1), 7.7 (d, 1), 8.10 (d, 1), 8.6 (d, 1).

Method N. 4,9-Dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carbonitrile. A suspension of 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxamide (5.05 g, 0.0195 mol) in phosphorus oxychloride (100 mL) was heated under reflux for 2 h. After the suspension was left standing for 2 days at room temperature, excess phosphorus oxychloride was removed under reduced pressure, and the residue was suspended in saturated sodium bicarbonate solution (100 mL). The solid was filtered off, washed with water, and dried: yield 3.0 g; mp 292–297 °C dec.

Method O. Substituted 2-Aminobenzoic Acid Hydrazide. The substituted 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (substituted isatoic anhydride) (0.14 mol) was slowly added to a cold (5–10 °C) 18% aqueous solution of hydrazine (225 mL). During the exothermic reaction, a white solid was formed. After the solution was stirred at room temperature overnight, the product was filtered off and washed with water. The hydrazide was used as is *or* was purified, if necessary, via crystallization before use.

Compounds **95** and **96** were prepared by catalytic (5% Pd/C) reduction of **97** and **92**, respectively.

Method P. Methyl 2-Amino-3,5-dimethoxybenzoate (14). A mixture of methyl 3,5-dimethoxy-2-nitrobenzoate[10] (39.0 g, 0.162 mol), 5% Pd on charcoal (2.0 g), methanol (200 mL), and tetrahydrofuran (200 mL) was shaken in an atmosphere of hydrogen at 52 lb of pressure for 46 h when the theoretical amount of hydrogen was taken up. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was recrystallized from methanol: yield 28.6 g; mp 93–95 °C. Anal. ($C_{10}H_{13}NO_4$) C, H, N.

Method Q. 8-Methoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (3-Methoxyisatoic Anhydride). To a solution of 2-amino-3-methoxybenzoic acid (8.36 g, 0.05 mol) in dioxane (75 mL) and benzene (25 mL) was added a 12.5% solution of phosgene in benzene (46 g) with cooling in an ice bath. After the addition, the reaction mixture was stirred at room temperature overnight. The precipitated product was filtered off, washed with benzene and ether, dried, and used without further purification: yield 9.1 g (94%); mp 263–264 °C dec.

Method R. 6,8-Dimethoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (3,5-Dimethoxyisatoic Anhydride; 105). A mixture of methyl 2-amino-3,5-dimethoxybenzoate (14; 21.2 g, 0.1 mol) and 1 N sodium hydroxide solution (100 mL) was refluxed for 2.0 h, cooled, and buffered with dry ice. The solution was treated with 12.5% phosgene in benzene (110 mL) in an ice bath. The mixture was stirred for 4.0 h, and the product was filtered off and dried in vacuo: yield 22.0 g; mp 263–265 °C dec.

Method S. 1,6-Dimethyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (*N*,5-Dimethylisatoic Anhydride; 109). A solution of 5-methylisatoic anhydride (100; 26.6 g, 0.15 mol) in DMF (150 mL) was treated with anhydrous sodium carbonate (17.5 g, 0.165 mol) and then with iodomethane (32 g), and the mixture was stirred at 20–25 °C for 18 h. The reaction mixture was poured into ice–water (1.25 L) and the resulting precipitate of *N*,5-dimethylisatoic anhydride was collected by filtration, washed with water, and dried: yield 26.3 g (92%); mp 166–169 °C.

Method T. 6-Carbomethoxy-1-methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (5-Carbomethoxy-*N*-methylisatoic Anhydride; 112). Diazomethane generated from Diazald (100 g, 0.467 mol) was slowly distilled with ether (1000 mL) into a stirring mixture of 5-carboxyisatoic anhydride (104; 27.8 g, 0.134 mol) in THF (650 mL) at 5 °C. After all the diazomethane had been distilled, the reaction mixture was stirred at room temperature for 1.0 h. It was cooled to 5 °C and decomposed with acetic acid, and the crystals were filtered off: yield 17.1 g (54%); mp 163–166 °C.

1-[(4,9-Dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazolin-2-yl)carbonyl]-1*H*-imidazole (10). To a warm (75 °C) solution of 4,9-dihydro-5-methoxy-9-oxopyrazolo[5,1-*b*]quinazoline-2-carboxylic acid (0.52 g) in DMF (100 mL) was added 1,1′-carbonyldiimidazole (0.49 g) and the mixture was heated at 85 °C for 15 min, after which a yellow solid slowly crystallized out: yield 0.24 g; mp 296–300 °C. Anal. ($C_{15}H_{11}N_5O_3$) C, H, N.

Compound **10** was converted to **59** and **72** by reacting it with 1*H*-tetrazol-5-amine and ammonia, respectively, in DMF.

Acknowledgment. The authors express their appreciation to Dr. C. F. Schwender for stimulating discussions and constant encouragement during the preparation of this paper. The authors thank Dr. F. MacKellar and A. D. Lewis and their associates of the Department of Analytical–Physical Chemistry for spectral determinations. Microanalyses were done by U. Zeek and C. Childs and their associates.

N-(Aminophenyl)oxamic Acids and Esters as Potent, Orally Active Antiallergy Agents

Dieter H. Klaubert,* John H. Sellstedt, Charles J. Guinosso, Robert J. Capetola,[1] and Stanley C. Bell

Research Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087. *Received September 12, 1980*

A series of *N*-(2-cyano-substituted-phenyl)oxamates was prepared by acylation of the appropriate anthranilonitrile with ethyloxalyl chloride. Hydrolysis with sodium hydroxide gave the corresponding oxamic acid sodium salts. These compounds were extremely potent when tested in the rat passive cutaneous anaphylaxis (PCA assay either by the ip or the po route of administration). One of the sodium salts, [[2-cyano-3-(methylamino)phenyl]oxoacetic acid sodium salt (**11a**, Wy-41 195), has an ED_{50} value of 0.07 mg/kg po and has been selected for further evaluation.

The search for compounds possessing antiallergic activity of the type displayed by disodium cromoglycate (1),[2] but orally active and more potent, has been undertaken by numerous laboratories.[3-5] This paper and an accom-

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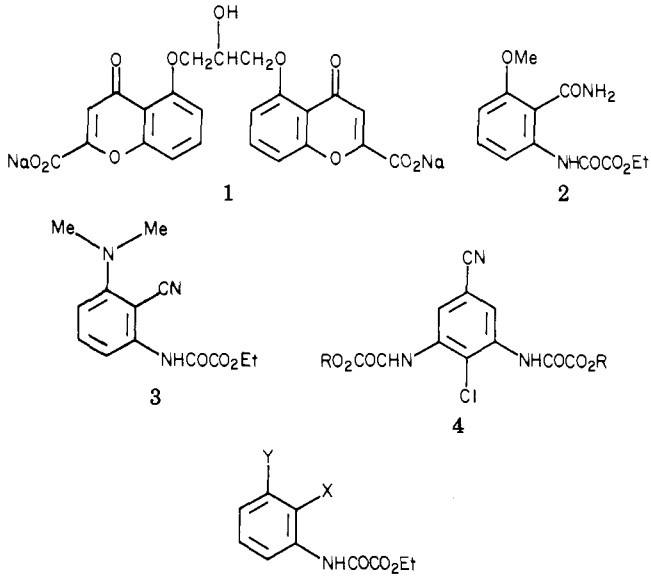


1 2 3 4

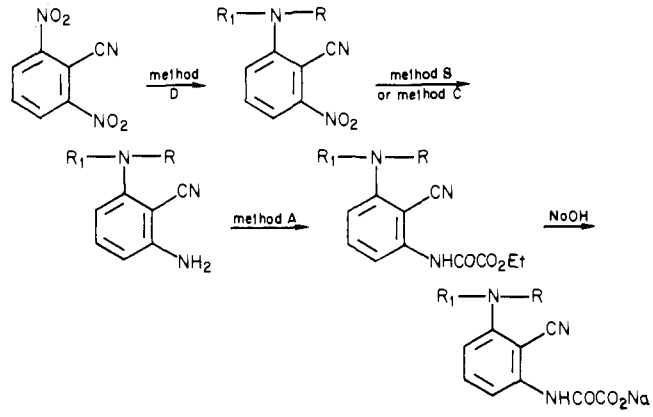
5, X = CN; Y = OMe
5a, X = $CONH_2$; Y = NMe_2

panying note[6] describe our efforts in this area.

Our initial attempts[3,7] led to the discovery of the oxanilic acids, with 2′-carbamoyl-3′-methoxyoxanilic acid ethyl ester (**2**) being chosen for further evaluation. Although orally active in the rat passive cutaneous anaphylaxis test (PCA),[8] this compound did not show the potency of some of the compounds, i.e., **3**, to be discussed in this report. Recently, Wright and Hall[9] published their results on a series of bisoxamic acids and esters, such as **4**, which appear to have a very high level of potency as well.

Chemistry. While pursuing routine structure modifications of **2** we found that replacing the carbamoyl group with a cyano group (**5**) or replacing the methoxy group with an amine substituent (**5a**) produced no improvement in the potency. Surprisingly, when both of these changes were made, i.e., compound **3**, a much greater level of potency was achieved. Our previous notions about the structure–activity relationships were obviously incorrect and we therefore set out to prepare a series of compounds with the largest possible spread of physicochemical parameters. As such, we chose the substituents suggested by Norrington et al.[10] Except for the ester **6** which was prepared by the dehydration[11] of the carbamoyl derivative

Scheme I



79 (vide infra) and the amine analogues **7** and **8** which were obtained by reduction of the nitro derivatives **25** and **27**, all of the oxamic acid esters (Scheme I and Table I) were prepared by the usual acylation[3,9,12] of the appropriately substituted anthranilonitrile (method A). The problem therefore reduced itself to the synthesis of these anthranilonitriles. Those which were not known (Table III) were usually prepared by the reduction of the corresponding *o*-nitrobenzonitrile with iron powder in the presence of hydrochloric acid (method B) or by transfer hydrogenation[13] using cyclohexene–palladium on charcoal (method C). Not surprisingly,[14] the use of Raney nickel–hydrazine[15] or hydrogenation over palladium on charcoal usually led to the anthranilamide contaminated with small amounts of the desired anthranilonitrile, presumably via the well-known intramolecular transfer of oxygen.[16] Many of the anthranilonitriles were isolated as oils (see Table III) and were acylated directly without further purification.

Four of the anthranilonitriles were prepared by different procedures and deserve some comment. 2-Amino-6-fluorobenzonitrile (**36**) was prepared by treatment of 2,6-difluorobenzonitrile[17] with ammonia, which resulted in displacement of one of the activated[18] fluorine atoms. 2-Amino-6-bromobenzonitrile (**37**) was prepared from 4-bromoisatin[19] by a modification of the method of Borsche and Sander,[20] while 2-amino-6-(methylsulfonyl)benzonitrile (**38**) could be obtained by *m*-chloroperbenzoic acid oxidation of the sulfide **39**. Of special interest is the preparation of 2-amino-6-nitrobenzonitrile (**40**), which allowed the preparation of three different oxamic acid esters, **8**, **27**, and **34**. Our first inclination was to attempt the reduction of 2,6-dinitrobenzonitrile[3] using one of the above methods of reduction, or stannous chloride, or one of the sulfide-derived reagents.[21] All of these reagents gave varying amounts of numerous products and were not

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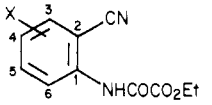
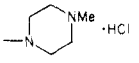
Table I. Physical and Pharmacological Data of Oxanilic Acid Esters



no.	X	mp, °C	recrystn solvent[a] (% yield)	formula	anal.	rat PCA ED_{50}, mg/kg ip	rat PCA ED_{50}, mg/kg po
3	3-NMe_2	124-126	I (69)	$C_{13}H_{15}N_3O_3$	C, H, N	0.2	4.2
5	3-OMe	144-146	II (91)	$C_{12}H_{12}N_2O_4$	*b*	5.3	55.5
6	4-NMe_2	150-152	II (66)	$C_{13}H_{15}N_3O_3$	C, H, N	1.0	2.4
7	4-NH_2	137-139	II (93)	$C_{11}H_{11}N_3O_3$	C, H, N	1.0	8.8
8	3-NH_2	133-136	II (84)	$C_{11}H_{11}N_3O_3$	C, H, N	0.05	0.07
9	5-NMe_2	139-142	II (81)	$C_{13}H_{15}N_3O_3$	C, H, N	1.9	>100
10	6-NMe_2	69-71	II (58)	$C_{13}H_{15}N_3O_3$	C, H, N	NA	*c*
11	3-NHMe	136-139	II (79)	$C_{12}H_{13}N_3O_3$	C, H, N	0.2	0.1
12	3-NHEt	99-102	I (77)	$C_{13}H_{15}N_3O_3$	C, H, N	0.03	0.03
13	3-NHPr	95-96	I (79)	$C_{14}H_{17}N_3O_3$	C, H, N	0.5	0.7
14	3-NHBu	101-105	II (86)	$C_{15}H_{19}N_3O_3$	C, H, N	0.3	0.3
15	3-NMeEt	81-82	II (85)	$C_{14}H_{17}N_3O_3$	C, H, N	0.3	0.5
16	3-NMe-*i*-Pr	64-67	III (71)	$C_{15}H_{19}N_3O_3$	C, H, N	0.3	1.2
17	3-NEt_2	57-59	II (83)	$C_{15}H_{19}N_3O_3$	C, H, N	0.7	0.9
18	3- 	138-141	II (87)	$C_{15}H_{17}N_3O_3$	C, H, N	(83)[d]	(83)[d]
19	3- 	98-100	IV (79)	$C_{16}H_{19}N_3O_3$	C, H, N	2.2	NA
20	3- 	204-206	V (71)	$C_{16}H_{20}N_4O_3 \cdot HCl$	C, H, N, Cl	0.04	10.3
21	3- 	115-117	II (84)	$C_{15}H_{17}N_3O_4$	C, H, N	1.2	6.3
22	3-Cl	103-106	VI (83)	$C_{11}H_9N_2O_3Cl$	C, H, N, Cl	(56)[d]	*c*
23	3-CH_3	106-108	VII (81)	$C_{12}H_{12}N_2O_3$	C, H, N	5.3	4.6
24	3-  , 4-CF_3	106-109	VI (79)	$C_{16}H_{16}N_3O_4F_3$	C, H, N	0.1	>100
25	4-NO_2	137-139	II (86)	$C_{11}H_9N_3O_5$	C, H, N	(33)[d]	*c*
26	H					0.4	2.9
27	3-NO_2	111-113	II (78)	$C_{11}H_9N_3O_5$	C, H, N	0.4	82
28	3-Br	128-130	II (82)	$C_{11}H_9N_2O_3Br$	C, H, N	NA	*c*
29	3-SO_2Me	159-162	II (64)	$C_{12}H_{12}N_2O_5S$	C, H, N, S	NA	*c*
30	3-$CHMe_2$	85-87	VII (80)	$C_{14}H_{16}N_2O_3$	C, H, N		(18)[d]
31	3-*i*-PrO	82-84	VI (77)	$C_{14}H_{16}N_2O_4$	C, H, N	2.0	1.0
32	3-CO_2Me	106-108	II (53)	$C_{13}H_{12}N_2O_5$	C, H, N	1.2	0.8
33	3-F	84-86	II (67)	$C_{11}H_9N_2O_3$	C, H, N	1.2	59
34	3-NHAc	188-190	II (60)	$C_{13}H_{13}N_3O_4$	C, H, N	(91)[d]	(91)[d]
35	3-*n*-AmO	78-81	VI (84)	$C_{16}H_{20}N_2O_4$	C, H, N	(25)[d]	*c*
1 (cromolyn sodium)						8	NA

[a] Solvents: I, benzene-hexane; II, EtOH; III, ether-hexane; IV, hexane; V, EtOH-HCl-ether; VI, EtOAc-hexane; VII, cyclohexane. [b] Reference 3. [c] Intraperitoneal test results dictated no further study. [d] Data expressed as percent inhibition of wheal size (PCA) at 50 mg/kg; $p < 0.001$ from control; NA = not active at 100 mg/kg.

suitable to our large-scale needs. Numerous failures in our efforts at alternate total synthesis of this intermediate forced us to return to a selective reduction technique whereupon we found that a simple change of solvents in the iron reduction (see Experimental Section) allowed for large-scale preparation of the highly desirable intermediate **40**.

Most of the requisite substituted nitrobenzonitriles (Table IV) were prepared by the facile[22,23,24] displacement of one of the nitro groups in 2,6-dinitrobenzonitrile (method D). Scheme II gives the alternate routes used to prepare a few of the nitrobenzonitriles.

3-Nitrophthalamic acid[25] (**64**) was esterified with diazomethane and then dehydrated with phosphorus oxychloride–triethylamine[11] (method E) to give the nitrile **65**. 2-(*o*-Aminophenyl)propene[26] (**66**) was hydrogenated to 2-isopropylaniline, which was converted to the nitrile **67** by the method of Howard[27] and Ashton and Hynes.[22] 3-Chloro-2-nitrobenzoic acid (**68**) was converted to the amide **69**, treated with dimethylamine to form the aniline **70**, and then dehydrated as above to give 2-(dimethylamino)-6-nitrobenzonitrile (**71**). 2-(Diethylamino)-6-nitrobenzonitrile (**72**) could not be prepared by treatment of 2,6-dinitrobenzonitrile with diethylamine and instead

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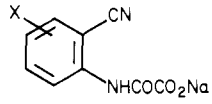
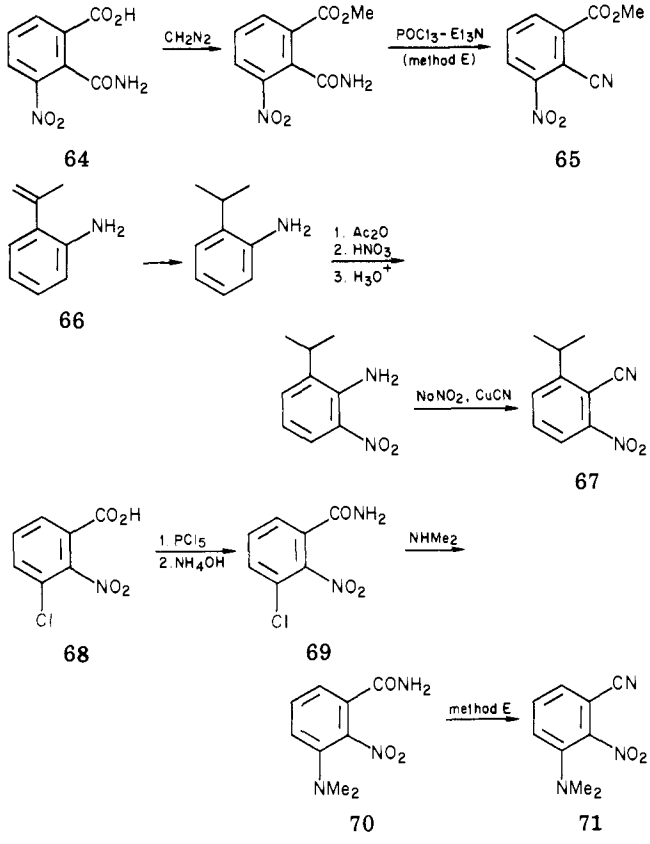
Table II. Physical and Pharmacological Data of Oxanilic Acid Sodium Salts



no.[a]	formula[b]	solvate	mp, °C	po act.[c] in rat PCA, % inhibn at 1.0 mg/kg
3a	$C_{11}H_{11}N_3O_3$	$0.5H_2O$	279-281	54.7
8a	$C_9H_7N_3O_3$	$0.4H_2O$	303 dec	21.2[d]
11a	$C_{10}H_9N_3O_3$	none	274-276	96.0
12a	$C_{11}H_{11}N_3O_3$	$0.25H_2O$, 0.2EtOH	135-137	58.9
13a	$C_{12}H_{13}N_3O_3$	$0.7H_2O$	125-129	83.1
14a	$C_{13}H_{15}N_3O_3$	none	252-254	93.5
15a	$C_{12}H_{13}N_3O_3$	$0.7H_2O$	87-89	56.3
17a	$C_{13}H_{15}N_3O_3$	$0.7H_2O$	115-120	99.2
21a	$C_{13}H_{13}N_3O_4$	$0.5H_2O$	154-158	14.1[d]
23a	$C_{10}H_8N_2O_3$	$0.7H_2O$	255-260	32.3[d]
31a	$C_{12}H_{12}N_2O_4$	$0.5H_2O$	228	75.1
32a	$C_{11}H_8N_2O_5$	$0.8H_2O$	130-150	24.5[d]

[a] Numbering corresponds to substituents in Table I. [b] Combustion analyses were correct for sodium salt, solvates; formula given for parent acid, unsolvated form. [c] Dosing at 10 min before challenge; $p \leq 0.001$ from control except where noted. [d] $p \leq 0.05$ from control.

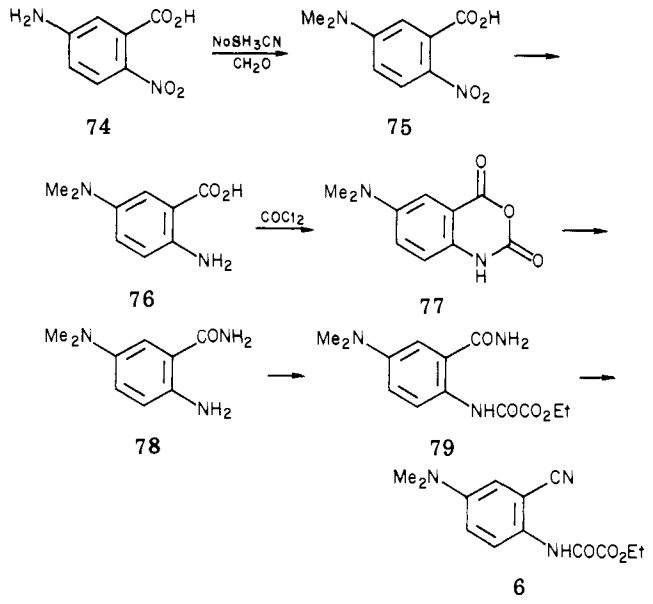
Scheme II



was obtained by ethyl iodide alkylation of the ethylamine derivative **73**.

Only the 4-(dimethylamino) derivative **6** required a different scheme (Scheme III). Reductive alkylation of 5-amino-2-nitrobenzoic acid (**74**) followed by reduction of the nitro group and conversion to the anthranilamide **78** via the isatoic anhydride **77** eventually led to the oxanilic

Scheme III



ester **79**. Although thermally these amides dehydrate to the corresponding quinazolines,[3] we found that the use of $POCl_3$–Et_3N readily results in formation of the nitrile **6**, although the reaction took 6 days in this case.

All of the salts in Table II were prepared by simple hydrolysis of the corresponding ester in ethanol with 1 equiv of aqueous sodium hydroxide. The salt invariably crystallized out, usually as a solvate.

Discussion

As can be seen from the data presented in Table I and II, many of the 3-amino-substituted oxanilic acids and esters are very potent, orally active antiallergy agents. This is a very interesting finding, since in our previous series[3] we noted a lack of oral activity in the rat PCA upon hydrolysis of the esters.

In comparing the oral activity of the esters in the present series, it is apparent that the most potent compounds have an amino substituent at position 3, and none of the compounds **26** to **35**, prepared for a structure–activity relationship, showed any improvement in potency. Also, the ring-positional isomers **3**, **6**, **9**, and **10** indicate that substitutions at positions 3 and 4 are much preferred over substitution at position 5 or 6, with the latter giving a compound devoid of activity. In addition, the compounds with the highest oral activity have at least one hydrogen on the amine group in position 3. That is, the secondary anilines, e.g., **11** are more active orally than the tertiary anilines, e.g., **3**. When the amine is part of a ring, the resultant tertiary anilines, e.g., **18** or **19**, show very poor oral activity.

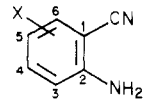
Finally, it should be noted that compound **11a** (Wy-41 195) has been extensively studied (ED_{50} = 0.07 mg/kg po) and will be further evaluated as a potential drug.

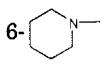
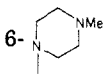
Experimental Section

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

Biological Methods. The antiallergic properties of the compounds were assessed using the passive cutaneous anaphylaxis (PCA) test in rats passively sensitized to ovalbumin as follows.

Table III. Physical Data of Anthranilonitriles



no.	X	mp, °C	recrystn solvent[a]	formula	anal.	method of reduction (% yield)
36	6-F	125-127	I	$C_7H_5N_2F$	C, H, N	*d* (55)
37	6-Br	152-154	VI	$C_7H_5N_2Br$	C, H, N	*d* (51)
38	6-SO_2Me	169-174	II	$C_8H_8N_2O_2S$	C, H, N, S	*d* (68)
39	6-SMe	84-86	VI	$C_8H_8N_2S$	C, H, N, S	B (65)
40	6-NO_2	192-196	VI	$C_7H_5N_3O_2$	C, H, N	B, *d* (56)
41	6-NMe_2	oil	*c*	$C_9H_{11}N_3$	C, H, N	B (70)
42	4-NMe_2	*b*				B (63)
43	3-NMe_2	*b*				C (54)
44	6-NHMe	*b*				B (74)
45	6-NHEt	*b*				B (69)
46	6-NHPr	*b*				B (87)
47	6-NHBu	63-65	VI	$C_{11}H_{15}N_3$	N; C, H[e]	C (71)
48	6-NMeEt	*b*				B (77)
49	6-NMe-*i*-Pr	*b*				B (81)
50	6-NEt_2					C (89)
51	6- 	112-114	VI	$C_{11}H_{13}N_3$	C, H, N	C (60)
52	6- 	oil	*c*	$C_{12}H_{15}N_3$	C, H, N	C (64)
53	6- 	151-154	VI	$C_{12}H_{16}N_4$	C, H, N	B (52)
54	6- 	154-157	II	$C_{11}H_{13}N_3O$	C, H, N	B (78)
55	6-Cl	132-136	VI	$C_7H_5N_2Cl$	C, H, N, Cl	B (66)
56	6-Me	129-131	V	$C_8H_8N_2$	C, H, N	B (83)
57	6-  , 4-CF_3	166-171	II	$C_{12}H_{12}N_3OF_3$	C, H, N	B (68)
58	6-OMe	136-140	II	$C_8H_8N_2O$	*f*	C (79)
59	6-$CHMe_2$	66-68	IV	$C_{10}H_{12}N_2$	C, H, N	B (77)
60	6-*i*-PrO	65-68	III	$C_{10}H_{12}N_2O$	C, H, N	C (74)
61	6-CO_2Me	107-109	I	$C_9H_8N_2O_2$	C, H, N	C (53)
62	6-NHAc	149-151	VI	$C_9H_9N_3O$	C, H, N	C (56)
63	6-*n*-AmO	73-76	III	$C_{12}H_{16}N_2O$	C, H, N	C (67)

[a] Solvents: I, benzene-hexane; II, EtOH; III, ether-hexane; IV, hexane; V, EtOH-H_2O; VI, EtOAc-hexane. [b] Used directly as a crude oil. [c] Chromatographed on silica gel, CH_2Cl_2. [d] See text for preparation. [e] C: calcd, 69.81; found, 69.06. H: calcd, 7.99; found, 7.49. [f] Reference 3.

Rat anti-ovalbumin serum containing IgE was elicited in male Sprague–Dawley rats (200–250 g) by injection (ip) of 0.1 mg of 2 × crystallized ovalbumin containing 1×10^{10} heat-killed *Bordetella pertussis* organisms (Connaught Labs) on day 0. On day 16 the animals with infected with 2500–3000 *Nippostrongylus brasiliensis* third-stage larvae subcutaneously. On day 21 the rats were boosted ip with 0.01 mg of ovalbumin and bled on day 30 by cardiac puncture after anesthetization with CO_2. The serum was frozen until use. The presence of IgE was confirmed by the existence of PCA activity after a 5-day latent period and by heat lability at 50 °C for 1 h. Male Sprague–Dawley rats (200 g) were passively sensitized with this serum by injection (id) of 0.05 mL of a 1:100 dilution on their shaved dorsal surface. After a 48-h latent period, the animals were challenged (iv) with 1.0 mL of an 0.8% solution of ovalbumin containing 5 mg of Evans blue. Forty minutes later the animals were sacrificed, the dorsal skin was reflected, and the resulting stained wheals were measured as the product (mm^2) of the longest diameter and its perpendicular. Drugs were administered ip and po 5 min before antigen challenge.

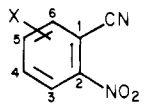
In order to estimate the median effective dose (ED_{50}), regression lines were found using at least four log-spaced doses and five rats for each dose. The ED_{50} value, defined as the dose (milligram/kilogram) which reduces the wheal size to one-half that of the control, was obtained by the method of inverse prediction.

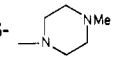
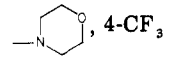
General Chemical Methods. Method A. [[2-Cyano-3-(methylamino)phenyl]amino]oxoacetic Acid Ethyl Ester (11). To a solution of 16 g (0.11 mol) of 2-amino-6-(methylamino)benzonitrile (**44**) and 8.7 g (0.11 mol) of pyridine in 150 mL of methylene chloride at 0 °C was added dropwise a solution of 14.9 g (0.11 mol) of ethyloxalyl chloride in 25 mL of methylene chloride. The reaction mixture was allowed to come to room temperature, stirred for 2 h, and poured into water. The organic phase was separated, dried, and evaporated, and the residue was recrystallized.

Method B. 2-Amino-6-(1-morpholinyl)benzonitrile (54). To a mixture of 8.5 g (0.036 mol) of 2-(1-morpholinyl)-6-nitrobenzonitrile (**89**) in 20 mL of methanol and 20 mL of concentrated hydrochloric acid was added 6.2 g of iron powder in portions. After the addition was complete, the reaction mixture was brought to reflux, stirred for 15 min, and poured into 200 mL of ice–water. The mixture was extracted with methylene chloride. After the organic phase was dried and evaporated, the residue was recrystallized.

Method C. 2-Amino-6-(butylamino)benzonitrile (47). A mixture of 14.8 g (0.07 mol) of 2-(butylamino)-6-nitrobenzonitrile (**83**), 6.8 g of 10% Pd on charcoal, and 27 g (0.33 mol) of cyclohexene in 200 mL of ethanol was heated at reflux for 15 min. The

Table IV. Physical Data of Nitrobenzonitriles



no.	X	mp, °C	recrystn solvent[a]	formula	anal.	method of preparation (% yield)
65	6-CO_2Me	140-142	II	$C_9H_6N_2O_4$	C, H, N	E (78)
67	6-$CHMe_2$	89-91	VI	$C_{10}H_{10}N_2O_2$	C, H, N	*b* (13)
71	3-NMe_2	99-101	II	$C_9H_9N_3O_2$	C, H, N	E (66)
72	6-NEt_2	39-41	IV	$C_{11}H_{13}N_3O_2$	C, H, N	*b* (71)
73	6-NHEt	114-116	III	$C_9H_9N_3O_2$	C, H, N	D (79)
80	6-NMe_2	115-117	I	$C_9H_9N_3O_2$	C, H, N	D (83)
81	6-NHMe	203-206	III	$C_8H_7N_3O_2$	C, H, N	D (74)
82	6-NHPr	80-82	III	$C_{10}H_{11}N_3O_2$	C, H, N	D (82)
83	6-NHBu	72-74	III	$C_{11}H_{13}N_3O_2$	C, H, N	D (77)
84	6-NMeEt	60-63	I	$C_{10}H_{11}N_3O_2$	C, H, N	D (78)
85	6-NMe-*i*-Pr	70-72	II	$C_{11}H_{13}N_3O_2$	C, H, N	D (84)
86	6- 	110-112	III	$C_{11}H_{11}N_3O_2$	C, H, N	D (77)
87	6- 	116-119	I	$C_{12}H_{13}N_3O_2$	C, H, N	D (74)
88	6- 	126-129	I	$C_{12}H_{14}N_4O_2$	C, H, N	D (83)
89	6- 	152-155	I	$C_{11}H_{11}N_3O_3$	C, H, N	D (88)
90	6-  , 4-CF_3	174-178	II	$C_{12}H_{10}N_3O_3F_3$		D (74)
91	6-SMe	179-181	V	$C_8H_6N_2O_2S$	C, H, N	D (71)
92	6-NHAc	186-188	V	$C_9H_7N_3O_3$	C, H, N	*b* (69)

[a] Solvent: I, benzene–hexane; II, ethyl acetate–hexane; III, ethanol; IV, hexane; V, ethyl acetate; VI, cyclohexane. [b] See text; yield is overall from the starting material given.

mixture was cooled, filtered through Celite, and evaporated to dryness. The residue was recrystallized from the appropriate solvent.

Method D. 2-(Methylamino)-6-nitrobenzonitrile (81). To a solution of 19.3 g (0.1 mol) of 2,6-dinitrobenzonitrile in 100 mL of DMF was added 30 mL (0.4 mol) of 40% aqueous methylamine. The temperature rose to 50 °C and was kept there for 10 min, and the reaction mixture was poured into ice–water. The resultant precipitate was filtered off, dried, and recrystallized.

Method E. 2-Carbomethoxy-6-nitrobenzonitrile (65). 2-Carbomethoxy-6-nitrobenzamide was prepared from 3-nitrophthalamic acid[25] (**64**) with diazomethane in ether–methanol. The product was recrystallized from methanol, mp 174–176 °C.

To 2.24 g (0.01 mol) of the above amide in 50 mL of chloroform was added 1.3 mL (0.013 mol) of $POCl_3$ in 10 mL of chloroform. After 3 h the mixture was cooled to 0 °C and 8 mL (0.06 mol) of triethylamine was added dropwise. The mixture was stirred overnight at room temperature and poured into dilute HCl, and after the usual aqueous washings the crude product was chromatographed on silica gel ($CHCl_3$) to give 1.6 g of the desired product.

2-Amino-6-fluorobenzonitrile (36). A solution of 19 g (0.14 mol) of 2,6-difluorobenzonitrile[17] in 200 mL of ethanol was saturated with ammonia gas at 0 °C and then heated in a bomb at 140 °C for 6 h. The solution was cooled, evaporated to dryness, and water was added. The solid was removed by filtration, dried, and recrystallized: yield 10.2 g.

2-Amino-6-bromobenzonitrile (37). A mixture of 22 g (0.1 mol) of 4-bromoisatin,[19] 8 g (0.13 mol) of hydroxylamine hydrochloride, and 16 g (0.2 mol) of sodium acetate in 250 mL of water was warmed to reflux for 2 h, cooled, and filtered. The product, mp 234–236 °C dec, was used directly in the next step.

To 24 g (0.16 mol) of $POCl_3$ was added 9 g (0.037 mol) of the above isatin oxime followed by 8 g (0.038 mol) of PCl_5. The mixture was heated on a steam bath for 1 h and poured into 140 g of sulfuric acid and 60 g of ice at 0 °C. After the mixture was stirred for 15 min, ice–water was added, the mixture was filtered, and the filtrate was neutralized with sodium hydroxide. The yellow product was collected, dried, and recrystallized: yield 4.5 g (51% overall).

2-Amino-6-(methylsulfonyl)benzonitrile (38). To 9 g (0.055 mol) of 2-amino-6-(methylthio)benzonitrile (**39**) in 500 mL of methylene chloride was added 22.4 g (0.11 mol) of *m*-chloroperbenzoic acid in portions. The reaction mixture was heated at reflux overnight, cooled, and washed successively with saturated $NaHCO_3$ and brine. Removal of solvent gave a white solid, which was recrystallized: yield 7.3 g.

2-Amino-6-nitrobenzonitrile (40). To 19.3 g (0.1 mol) of 2,6-dinitrobenzonitrile in 400 mL of methanol and 250 mL of dioxane at reflux was added 60 mL of concentrated HCl and then 18 g of iron powder in portions. Reflux was continued for 1 h after the addition, and the mixture was cooled and evaporated to dryness. Water was added and the solid was filtered off and dried. The crude product was extracted with hot ethyl acetate, evaporated to minimum volume, and allowed to crystallize to give 9.2 g of pure product.

2-Nitro-3-chlorobenzamide (69). A mixture of 30 g (0.15 mol) of 2-nitro-3-chlorobenzoic acid and 34.5 g (0.17 mol) of phosphorus pentachloride in 100 mL of benzene was heated at reflux for 3 h. The reaction mixture was evaporated to dryness and poured into a solution of 75 mL of concentrated NH_4OH in 400 mL of water. The product was collected by filtration: mp 199–201 °C; yield 30 g (99%). Anal. ($C_7H_5N_2O_3Cl$) C, H, N.

2-Nitro-3-(dimethylamino)benzamide (70). A mixture of 30 g (0.15 mol) of the preceding chlorobenzamide **69** and 45 mL of 40% aqueous dimethylamine in 300 mL of DMF was heated at 130 °C overnight. An additional 30 mL of dimethylamine solution was added, and heating was continued for 6 h. The mixture was evaporated to dryness and the residue was chromatographed on silica gel with chloroform. The product, 15 g (48%), was recrystallized from ethyl acetate, mp 159–161 °C. Anal. ($C_9H_{11}N_3O_3$) C, H, N.

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).

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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.

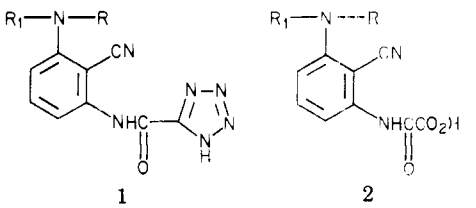
5-Tetrazolecarboxamides and Their Salts: New Orally Active Antiallergy Agents

Dieter H. Klaubert,* John H. Sellstedt, Charles J. Guinosso, Stanley C. Bell, and Robert J. Capetola[1]

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.

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(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.
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