Et_2O was added to the cooled reaction, and the white solid that formed (benzylamine hydrochloride) was filtered. The filtrate was distilled at atmospheric pressure to remove Et_2O, then at water aspirator vacuum to remove benzylamine (bp 78–85 °C), and then at 0.1 mmHg to yield 1.24 g (52%) of colorless liquid **19**, bp 85–88 °C. The HCl salt, mp 113–118 °C, was prepared in Et_2O and analyzed as an hydrate. Anal. ($C_{12}H_{18}N_2 \cdot 2HCl \cdot H_2O$) C, H, N.

3-(*N*-Diethylcarbamyl)amino-1-methylpyrrolidine (5). To a solution of compound **19**, 10.0 g (0.053 mol), and triethylamine, 8.1 mL (0.058 mol), in 40 mL of dry dioxane was added 7.85 g (0.058 mol) of diethylcarbamyl chloride. A voluminous solid was present after 10 min. The reaction was stirred at room temperature for 18 h. After 2 h, 15 mL of additional dioxane was added to enable resumption of stirring. Et_2O was added to precipitate all triethylamine hydrochloride, and the mixture was filtered, rinsing with Et_2O. The filtrate was evaporated to dryness to give a theoretical yield of a yellow oil. A solution of this crude intermediate, 14.7 g (0.051 mol), in 500 mL of EtOH and 16 mL of 6 N ethanolic HCl was hydrogenated at room temperature and atmospheric pressure in the presence of 1.6 g of 10% Pd/C for 24 h. The reaction was filtered and evaporated to dryness. The purplish solid was triturated in acetone. Filtration yielded a white solid, 7.1 g, mp 150–155 °C. Anal. ($C_{10}H_{21}N_3O \cdot HCl$) C, H, N.

3-(*N*-Benzyl-*N*-methyl)amino-1-methylpyrrolidine (20). Compound **19** was methylated as reported for compound **16**. A theoretical yield of the crude product was isolated as an oil and characterized as a yellow-orange picrate, mp 215–220 °C dec (trituration in hot EtOH). Anal. ($C_{13}H_{20}N_2 \cdot 2C_6H_3N_3O_7$) C, H, N.

1-Methyl-3-(*N*-methyl)aminopyrrolidine (21). A solution of 3.08 g of compound **20** in 150 mL of 95% EtOH and 6 mL of 6 N ethanolic HCl combined with 0.3 g of 10% Pd/C was hydrogenated at room temperature and atmospheric pressure for 21 h. The reaction was filtered and evaporated to a viscous oil which was characterized as a yellow picrate salt, mp 218–220 °C dec (trituration in hot EtOH). Anal. ($C_6H_{14}N_2 \cdot 2C_6H_3N_3O_7$) C, H, N.

A reaction run on a larger scale (16.0 g of compound **20**) required addition of fresh 10% Pd/C after 24 h to effect complete hydrogenolysis.

3-(*N*-Carbethoxy-*N*-methyl)amino-1-methylpyrrolidine (6). Compound **21**·2HCl, 14.8 g (0.0792 mol), as a gum, was combined with 110 mL of dioxane (**21**·2HCl initially insoluble) and 45 mL (0.324 mol) of triethylamine. This combination was stirred in the presence of Linde 3A molecular sieves for 2 h at room temperature. Then, with ice cooling, 11.4 mL (0.119 mol) of ethyl chloroformate was added rapidly from a pipet. Stirring at room temperature was resumed. Within 2–3 h, much solid $Et_3N \cdot HCl$ was present; stirring was continued for 66 h. Hot H_2O (200 mL) was added and stirred 1 h to decompose excess ethyl chloroformate; the pH 7 solution, opaque due to disintegrated molecular sieves, was extracted two times with $CHCl_3$. NaOH (10%) was then added and the solution again was extracted two times with $CHCl_3$. After drying (Na_2SO_4), filtering, and evaporating the extracts, a total of 7.4 g of amber oil was obtained which was distilled twice at 1 mmHg to yield 1.8 g of oil, bp 81.5–95 °C, after the second distillation. This material was combined with 0.5 g of equivalent product isolated from a previous reaction and redistilled at 0.55–0.65 mmHg to yield 1.6 g of a pale yellow oil, bp 73–77 °C (9.2%). Anal. ($C_9H_{18}N_2O_2$) C, H, N.

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Quinoline Derivatives as Antiallergy Agents. 2. Fused-Ring Quinaldic Acids[1]

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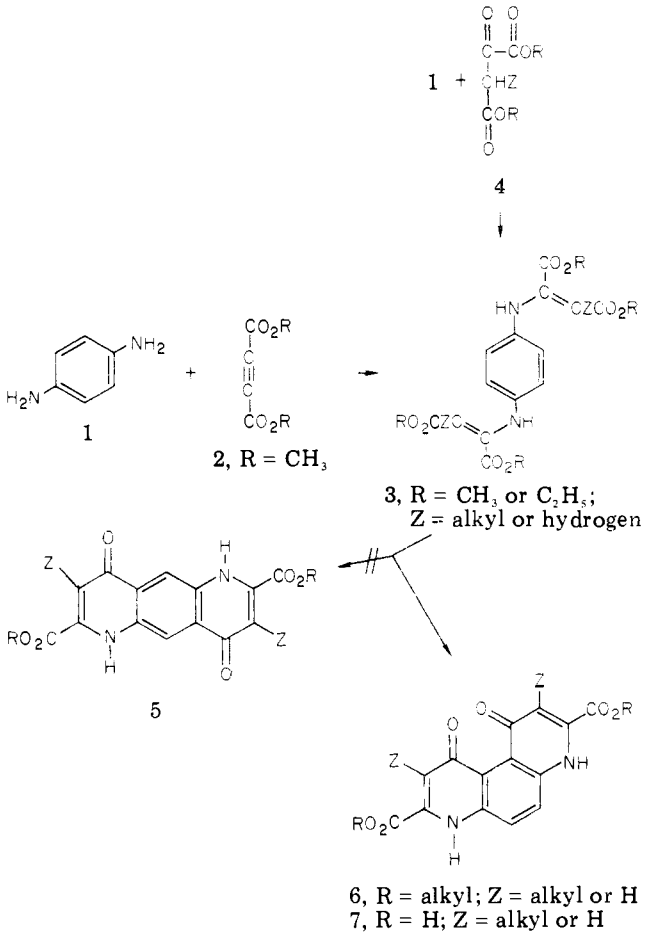
A series of compounds containing two or more 4-oxo-1,4-dihydropyridine-2-carboxylic acid units fused to a central aromatic nucleus was synthesized and tested in the rat passive cutaneous anaphylaxis (PCA) assay for potential antiallergy activity. Most of the compounds of this series showed significant activity in the PCA assay. Three of these compounds, **11d**, **13f**, and **21**, were more than 250 times as active as the standard drug, cromolyn sodium. The synthesis and biological activity are discussed.

Since the discovery that cromolyn sodium inhibits the release of the mediators from mast cells and that it is a useful agent in the prophylactic treatment of bronchial asthma, several other classes of compounds have been

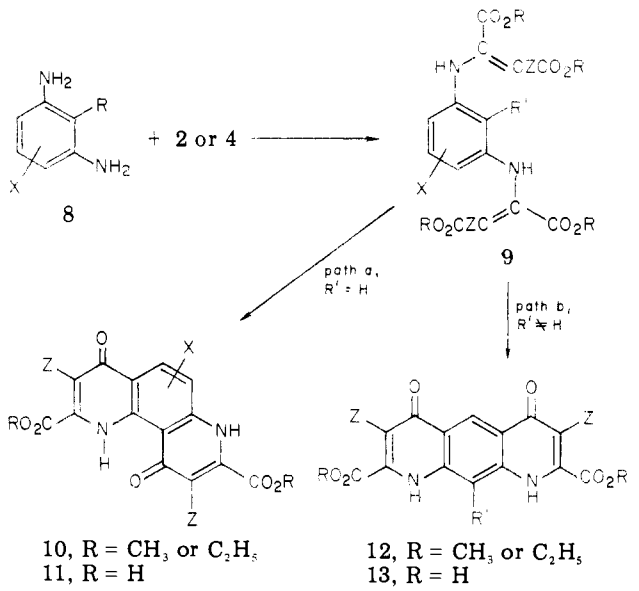
Scheme I. Preparation of 1,4,7,10-Tetrahydro-1,10-dioxo-4,7-phenanthroline-3,8-dicarboxylic Acids



shown to be potential antiallergy agents. These include xanthonecarboxylic acids,[2a] quinolonecarboxylic acids,[2b] nitroindandiones,[2c] nitrocoumarins,[2d] and oxanilic acids.[2e,f] In a previous report,[2] we described the antiallergy properties of a series of 4-oxoquinoline-2-carboxylic acids as evidenced by their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in rats. Note was made of the large enhancement in activity when two quinaldic acid units were coupled in a specific fashion. In order to further explore the importance of this "bis-functionality" on the biological activity, we prepared a series of compounds in which two 4-oxo-1,4-dihydropyridine-2-carboxylic acids were fused to a central aromatic nucleus. This series of compounds incorporates the bis-functionality of the previous series but in a conformationally rigid form which may be varied by a judicious choice of starting materials. The results of this study are described below.

Chemistry. The 1,4,7,10-tetrahydro-1,10-dioxo-4,7-phenanthroline-3,8-dicarboxylic acids may be prepared readily by either of two routes (Scheme I). Reaction of *p*-phenylenediamine (1) with dimethyl acetylenedicarboxylate (2) or diethyl oxalalkanoate 4 gives a 2,2′-(phenylene-1,4-diimino)dibutenedioate (3) in good yield. The 1:2 adducts 3 are initially formed as a mixture of geometrical isomers. Purification or solution in nonpolar solvents gave essentially the pure *Z,Z* isomer. Since isomerization about the double bond apparently occurs readily at elevated temperature, a mixture of isomers may be used in the thermal ring closure. Ring closure was effected at ~250 °C in a high boiling solvent such as Dowtherm A or diphenyl ether to give a solid product in good yield. A priori ring closure may occur in either of two

Scheme II

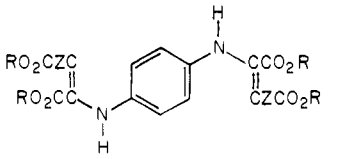


directions to give the 4,7-phenanthroline nucleus or the pyrido[2,3-g]quinoline ring system. Previous literature reports are conflicting. L'Italien and Banks[3] reported the preparation of diethyl 1,4,7,10-tetrahydro-2,9-dimethyl-1,10-dioxo-4,7-phenanthroline-3,8-dicarboxylate (6, R = C_2H_5; Z = CH_3) but gave no supporting evidence for the structural assignment other than elemental analysis. Khetan and George[4] isolated a product from the thermal cyclization of 3 (R = CH_3; Z = H) to which they assigned the structure 5 (R = CH_3; Z = H) on the basis of the NMR spectrum. Their reported NMR spectrum would support structure 6 (R = CH_3; Z = H) as well. Their assertion that the aromatic protons should appear as a quartet if the structure were 6 is incorrect. In our hands, thermal cyclization of 4 (R = CH_3; Z = H) gave a product whose structure was shown by x-ray analysis[5] to be 6 (R = CH_3; Z = H). Hydrolysis of the diester 6 was accomplished by stirring in 1.0 N NaOH (with warming) until solution was complete and then acidifying with hydrochloric acid to pH 3. The desired acid precipitated in good yield. Likewise, 3 (R = CH_3; Z = CH_3) gave a product whose ultraviolet spectra corresponded closely to that obtained from 3 (R = CH_3; Z = H) indicating that it too had closed to the 4,7-phenanthroline system rather than the pyrido[2,3-*g*]quinoline system.

Reaction of a *m*-phenylenediamine 8 with dimethyl acetylenedicarboxylate (2) gave a 2,2′-(phenylene-1,3-diimino)dibutenedioate 9. When R′ = H, 9 may undergo cyclization to either a 1,7-phenanthroline ring system (Scheme II, path a) or to a pyrido[3,2-*g*]quinoline ring system. Thermal cyclization (~250 °C) of 9 (R′ = H) gave the corresponding diester 10 in good yield. Treatment of 10 with 1.0 N NaOH, followed by acidification with HCl to pH 3, gave the desired 1,4,7,10-tetrahydro-4,10-dioxo-1,7-phenanthroline-2,8-dicarboxylic acid (11) in good yield. When R′ ≠ H, ring closure by path a is not possible. Accordingly, cyclization at 250 °C of 9 (R′ ≠ H) gave the diester 12 cleanly. Hydrolysis of 12 gave the corresponding 1,4,6,9-tetrahydro-10-substituted 4,6-dioxopyrido[3,2-*g*]-quinoline-2,8-dicarboxylic acid (13) in good yield. See Tables I–V.

Variants of the above compounds in which the 1,4-dihydro-4-oxopyridine ring is fused to other aromatic nuclei may be prepared in a similar fashion. Reaction of triaminobenzene with dimethyl acetylenedicarboxylate in methanol gave a yellow solid. Spectral data indicated that

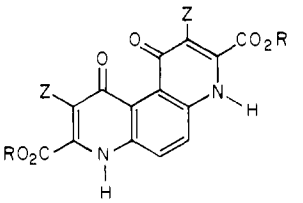
Table I. *p*-Phenylenediiminobutenedioates



Compd	Z	R	Formula	Mp, °C (lit.)	Yield, %	Analyses
3a	H	C_2H_5	$C_{22}H_{28}N_2O_8$	105-109	21	Used crude
3b	CH_3	C_2H_5	$C_{24}H_{32}N_2O_8$	83-87	31	C, H, N
3c	H	CH_3	$C_{18}H_{20}N_2O_8$	133-134 (129.5-130.5)[a]	51	

[a] S. K. Khetan and M. V. George, *Can. J. Chem.*, **47**, 3545 (1969).

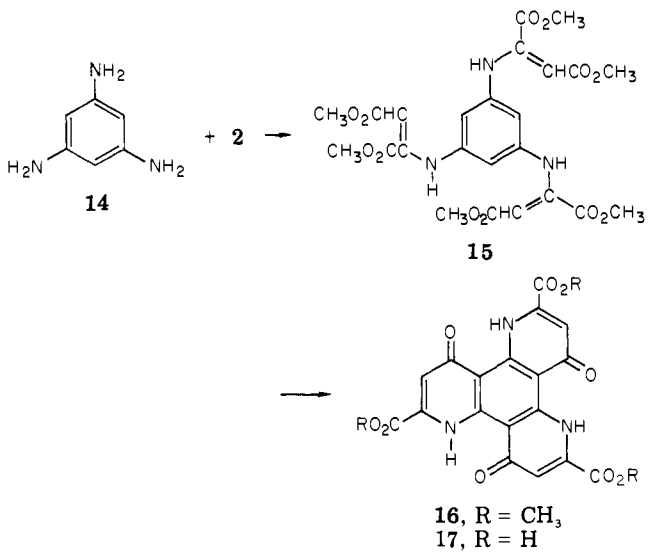
Table II. 1,4,7,10-Tetrahydro-1,10-dioxo-4,7-phenanthroline-3,8-dicarboxylates



Compd	Z	R	Formula	Mp, °C (lit.)	Yield, %	Analyses[c]
6a	H	C_2H_5	$C_{18}H_{16}N_2O_6$	294-295	63	C, H, N
7a	H	H	$C_{14}H_8N_2O_6$	>320	95	H, N; C[a]
6b	H	CH_3	$C_{16}H_{12}N_2O_6$	286-287 dec (262-263 dec)[b]	86	
6c	CH_3	C_2H_5	$C_{20}H_{20}N_2O_6$	300-305 (285-290)[d]	61	C, H, N
7b	CH_3	H	$C_{16}H_{12}N_2O_6$	295-300 dec	99	

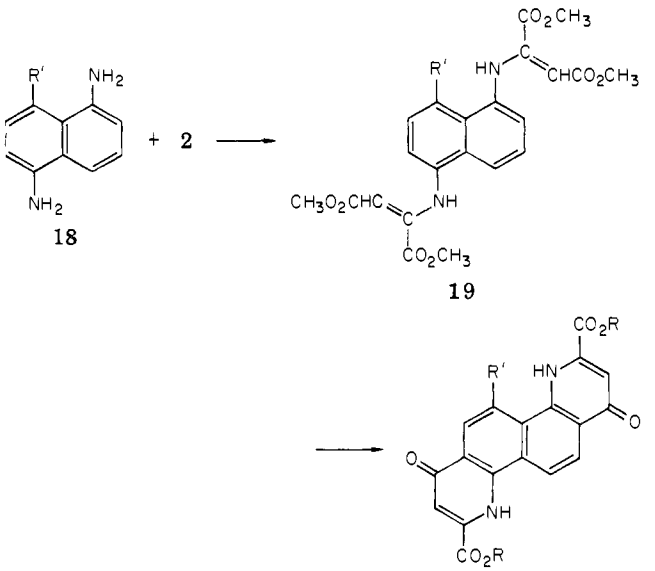
[a] C: calcd, 55.96; found, 54.87. [b] S. K. Khetan and M. V. George, *Can. J. Chem.*, **47**, 3545 (1969). [c] See Experimental Section for explanation of missing analytical results. [d] Y. J. L'Italien and C. K. Banks, *J. Am. Chem. Soc.*, 73, 3246 (1951).

Scheme III



16, R = CH_3
17, R = H

Scheme IV

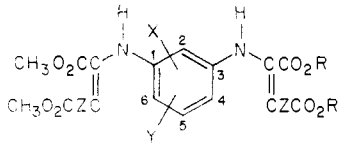


20, R = CH_3; R′ = H
21, R = H; R′ = H
22, R = CH_3; R′ = Cl
23, R = H; R′ = Cl

the solid was the 3:1 adduct (Scheme III). Ring closure gave the insoluble diester **16**. Hydrolysis in the usual fashion gave 1,4,5,8,9,12-hexahydro-4,8,12-trioxopyrido-[2,3-*f*][1,7]phenanthroline-2,6,10-tricarboxylic acid (**17**). Reaction of 1,5-diaminonaphthalene (**18**) in a similar sequence (Scheme IV) gave 1,4,7,10-tetrahydro-1,7-dioxoquino[8,7-*h*]quinoline-3,9-dicarboxylic acid (**21**).

Biological Results and Discussion. The results of the biological testing are given in Table VI as the doses which inhibited 50% of the PCA reaction in rats. While no well-defined structure–activity pattern emerged, it is clear that this series of compounds is generally more active than the corresponding simple quinaldic acids and biquinaldic acids reported earlier. Presumably the increased activity is due to the bifunctionality and more rigid structural features of these compounds. The nature of the ring system appeared to play an important role in de-

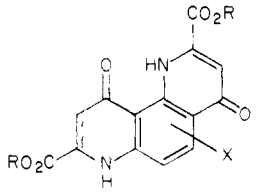
Table III. *m*-Phenylenediiminobutenedioates



Compd	X	Y	Z	R	Formula	Mp, °C	Yield, %	Analyses
9a	H	H	H	CH_3	$C_{18}H_{20}N_2O_8$	146-147	47	C, H, N
9b	5-CO_2H	H	H	CH_3	$C_{19}H_{20}N_2O_{10}$	191	59	C, H, N
9c	4-$(CH_2)_4CH_3$	H	H	CH_3	$C_{23}H_{30}N_2O_8$	Oil	89[a] crude	
9d	4-$(CH_2)_3CH_3$	H	H	CH_3	$C_{18}H_{24}N_2O_6$	Oil	Used crude	
9e	2-CH_3	H	H	CH_3	$C_{19}H_{22}N_2O_8$	190-195	25, used crude	
9f	2-Cl	H	H	CH_3	$C_{18}H_{19}ClN_2O_8$	202-204	28	C, H, N, Cl
9g	2-CN	H	H	CH_3	$C_{19}H_{19}N_3O_8$	218-220 dec	33	C, H, N
9h	2-F	H	H	CH_3	$C_{18}H_{19}FN_2O_8$	170-174	57[b]	C, H, N, F
9i	2-OCH_3	H	H	CH_3	$C_{19}H_{22}N_2O_9$	105-110	84[c]	C, H; N[d]
9j	2-Cl	5-CH_3	H	CH_3	$C_{19}H_{22}ClN_2O_8$	216.5-218	55	C, H, N, Cl
9k	2-CO_2CH_3	H	H	CH_3	$C_{20}H_{22}N_2O_{10}$	147-149	76[e]	C, H, N
9l	2-CH_3	H	CH_3	C_2H_5	$C_{25}H_{34}N_2O_8$	90	30	H, N; C[f]
9m	2-Cl	5-CF_3	H	CH_3	$C_{19}H_{18}ClF_3N_2O_8$	205-208	62, used crude	
9n	2-Cl	5-CN	H	CH_3	$C_{19}H_{18}ClN_3O_8$	233.5-235	73	C, H, N, Cl

[a] From 2,4-dinitrobutylbenzene. [b] From 2,6-dinitrofluorobenzene. [c] From 2,6-dinitroanisole. [d] N: calcd, 6.63; found, 6.13. [e] From methyl 2,6-dinitrobenzoate. [f] C: calcd, 61.22; found, 60.79.

Table IV. 1,4,7,10-Tetrahydro-4,10-dioxo-1,7-phenanthroline-2,8-dicarboxylates



Compd	X	R	Formula	Mp, °C (lit.)	Yield, %	Analyses[c]
10a	H	CH_3	$C_{16}H_{12}N_2O_6$	292[a]	78	H, N; C[b]
10b	5-CO_2H	CH_3	$C_{17}H_{12}N_2O_8$	308 dec	75	
10c	6-$(CH_2)_4CH_3$	CH_3	$C_{21}H_{22}N_2O_6$[d]	185 dec	17	C, H, N
10d	6-$(CH_2)_3CH_3$	CH_3	$C_{20}H_{20}N_2O_6$[d]	185-191	4	C, H, N
11a	H	H	$C_{14}H_8N_2O_6$	>320	98	
11b	5-CO_2H	H	$C_{15}H_6N_2O_6Na_2$	>320	97	H, N; C,[e] Na[f]
11c	6-$(CH_2)_4CH_3$	H	$C_{19}H_{18}N_2O_6$[d]	300-305 dec (297-300 dec)[d]	99	
11d	6-$(CH_2)_3CH_3$	H	$C_{18}H_{16}N_2O_6$[d]	305-310 dec (300 dec)[d]	97	

[a] Lit. mp 273.5 °C. [b] C: calcd, 58.54; found, 57.66. [c] See Experimental Section for explanation of missing analytical results. [d] W. S. Waring, U.S. Patent 3 790 577. [e] Corrected for 8.03% H_2O (Karl Fischer). C: calcd, 46.39; found, 45.70. [f] Na: calcd, 11.86; found, 11.28.

termining the level of activity. This is clearly seen in the following series: quinaldic acid (ID_{50} = 50 mg/kg), **7a** (2.5 mg/kg), **11a** (1 mg/kg), **13a** (0.25 mg/kg), and **21** (0.005 mg/kg), which covers a 10 000-fold activity range. The nature and position of ring substituent also have an important effect on the biological activity. For example, the biological activity within the pyrido[3,2-*g*]quinolinedicarboxylic acid series **13** varies over a 500-fold range as a function of the substitution pattern. Of particular note are compounds **11d** and **21**, which have ID_{50} values of 0.005 mg/kg and are approximately 500 times as active as cromolyn sodium, the standard drug, in this assay. It is noteworthy that compound **11d** has been reported[6] recently to protect patients with allergic rhinitis in an antigen challenge setting.

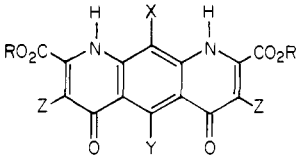
In summary, this series of rigid, bifunctional pyridoquinolinedicarboxylic acids has been shown to possess potent activity in the rat PCA assay and are potential antiallergy agents. Most of these compounds were found to be considerably more active than the currently available cromolyn sodium.

Experimental Section

The melting points (capillary) are uncorrected. The IR spectra were measured with a Perkin-Elmer Infracord spectrometer. For those compounds with sufficient solubility in D_2O, Me_2SO-d_6, or $DCCl_3$, the NMR spectra were measured on a Varian A-60 or T-60 spectrometer. The IR and NMR spectra were consistent with the assigned structure in all cases. In several instances, meaningful elemental analyses were not obtained because the low solubility of these compounds prevented recrystallization. In these cases, a minimum level of purity, 95% (after correction for H_2O present), was established by quantitative NMR measurements using either fumaric or maleic acid as an internal standard. Duplicate samples were measured and each determination was the mean of eight integrations.

Biological Methods. The compounds shown in Table VI were tested for their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in rats passively sensitized to egg albumin as follows.[27]

Table V. 1,4,6,9-Tetrahydro-4,6-dioxopyrido[3,2-*g*]quinoline-2,8-dicarboxylates



Compd	X	Y	Z	R	Formula	Mp, °C	Yield, %	Analyses
12a	CH_3	H	H	CH_3	$C_{17}H_{14}N_2O_6$	291.5-292.5 dec	78	
12b	Cl	H	H	CH_3	$C_{16}H_{11}ClN_2O_6$	266-267 dec	73	C, H, N, Cl
12c	CN	H	H	CH_3	$C_{17}H_{11}N_3O$	281-283 dec	50	C, H, N
12d	F	H	H	CH_3	$C_{16}H_{11}FN_2O_6$	299-302 dec	65	C, H, N, F
12e	OCH_3	H	H	CH_3	$C_{17}H_{14}N_2O_7$	282 dec	78	C, H, N
12f	Cl	CH_3	H	CH_3	$C_{17}H_{13}ClN_2O_6$	278-280 dec	69	C, H, N; Cl[a]
12g	CO_2CH_3	H	H	CH_3	$C_{18}H_{14}N_2O_8$	282-286	31	H, N; C[b]
12h	CH_3	H	CH_3	C_2H_5	$C_{21}H_{22}N_2O_6$	258-260	96	H, N; C[c]
13a	CH_3	H	H	Na	$C_{15}H_8N_2O_6Na_2$	>310	99	H, N; C,[d] Na[e]
13b	Cl	H	H	H	$C_{14}H_7ClN_2O_6$	>310	96	H; C,[f] N[g]
13c	CN	H	H	H	$C_{15}H_7N_3O_6 \cdot 0.5H_2O$	>320	99	C, H, N
13d	F	H	H	H	$C_{14}H_7FN_2O_6$	310-319 dec	99	*h*
13e	OCH_3	H	H	H	$C_{15}H_{10}N_2O_7$	~305 dec	84	*h*
13f	Cl	CH_3	H	Na	$C_{15}H_7ClN_2O_6Na_2$	>320	98	C, H, N, Na
13g	CO_2H	H	H	Na	$C_{15}H_5N_2O_8Na_3$	>320	96	C, H, N, Na[i]
13h	CH_3	H	CH_3	H, Na	$C_{17}H_{13}N_2O_6Na$	>320	98	H, N, Na; C[j]
12i	Cl	CF_3	H	CH_3	$C_{17}H_{10}ClF_3N_2O_6$	273 dec	30	C, H, F, N; Cl[k]
13i	Cl	CF_3	H	H	$C_{15}H_6ClF_3N_2O_6$	>300	73	F
12j	Cl	CN	H	CH_3	$C_{17}H_{10}ClN_3O_6$	>320	23[l]	C, H, Cl, N
13j	Cl	CN	H	H	$C_{15}H_6ClN_3O_6$	>320	76	*h*

[a] Cl: calcd, 9.41; found, 12.61. [b] C: calcd, 55.96; found, 55.18. [c] C: calcd, 63.31; found, 62.38. [d] C: calcd, 49.73; found, 49.20. [e] Na: calcd, 13.80; found, 12.62. [f] Corrected for 9.18% H_2O (Karl Fischer). [g] N: calcd, 8.37; found, 7.95. [h] See Experimental Section for explanation of missing analytical results. [i] Corrected for 12.33% H_2O (Karl Fischer). Na: calcd, 16.82; found, 16.32. [j] Corrected for 4.67% H_2O (Karl Fischer). C: calcd, 55.99; found, 54.72. [k] Cl: calcd, 8.23; found, 7.71. [l] Silica gel chromatography required for isolation.

Table VI. Results of the PCA Assay

Compd	ID_{50}, mg/kg	Compd	ID_{50}, mg/kg
Cromolyn sodium	2.5	13d	0.5
7a	2.5	13e	0.1
7b	10	13f	0.01
11a	1	13g	0.1
11b	10	13h	5
11c	0.05	13i	5
11d	0.005	17	0.5
13a	0.25	21	0.005
13b	0.05	23	0.05
13c	0.05	13j	0.05

Rat homocytotropic antibody was elicited to egg albumin (EA) by the injection (ip) of 0.5 mg of EA + 0.5 cm^3 of *H. pertussis* vaccine (Michigan Department of Public Health, 4.5×10^{10} heat killed organisms) per rat. After 18–20 days the serum was collected and frozen until use. The antibody was shown to be of the 72-h latency type and to be destroyed by heating 1.0 h at 56 °C. Five 0.1-mL vol of an appropriate dilution of this serum were inoculated into the shaved dorsal surface of a 200-g Sprague–Dawley rat. Saline controls were run and showed less than 4-mm spots. After 72 h the rat was challenged iv with 4 mg per animal of EA + 0.5% Evans blue dye. In the case of drug-treated animals the drug was given iv at the time of antigen challenge or it was given ip 30 min before challenge with antigen. Results were reported as the inhibition of the number of spots per animal (regardless of size) that were seen at five dilutions of serum. The spot score (total number of spots divided by the number of animals) in drug-treated animals at each dose was compared with the spot score in untreated animals: % inhibition = (spot score of treated ÷ spot score of control) × 100.

The significance of the difference between drug-treated spot score and control (non-drug-treated spot score) in this PCA test has been analyzed and found to be significant with a p value of <0.001. The procedure is to find the highest dilution of the control serum for which some of the animals do not have spots and some of the animals have spots. The number of animals not having spots at the next higher dilution of serum is counted and added to past control data. A new average is taken. We then graphed the probability of not getting a spot at this dilution vs. the sample size and got a probability of about 0.1. This probability p (0.1) or N for the number of animals gives a degree of certainty of assuming there is a difference in control and treated.

Phenylenediiminobutenedioates. The phenylenediiminobutenedioates were readily prepared by either of the following procedures.

Procedure A. To a solution (suspension) of the appropriate phenylenediamine (0.10 mol) in methanol (200 mL) was added dimethyl acetylenedicarboxylate (0.21 mol) dropwise. The reaction mixture was stirred for 18 h at room temperature. The desired product was isolated by filtration or removal of the solvent, followed by recrystallization.

Procedure B. A mixture of the appropriate phenylenediamine (0.1 mol), benzene (250 mL), diethyl alkyloxalalkonate (0.22 mol), and *p*-toluenesulfonic acid (0.5 g) was refluxed for 18 h with constant water removal. Removal of the solvent from the reaction mixture left an oil, which crystallized when trituated with methanol. Recrystallization gave the desired product in good yield.

Dialkyl fused-ring quinolinedicarboxylates were prepared by carefully adding the appropriate phenylenediiminobutenedioate to refluxing Dowtherm A for 2–30 min. The desired product precipitated from the cooled reaction mixture and was collected by filtration.

Fused-ring quinolinedicarboxylic acids were prepared by heating the appropriate diester in 1.0 N NaOH at reflux for 10–20 min. The cooled mixture was diluted with water and the solution was acidified to pH 3. The desired diacid precipitated and was collected by filtration in good yield. Many of these diacids were sufficiently insoluble that they could not be recrystallized and meaningful analyses were not obtained (see tables). In all cases the diacids were soluble in dilute base and the IR spectra were consistent with the assigned structure.

Phenylenediamines. The phenylenediamines were readily available by reduction of the appropriate dinitro compound. Typical reduction conditions are given below.

Procedure C. The appropriate dinitrobenzene (0.05 mol) was dissolved (suspended) in methanol (250 mL). Palladium-on-charcoal catalyst (~0.5–1.0 g) was added. The reaction was shaken 2–4 h on a Parr hydrogenator at 40 psi of hydrogen. The catalyst was removed by filtration and the desired amine could be isolated by removal of the solvent. In several cases the methanolic diamine solution was used without isolation or further purification.

Procedure D. The appropriate dinitrobenzene (0.1 mol) was dissolved in hot EtOH (100 mL). An equal amount of water was added dropwise to the solution. Additional EtOH was occasionally added to maintain solution. Electrolytically reduced iron (0.5 g-atom) was added and the reaction mixture was heated to reflux. Concentrated HCl (5 mL) in 50% aqueous EtOH was added slowly. The reaction mixture was refluxed for 2 h. The excess iron was removed by filtration and the filtrate was made basic (pH 8–9) with aqueous NaOH. The residual iron oxides were removed by filtration. Removal of the solvent from the filtrate and recrystallization gave the desired diamine.

Methyl 2,6-diaminobenzoate (procedure C) was used without isolation.

4-Chloro-3,5-toluenediamine (procedure D) gave mp 115–116 °C, 80%. Anal. ($C_7H_9ClN_2$) C, H, Cl, N.

2-Methoxy-1,3-phenylenediamine (procedure C) was used without isolation.

2-Fluoro-1,3-phenylenediamine (procedure C) was used without isolation.

2-Chloro-1,3-phenylenediamine (procedure D) gave mp 82.0–83.5 °C (lit.[8] 85–86 °C, 81%).

4-Butyl-1,3-phenylenediamine (procedure C) was used without isolation.

4-Pentyl-1,3-phenylenediamine (procedure C) was used without isolation.

4-Chloro-1,5-diaminonaphthalene (procedure D) was used without purification.

Methyl 2,6-Dinitrobenzoate. 2,6-Dinitrobenzoic acid (10.6 g) was suspended in ether (125 mL) at 0 °C. 1-Methyl-3-*p*-tolyltriazene (8.2 g) in ether (75 mL) was added dropwise to the stirred reaction mixture in an ice bath. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h. The reaction mixture was diluted to 1 L with ether and the insoluble product collected by filtration. Recrystallization from methanol gave colorless crystals (7.7 g, mp 150–151.5 °C, 69%). Anal. ($C_8H_6N_2O_6$) C, H, N.

2,6-Dinitroanisole. Chlorodinitrobenzene (20.0 g, 0.10 mol) was dissolved in anhydrous methanol (100 mL). Sodium methoxide solution (25% in methanol, 14 mL) was added and the mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water (500 mL) and the resulting solution was extracted with ether (3 × 200 mL). The combined ether extracts were washed with water (100 mL) and were dried with anhydrous sodium sulfate. Removal of the solvent left a solid which gave yellow needles after Darco treatment and recrystallization from ethanol (11.15 g, mp 118 °C, 57%). Anal. ($C_7H_6N_2O_5$) C, H, N.

1-Fluoro-2,6-dinitrobenzene. A mixture of 1-chloro-2,6-dinitrobenzene (30 g, 0.15 mol), anhydrous potassium fluoride (35 g, 0.60 mol), and dimethylformamide (50 mL) was refluxed for 24 h. The reaction mixture was poured into water (250 mL) and extracted with ether (3 × 100 mL). The combined ether extracts were dried with anhydrous sodium sulfate. Removal of the solvent left a brown solid. Chromatography of the solid on silica gel with methylene chloride as the eluent gave a light yellow solid after recrystallization from pentane–methylene chloride (20.30 g, mp 59 °C, 73.7%). Anal. ($C_6H_3FN_2O_4$) C, H; N: calcd, 15.06; found, 13.13; F: calcd, 10.21; found, 9.28; mass spectrum *m/e* 186 (mol ion).

2,6-Dinitrobenzonitrile. 1-Chloro-2,6-dinitrobenzene (40.4 g, 0.20 mol) was dissolved in anhydrous DMF (200 mL). Cuprous cyanide (72 g, 0.80 mol) was added and the stirred reaction mixture was heated to reflux for 6 h. The dark brown reaction mixture was cooled and poured into water (1.5 L) with stirring. The tan precipitate was collected by filtration and then extracted three times with hot ethanol (300 mL). Removal of two-thirds of the solvent from combined ethanol extracts under reduced pressure gave a tan precipitate. The precipitate was collected by filtration and recrystallized from ethanol to give a tan product [7.2 g, mp 143–146.5 °C (lit.[9] mp 143–145 °C, 19%)].

2,6-Diaminobenzonitrile. 2,6-Dinitrobenzonitrile (10.0 g, 0.052 mol) was added in portions to a stirred solution of stannous chloride (82.5 g, 0.44 mol) in concentrated HCl (230 mL) at room temperature. Stirring was continued at room temperature for 2.5 h and then the reaction mixture was cooled to 0 °C and was made strongly basic with 50% NaOH. The reaction mixture was diluted with water (1 L) and was extracted four times with methylene chloride (200 mL). The combined extracts were washed once with water (200 mL), were dried over sodium sulfate, and then were taken to dryness under reduced pressure. Recrystallization from benzene–Skellysolve B gave the desired product (4.15 g, mp 91–92 °C, 60%). Anal. ($C_7H_7N_3$) H; C: calcd, 63.14; found, 64.04; N: calcd, 31.56; found, 32.06.

Hexamethyl 2,2′,2″-(Phenylene-1,3,5-triimino)tributanedioate. A solution of 3,5-dinitroaniline (1.0 g, 0.0055 mol) in 50 mL of absolute methanol was shaken in a Parr hydrogenator at 40 psi in the presence of 100 mg of 10% palladium on charcoal catalyst for 2 h. The solution was filtered and dimethyl acetylenedicarboxylate (2.5 g) was added dropwise to the filtrate at room temperature. The reaction mixture was stirred for 18 h at room temperature during which time the yellow product precipitated. The product was collected by filtration (1.67 g, mp 151–156 °C, 57%). Recrystallization from methanol gave a solid melting at 156–158 °C. Anal. ($C_{24}H_{27}O_{12}N_3$) C, H, N.

Trimethyl 1,4,5,8,9,12-Hexahydro-4,8,12-trioxopyrido[2,3-*f*][1,7]phenanthroline-2,6,10-tricarboxylate. The 1:3 adduct (2.0 g) was added to refluxing Dowtherm A (200 mL) (~250 °C) (a dilution factor of 1.0 g of the adduct to 100 mL of Dowtherm A was quite critical as a more concentrated solution gave an impure product) and the mixture heated at the reflux temperature for 10 min. Upon cooling the yellow crystalline product precipitated and was collected by filtration (1.35 g, mp >325 °C). The yellow product was ground in a mortar, heated to reflux in chloroform–methanol (1:4, 100 mL), and filtered (1.27 g, mp >325 °C, 77%). Meaningful elemental analysis was not obtained because the low solubility of the compound of the product in common solvents prevented its recrystallization. The structural assignment is based on the IR, UV, and mass spectral data: IR (Nujol) =CH 3100, C=O or C=N/C=C 1635, 1595, 1560, 1495; UV ($CHCl_3$) λ max (ε) 245 sh (24 200), 297 sh (14 650), 309 (23 900), 323 (35 000), 340 sh (14 050), 356 (11 600), 366 sh (2850); mass spectrum (70 eV) *m/e* 453 (mol ion).

Trisodium 1,4,5,8,9,12-Hexahydro-4,8,12-trioxopyrido[2,3-*f*][1,7]phenanthroline-2,6,10-tricarboxylate. The trimethyl ester (1.0 g) was heated in 1.0 M aqueous NaOH (35 mL) at reflux for 1 h. The suspension was cooled and the light yellow solid was collected by filtration, washed with water (5 mL) and acetone (25 mL), and dried at reduced pressure at 60 °C (1.17 g, mp >320 °C). Anal. Calcd for $C_{18}H_6N_3Na_3O_5$: C, 45.30; H, 1.27; N, 8.80; Na, 14.46. Found: C, 43.75; H, 1.27; N, 8.44; Na, 15.00. IR (Nujol) NH/OH 3400, C=O/C=N/CO_2^-/C=C 1660 sh, 1625, 1595, 1555, 1510, CO_2^-/CH 1365 probable hydrates; UV (H_2O) λ max (ε) 213 (49 800), 232 (38 050), 284 sh (22 950), 298 (32 550), 310 (36 750), 325 sh (13 550), 343 (10 900), 357 (3050).

1,4,5,8,9,12-Hexahydro-4,8,12-trioxopyrido[2,3-*f*][1,7]phenanthroline-2,6,10-tricarboxylic Acid. Trisodium 1,4,5,8,9,12-hexahydro-4,8,12-trioxopyrido[2,3-*f*][1,7]phenanthroline-2,6,10-tricarboxylate (13.3 g) was dissolved in water (1500 mL) and acidified with 3 N HCl to give the desired triacid as a jelly-like precipitate. Most of the aqueous phase was removed by centrifugation and the remainder removed by filtration. The off-white product was washed with water and then acetone and dried at reduced pressure at 50 °C (7.0 g, mp >330 °C, 61%).

Tetramethyl 2,2′-(Naphthalene-1,5-diimino)dibutenedioate. Dimethyl acetylenedicarboxylate (30 g, 0.21 mol) was added slowly to a solution of 1,5-naphthalenediamine (15.8 g, 0.10 mol) in methanol (250 mL). The mixture was stirred at room temperature for 6 h during which time a yellow solid precipitated. The desired product was collected by filtration (29.9 g, mp 220 °C dec, 36%) and was recrystallized to give yellow needles (mp 220 °C dec). Anal. ($C_{22}H_{22}N_2O_8$) C, H, N.

Dimethyl 1,4,7,10-Tetrahydro-1,7-dioxoquino[8,7-*h*]quinoline-3,9-dicarboxylate. Tetramethyl 2,2′-(naphthalene-1,5-diimino)dibutenedioate (50 g) was added to refluxing Dowtherm A (300 mL). Reflux was maintained for 5 min, and

then the reaction mixture was allowed to cool to room temperature. The resulting solid was collected by filtration and was washed with acetone (38.5 g, mp >320 °C, 90%).

1,4,7,10-Tetrahydro-1,7-dioxoquino[8,7-*h*]quinoline-3,9-dicarboxylic Acid. Dimethyl 1,4,7,10-tetrahydro-1,7-dioxoquino[8,7-*h*]quinoline-3,9-dicarboxylate (10 g) was heated at reflux in 1.0 N aqueous sodium hydroxide (125 mL) for 0.5 h. The reaction mixture was cooled to room temperature and diluted with water (150 mL), and the pH of the solution was adjusted to 3. The desired product precipitated as a yellow solid. The solid was collected and was washed with acetone (9.97 g, mp >320 °C, 100%). Anal. ($C_{18}H_8N_2O_6Na_2$) H, N, Na; C: calcd, 54.82; found, 54.16.

2,4-Dinitrobutylbenzene. Butylbenzene (10 g) was added slowly to a cold (ice bath) solution of concentrated sulfuric acid (20 mL) and fuming nitric acid (20 mL). The reaction mixture was stirred 5 min in an ice bath, 30 min at room temperature, and 30 min on a steam bath. The reaction mixture was poured into ice–water (250 mL) and extracted with ether (3 × 100 mL). The combined ether extracts were washed with aqueous saturated sodium bicarbonate (3 × 100 mL), and the organic phase was dried with sodium sulfate. Removal of the solvent left a yellow oil. Distillation gave a yellow oil [bp 142–147 °C (1 mm), 8.8 g, n^{25}_D 1.545, 52%].

2-Chloro-5-α,α,α-trifluoromethyl-*m*-phenylenediamine. To a stirred solution of 90.24 g (0.4 mol) of stannous chloride dihydrate in 220 mL of concentrated hydrochloric acid was added, portionwise, 15.22 g (0.0564 mol) of 3,5-dinitro-4-chlorobenzyl trifluoride. The stirred mixture was warmed to 60 °C and allowed to stand overnight at room temperature.

To the stirred mixture was added with cooling a 50% solution of sodium hydroxide until the mixture was strongly basic. The mixture was filtered, the precipitate was added to water, and the mixture was extracted with methylene chloride. The filtrates were extracted with additional methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate and the solvent was removed. The residue upon recrystallization from ethanol–water gave 9.02 g (76%) of material melting at 95–96 °C. Anal. ($C_7H_6ClFN_2$) C, H, N, F, Cl.

Tetramethyl 2,2′-(4-Chloronaphthalene-1,5-diimino)dibutenedioate. Dimethyl acetylenedicarboxylate (2.43 g, 0.0171 mol) was added dropwise to a solution of 4-chloro-1,5-diaminonaphthalene (1.5 g, 0.0078 mol) in methanol (50 mL) at room temperature. The reaction mixture was stirred at room temperature for 48 h during which time the yellow product precipitated. Recrystallization from $CHCl_3$–MeOH gave yellow prisms (1.77 g, mp 210–211 °C, 47.7%). Anal. ($C_{22}H_{21}ClN_2O_8$) C, H, N; Cl: calcd, 7.44; found, 8.32; mass spectrum (70 eV) *m/e* 476 (mol ion).

Dimethyl 5-Chloro-1,4,7,10-tetrahydro-1,7-dioxoquino[8,7-*h*]quinoline-3,9-dicarboxylate. Tetramethyl 2,2′-(4-chloronaphthalene-1,5-diimino)dibutenedioate (1.0 g, 0.0021 mol) was added to refluxing Dowtherm A (25 mL, ~250 °C.). The reflux temperature was maintained for 7 min and then the reaction mixture was allowed to cool. The desired product was collected and washed with chloroform and then methanol (0.65 g, mp 317–318 °C dec, 75%). Anal. ($C_{20}H_{13}ClN_3O_6$) C, H, N, Cl.

5-Chloro-1,4,7,10-tetrahydro-1,7-dioxoquino[8,7-*h*]quinoline-3,9-dicarboxylic Acid. Dimethyl 5-Chloro-1,4,7,10-tetrahydro-1,7-dioxoquino[8,7-*h*]quinoline-3,9-dicarboxylate (200 mg, 0.48 mmol) was stirred in 1 N NaOH (10 mL) for 15 min at room temperature. The solution was acidified to pH 3 with 3 M HCl to give the desired diacid as a greenish yellow solid. The product was collected by filtration, washed with water, and dried at reduced pressure at 60 °C (0.16 g, mp >325 °C, 86%).

2,4-Dinitropentylbenzene. Pentylbenzene (2.0 g) was slowly added to a solution of fuming nitric acid (5 mL) and concentrated sulfuric acid (5 mL) maintained at 0 °C in an ice bath. The reaction mixture was allowed to warm to room temperature for 30 min and then it was heated on a steam bath for 0.5 h. The reaction mixture was poured into ice–water and extracted with ether (3–50 mL). The combined ether extracts were washed with saturated aqueous sodium bicarbonate (3–50 mL) and water (50 mL) and were dried with anhydrous sodium sulfate. Removal of the solvent left an oil (2.5 g, 7.8%). TLC (silica gel, benzene) indicated only minor impurities, as did the NMR spectra. The NMR spectra were consistent with the desired product. No attempt was made to purify the product further.

References and Notes

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