1,2,4-Triazolo[4,3-*a*]quinoxaline-1,4-diones as Antiallergic Agents

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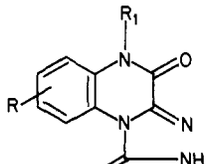
A series of new 1,4-dihydro-1,2,4-triazolo[4,3-*a*]quinoxaline-1,4-diones has been prepared. These compounds were tested as inhibitors of antigen-induced release of histamine (AIR) in vitro from rat peritoneal mast cells (RMC) and as inhibitors of IgE-mediated rat passive cutaneous anaphylaxis (PCA). Most of this new class of antiallergic agents showed good activity in the RMC and PCA tests. The most potent compound, 2-acetyl-7-chloro-5-*n*-propyl-1,2,4-triazolo[4,3-*a*]quinoxaline-1,4-dione (**1x**), with an I_{50} value of 0.1 μM, is 30 times more potent than disodium cromoglycate (DSCG) in the RMC assay.

We describe herein, 1,2,4-triazolo[4,3-*a*]quinoxaline-1,4-diones **1** as potent antiallergic agents as judged by their ability to inhibit antigen-induced histamine release from rat mast cells (RMC) and activity in the rat passive cutaneous anaphylaxis test (PCA). This work is a continuation of the search for orally effective prophylactic agents for the treatment of asthma. These compounds represent a new chemical class of compounds possessing antiallergic activity. Most antiallergic compounds, including disodium cromoglycate (DSCG,[1] **2**), have carboxyl[2] or tetrazoyl[3] functional groups.



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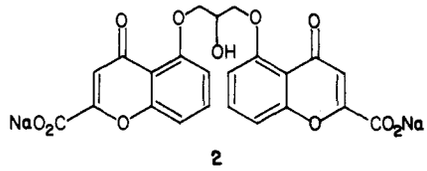

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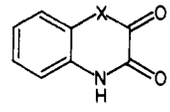
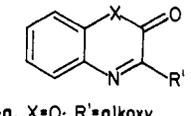
Recently, we reported the synthesis of a series of benzoxazinediones **3a**, which were found to possess interesting antiallergic activity.[4] In an attempt to search for more potent compounds, we initiated a program to modify structure **3** and prepared a series of 3-substituted compounds, **4**, for screening. This paper describes the synthesis of **4c** and its cyclization, leading to molecules of type **1**, which were found to possess significant activity as inhibitors of mediator release in vitro and in vivo.



3a. X=O
b. X=NR



4a. X=O; R'=alkoxy
b. X=NR; R'=alkoxy
c. X=NR; R'=NHNHCO$_2$Et

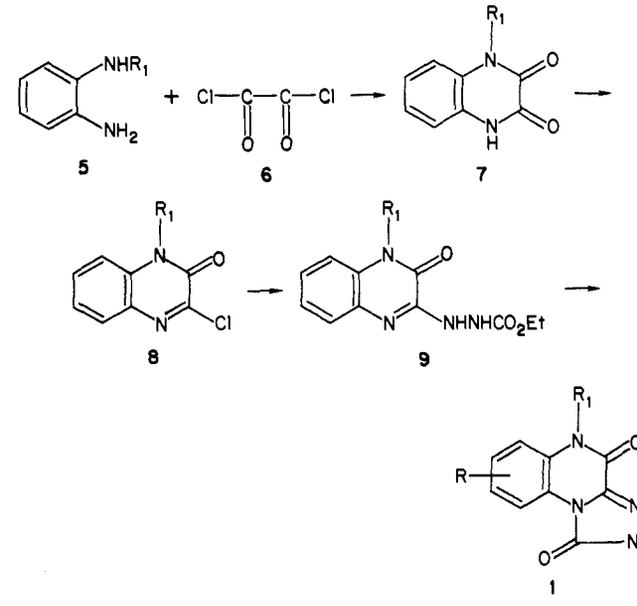
Chemistry. 1,2,4-Triazolo[4,3-*a*]quinoxaline-1,4-diones were prepared readily according to Scheme I.

Reaction of the appropriate substituted o-phenylenediamine **5** with oxalyl chloride (**6**) in boiling toluene gave the quinoxaline-2,3-diones **7**, which were readily converted to the imino chlorides **8** by thionyl chloride. Reaction of **8** with ethyl carbazate gave **9** in good yield. Ring closure was accomplished either thermally or by sodium alkoxide.

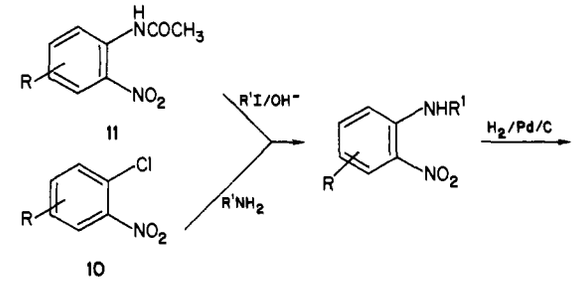
Substituted *o*-phenylenediamines **5** were prepared either by direct displacement of *o*-chloronitrobenzene **10** or by phase-transfer-catalyzed alkylation of *N*-acetyl compounds **11** (Scheme II).

The chlorine atom at the 7-position of the triazoloquinoxalines was introduced by a novel synthetic method shown in Scheme III. Hydrogenation of **13a** gave exclusively the hydroxamic acid **14a**; no **14b** (R = H) was observed. Treatment of **14a** with thionyl chloride and DMF at room temperature gave 7-chloroquinoxalinedione **7**. The structure of **7** was confirmed by converting it to the tri-

Scheme I



Scheme II



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(2) For recent examples, see: Althuis, T. H.; Moore, P. F.; Hess, H. J. *J. Med. Chem.* **1979**, *22*, 44. Juby, P. E.; Hudyma, T. W.; Brown, Essery, J. M.; Partyka, R. A. *J. Med. Chem.* **1979**, *22*, 263. Philipp, A.; Jirkousky, I.; Martel, R. R. *J. Med. Chem.* **1980**, *23*, 1372. Klaubort, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* **1981**, *24*. Sirean, J. C.; Capiris, T.; Kesten, S. J.; Herzig, D. J. *J. Med. Chem.* **1981**, *24*, 735.
(3) For recent examples, see: Erickson, E. H.; Hainline, C. F.; Lenon, L. S.; Matson, C. J.; Rice, T. K.; Swingle, K. F.; Van Winkle, M. *J. Med. Chem.* **1979**, *22*, 816. Tinney, F. J.; Cetenko, W. A.; Kerbleski, J. J.; Connor, D. T.; Sorenson, R. J.; Herzig, D. J. *J. Med. Chem.* **1981**, *24*, 878.
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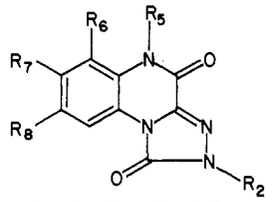
Table I. Triazoloquinoxalinones



compd	substituents R_2	R_5	R_6	R_7	R_8	formula[c]	mp, °C	RMC:[b] I_{50}, μM	PCA (po)[a] % of inhibn at 25 mg/kg	PCA (po)[a] ED_{50}, mg/kg
1a	H	H	H	H	H	$C_9H_6N_4O_2$	>300	20% (100 μM)	40[d]	
1b	H	CH_3	H	H	H	$C_{10}H_8N_4O_2$	>300	40 (13)	38[d]–56[d,e] (6)	6
1c	H	CH_3	CH_3	H	H	$C_{11}H_{10}N_4O_2$	>300	17 (3)	35–53[d] (3)	
1d	H	CH_3	H	CH_3	H	$C_{11}H_{10}N_4O_2$	>300	6 (2)	18 (3)	
1e	H	CH_3	H	CF_3	H	$C_{11}H_7F_3N_4O_2$	210–225	1.0 (3)	52[d]–69[d] (4)	12
1f	H	CH_3	H	OCH_3	H	$C_{11}H_{10}N_4O_3$	>300	3.0 (2)	10 (2)	
1g	H	CH_3	H	H	Cl	$C_{10}H_7ClN_4O_2$	>300	0.4 (3)	42[d] (2)	
1h	H	CH_3	H	$COCH_3$	H	$C_{12}H_{10}N_4O_4$	>300	1.0 (3)	49[d]	
1i	H	CH_3	H	OH	H	$C_{10}H_8N_4O_3$	>300	29% (100 μM)	20[f]	
1j	H	CH_3	H	CH_3	CH_3	$C_{12}H_{12}N_4O_2$	>300	12 (3)	2–47[g] (2)	
1k	CH_3	CH_3	H	H	H	$C_{11}H_{10}N_4O_2$	235–238	30% (100 μM) (2)	0	
1l	$COCH_3$	CH_3	H	H	H	$C_{12}H_{10}N_4O_3$	290–292	25 (3)	27–63[d] (3)	
1m	CO_2CH_3	CH_3	H	H	H	$C_{13}H_{12}N_4O_4$	263–265	30% (100 μM) (3)	0–78[d] (3)	
1n	SO_2CH_3	CH_3	H	H	H	$C_{11}H_{10}N_4O_4S$	268–272	2% (100 μM)	25[d]	
1o	$COCH_3$	CH_3	H	CH_3	CH_3	$C_{14}H_{14}N_4O_3$	>300	43 (2)	26[g]	
1p	$COCH_3$	$COCH_3$	H	H	H	$C_{13}H_{14}N_4O_4$	283–286	10	36[g] (2)	
1q	H	CH_3	Cl	OCH_3	OCH_3	$C_{13}H_{11}ClN_4O_4$	283–286	35	27	
1r	CH_3	n-C_3H_7	H	Cl	H	$C_{13}H_{13}ClN_4O_2$	222–224	1 (3)		>100
1s	H	n-C_6H_7	H	H	H	$C_{12}H_{12}N_4O_2$	235–236	8 (3)	58[d]–84[d,e] (4)	3
1t	H	CH_3	H	Cl	H	$C_{10}H_7ClN_4O_2$	>300	10 (3)	22 (2)	>125
1u	H	n-C_3H_7	H	Cl	H	$C_{12}H_{11}ClN_4O_2$	273–276	0.4 (9)	53[d]–88[d] (6)	3
1v	$CH_2CO_2C_2H_5$	n-C_6H_7	H	Cl	H	$C_{16}H_{17}ClN_4O_4$	165–166	20% (100 μM)	14 (ip)	
1w	$CH_2CH{=}CH_2$	n-C_3H_7	H	Cl	H	$C_{15}H_{15}ClN_4O_2$	145–148	20% (100 μM)		
1x	$COCH_3$	n-C_6H_7	H	Cl	H	$C_{14}H_{13}ClN_4O_3$	202–203	0.1 (3)	42[f] (ip)	
1y	$COCHCHC_6H_5$	n-C_3H_7	H	Cl	H	$C_{21}H_{17}ClN_4O_3$	227–228	1 (3)	38[g]	>100
DSCG								3 (10)		6 (ip)

[a] Number of experiments indicated in parentheses. [b] DSCG was routinely used as positive control in each experiment. Values are the average number of experiments (indicated in parentheses). [c] All compounds except **1i**, **1p**, and **1w** had elemental analysis within ±0.4% of theory. For **1i**, anal. ($C_{10}/H_8N_4O_3$) H, N; C: calcd, 48.71; found 48.20. For **1p**, anal. ($C_{13}H_{14}N_4O_4$) C, H; N: calcd, 19.58; found 20.48. For **1w**, anal. ($C_{15}H_{15}ClN_4O_2$) C, H; N: calcd, 17.58; found 18.02. [d] $p < 0.001$. [e] Inhibition at 10 mg/kg. [f] $p < 0.05$. [g] $p < 0.01$.

azoloquinoxalinedione **1**, which showed the characteristic low-field chemical shift of Hg at δ 8.6 and a AX pattern of H_8–H_9 (J_{8-9} = 9 Hz) and a long-range meta coupling of H_8–H_6 (J_{8-6} = 1.5 Hz). Furthermore, the NMR spectrum for the isomeric 8-chlorotriazoloquinoxalinedione **1g** is different from that of **1t** (data are included in the Experimental Section for comparison).

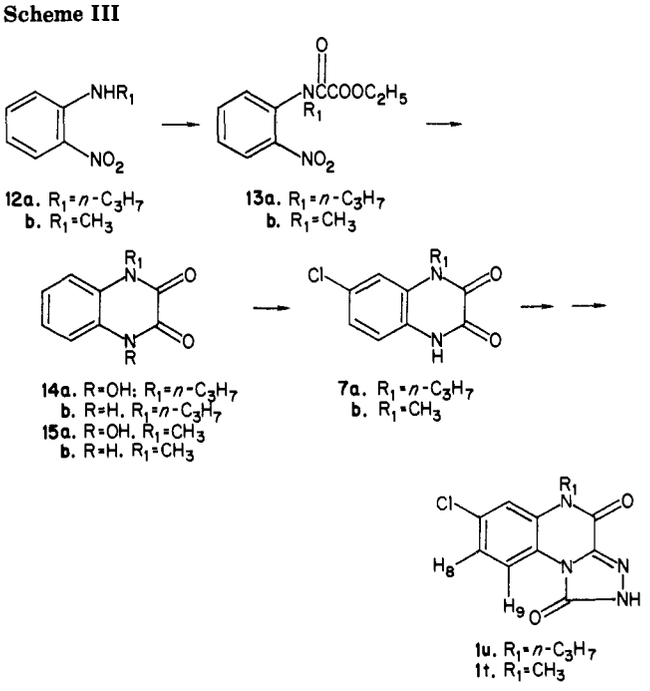
Results and Discussion

The results obtained for triazoloquinoxalinediones in the antigen-induced release of histamine from passively sensitized RMC and in the po rat PCA assays are listed in Table I.

In the in vitro screen (RMC), several compounds (**1e**, **1g**, **1h**, **1u**, **1x**) are more potent than DSCG (I_{50} = 3 μM). The most potent compound (**1x**) with an I_{50} value of 0.1 μM is approximately 30 times as active in the RMC assay as DSCG. Substitution on the aromatic ring, with the exception of a hydroxyl group (**1i**), resulted, in general, in increasing activity relative to the unsubstituted compounds. An alkyl substitution at position 5 (R_5) also showed pronounced effect on inhibitory activity in RMC assay, the order of activity decreases with substituents propyl > methyl > hydrogen as exemplified by compounds **1s**, **1b**, and **1a**. An alkyl substitution at the 2-position (R_2) showed decreased RMC and PCA activity (**1k**, **1v**, **1w**).

Several of the triazoloquinozalinediones showed oral PCA activity. Compound **1u** had an ED_{50} value of 3 mg/kg. There is no clear SAR correlation between the in vitro and in vivo screens.

Scheme III



A more detailed biological study indicated that both DSCG and quinoxalinones **1u** gave a maximum of 80% of inhibition (RMC). Furthermore, recently it has been shown in RMC that **1u** had an activity profile identical

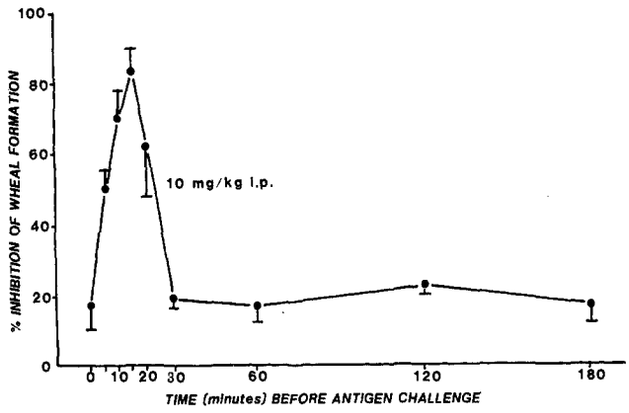


Figure 1. Effect of varying the time of intraperitoneal admission of compound **1u** on the inhibition of passive cutaneous anaphylaxis in the rat. The values shown represent the mean percent inhibition plus or minus the standard error for each group of four to eight rats.

with that of DSCG in the following respects: loss of inhibitory activity with increasing preincubation time, tachyphylactic properties, cross-tachyphylaxis to DSCG, and inability to inhibit nonimmunological release of histamine induced by dextran/phosphatidyl serine or Ca^{2+} ionophore A23187.[5]

Recently it has been shown that several of the triazoloquinoxalinediones were more potent than theophylline as inhibitors of cAMP- and/or cGMP-PDE from RMC. However, a detailed study reveals no statistically significant correlation between the inhibition of cAMP-PDE and inhibition of AIR from RMC, and it was concluded that the inhibition of cAMP or cGMP hydrolysis by these compounds is not the biochemical mechanism by which they inhibit AIR from RMC.[5]

In the in vivo test, compound **1u** showed peak inhibition in the PCA test when the compound was given intraperitoneally 10–15 min prior to antigen challenge but fell off rapidly when the interval between dosing and challenge was extended (Figure 1). Such a PCA time course activity profile is similar to that of DSCG.

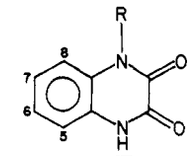
In summary, the triazoloquinoxazolinediones described here exemplify a novel class of orally active antiallergic agents with an activity profile similar to that of DSCG.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with the assigned structure. NMR were recorded on a Varian EM-390 spectrometer at 90 MHz. IR spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. All compounds had elemental analyses for C, H, and N within ±0.4% of the theoretical value unless otherwise indicated.

General Procedure for Preparation of Quinoxaline-2,3-diones. The appropriate 2-(alkylamino)aniline (0.1 mmol) was added in five portions over a period of 30 min to an oxalyl chloride (0.11 mmol) solution in *o*-dichlorobenzene at 60 °C. The reaction mixture was then heated at 130 °C for 1 h and filtered while hot, and the solid was washed with ether. Recrystallization gave the desired diones. Compounds **7c–h** were prepared according to the above procedure (Table II). Other diones, prepared according to the above procedure, were used without further purification.

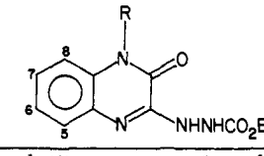
Table II. Substituted Quinoxaline-2,3-diones



no.	substit	formula	mp, °C
7a	R = *n*-C_3H_7, 7-Cl	$C_{11}H_{11}ClN_2O_2$	188–192
7b	R = CH_3, 7-Cl	$C_9H_7ClN_2O_2$	215–220
7c	R = H	$C_8H_6N_2O_2$[a]	>300
7d	R = CH_3	$C_9H_8N_2O_2$[b]	286–289
7e	R = CH_3, 6-CH_3	$C_{10}H_{10}N_2O_2$	287–292
7f	R = CH_3, 6-CO_2CH_3	$C_{11}H_{10}N_2O_4$	279–284
7g	R = CH_3, 6-CF_3	$C_{10}H_7F_3N_2O_2$	190–197
7h	R = CH_3, 6-OCH_3	$C_{10}H_{10}N_2O_3$	>300

[a] Reference 6. [b] Reference 7.

Table III. Substituted 3-(Carbethoxyhydrazino)quinoxalin-2-ones



no.	substit	formula	mp, °C
9a	R = CH_3	$C_{12}H_{14}N_4O_3$	200–202
9b	R = CH_3, 6-Cl	$C_{12}H_{13}ClN_4O_3$	186–189
9c	R = CH_3, 6-CH_3	$C_{13}H_{16}N_4O_3$[a]	>300
9d	R = CH_3, 6-OCH_3	$C_{13}H_{16}N_4O_4$[a]	>300
9e	R = CH_3, 6-CF_3	$C_{13}H_{13}F_3N_4O_3$	153–157
9f	R = CH_3, 6-CO_2CH_3	$C_{14}H_{16}N_4O_5$[a]	192–194
9g	R = *n*-C_3H_7, 7-Cl	$C_{14}H_{17}ClN_4O_3$	189–192

[a] As HCl salt.

General Procedure for the Preparation of Imino Chlorides 8. A mixture of 5 mL of thionyl chloride (68.53 mmol), DMF (5 mL), and 50 mmol of the appropriate dione in 200 mL of toluene was stirred at 130 °C for 2 h and filtered while hot to remove any insoluble material and the filtrate was concentrated. An ether–hexane (1:1) solution was added to precipitate the imino chloride, which was collected on a filter and used without further purification. For 3-chloro-1,6,7-trimethylquinoxalin-2-one: NMR ($CDCl_3$) δ 2.3 (s, 3 H), 2.4 (s, 3 H), 3.7 (s, 3 H), 7.1 (s, 1 H), 7.5 (s, 1 H).

General Procedure for Preparation of 3-(Carbethoxyhydrazino)-1-methylquinoxalin-2-ones. A mixture of imino chloride **8** (14.2 mmol) and ethyl carbazate (14.5 mmol) in 120 mL of acetonitrile was heated at 120 °C for 2 h. The reaction mixture was cooled and the product was collected on a filter and recrystallized from acetonitrile to give the pure product.

Compounds **9a–g** were prepared according to the above procedure (Table III). Other carbazate intermediates were used without further purification.

A typical NMR spectrum is shown for **9d**: NMR (Me_2SO-d_6) δ 1.3 (t, 3 H), 3.6 (s, 3 H, NCH_3), 3.8 (s, 3 H, OCH_3), 4.15 (q, 2 H, OCH_2), 7.0 (dd, 1 H, H_7, J_{7-8} = 9 Hz, J_{5-7} = 3 Hz), 7.4 (d, 1 H, H_5), 7.5 (d, 1 H, H_8).

General Procedure for Preparation of Triazoloquinoxalinediones. Method A. The ethyl carbazate derivative **9** (20 mmol) in 100 mL of Dowtherm A was heated at 220–230 °C for 25 min. After cooling, the product was filtered and washed with ether. Recrystallization from acetonitrile or dimethylformamide–water gave pure triazoloquinoxalinones. Compound **1a–j** and **1q–v** were prepared according to the above procedure (Table I). The NMR spectral data for **1t** and **1g** are as follows. For **1t**: NMR (Me_2SO-d_6) δ 3.5 (s, 3 H), 7.2 (dd, 1 H), 7.5 (d, J = 1.5 Hz, 1 H), 8.6 (d, J = 9 Hz, 1 H). For **1g**: NMR (Me_2SO-d_6) δ 3.5 (s, 3 H), 7.4 (br s, 2 H, H_6 and H_7), 8.5 (br s, 1 H, H_9).

Method B. The ethyl carbazate derivative **9** (10 mmol) in 10 mL of 1 N NaOH was stirred at room temperature overnight. The

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(6) Burakench, J. V.; Love, A. M.; Volpp, G. P. *J. Org. Chem.* **1970**, *35*, 2102.
(7) Atkinson, C. M.; Brown, C. W.; Simpson, J. C. E. *J. Chem. Soc.* **1956**, 26.

product precipitated upon acidification and was collected on the filter. The triazaloquinoxalinediones obtained this way was identical with that obtained by method A.

General Procedure for the Preparation of 2-Acyltriazoloquinoxalinediones. A solution of appropriate triazoloquinoxalinedione (10 mmol) and excess acid anhydride (or acid chloride, 12 mmol) in 20 mL of pyridine was heated at 100 °C for 3 h. Upon cooling, the product precipitated and was collected on a filter and washed with ether. Recrystallization from acetonitrile gave the desired product. Compounds **1l–p**, **1x**, and **1y** were prepared according to this procedure (Table I). For **1x**: NMR (Me_2SO-d_6) δ 0.9 (t, 3 H), 1.7 (m, 2 H), 2.6 (s, 3 H), 4.1 (m, 2 H), 7.4 (dd, 1 H, J = 9 and 2 Hz), 7.7 (d, 1 H, J = 2 Hz), 8.6 (d, 1 H, J = 9 Hz).

General Procedure for the Preparation of 2-Alkyltriazoloquinoxalinediones. To the appropriate triazoloquinoxalinedione (16 mmol) in 50 mL of DMF was added sodium hydride (50% oil dispersion, 16 mmol) followed by an excess alkyl halide (20 mmol). The reaction mixture was warmed at 60 °C for 5 h. After evaporation of solvent, the residue was washed with water and finally recrystallized from methylene chloride (or acetonitrile).

Compounds **1k**, **1r**, **1w**, and **1z** were prepared according to this method (Table I).

Ethyl *N*-Propyl-*N*-(2-nitrophenyl)oxalinate (13a). To a mixture of 2-nitro-*N*-propylaniline 18 g (0.1 mol) and a solution of 15 mL (0.11 mol) of triethylamine in 150 mL of ether was added dropwise a solution methoxalyl chloride (14 g, 0.13 mol) at room temperature over a period of 30 min. After stirring for an additional 1 h, the organic solution was washed with water, dried, and evaporated to give 20 g (74%) of oily product: NMR ($CDCl_3$) δ 0.9 (t, 3 H), 1.4 (t, 3 H), 1.7 (m, 2 H), 4.1 (q, 2 H), 7.6 (m, 3 H), 8.1 (dd, 1 H). This compound was used without further purification.

1,4-Dihydro-1-hydroxy-4-*n*-propyl-2,3-quinoxalinedione (14a). A mixture of the nitro compound **13a** (10 g, 30 mmol) and 1.2 g of 5% Pd–C in 150 mL of DMF was hydrogenated at 50 psi for 3 h. The reaction mixture was filtered and solvent was removed under vacuum. The residue was recrystallized from DMF–H_2O to give 7 g (84.6%) of **14a**: mp 188–190 °C; NMR (Me_2SO-d_6) δ 0.95 (t, 3 H), 1.7 (m, 2 H), 4.1 (m, 2 H), 7.4 (m, 4 H). Anal. ($C_{11}H_{12}N_2O_3$) C, H, N.

Compound **15a** (mp 246–248 °C) was prepared in the same manner except ethyl *N*-methyl-*N*-(2-nitrophenyl)oxanilate was used as starting material.

1,4-Dihydro-1-propyl-7-chloroquinoxaline-2,3-dione (7a). A mixture of hydroxamic acid **14a** (25 g, 0.114 mol), DMF (3 mL, 0.039 mol), thionyl chloride (9.1 mL, 0.125 mol) in 450 mL of toluene was stirred at room temperature overnight. The precipitate was filtered and washed with ether to give 23.9 g (88%) of **7a**: mp 188–192 °C; NMR (CF_3CO_2H) δ 1.1 (t, 3 H), 1.9 (m, 2 H), 4.3 (m, 2 H), 7.5 (m, 3 H). Anal. ($C_{11}H_{11}ClN_2O_2$) C, H, N.

Compound **7b** was prepared in the same manner.

Typical Procedure for Scheme II. Substituted *N*-Methyl-2-nitroanilines. To a mixture of the appropriate substituted 2-nitroanilide 11 (0.04 mol), tetra-*n*-butylammonium bromide (2.5 g, 7.8 mmol), and dimethyl sulfate (12 g, 98 mmol) in 60 mL of toluene was added 15 mL of 50% NaOH solution and the reaction mixture was stirred at room temperature for 30 min. The organic layer was separated, washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to dryness. The residue thus obtained was treated with 40 mL of 6 N HCl solution at 110 °C for 4 h. After cooling, the crude reaction mixture was poured into ice and the solid product was filtered and dried to give the desired *N*-methyl-2-nitroanilines in 80% overall yield. Most of the starting *N*-methyl-2-nitroanilines for the syntheses triazologuinozalinediones were prepared by this method and were hydrogenated directly to give the desired 2-(methylamino)anilines **5** without further purification.

***N*-Propyl-2-nitroaniline (12a).** A mixture of 2-chloronitrobenzene (23.7 g, 0.15 mol), propylamine (26.56 g, 0.45 mol), ethanol (50 mL), and water (10 mL) in a pressure bottle was heated at 130 °C overnight. The reaction mixture was cooled, diluted with water, and extracted with ether. The combined ether extract was dried and concentrated to give 26.7 g (99%) of oil. The crude product was used without further purification. For **12a**: NMR ($CDCl_2$) δ 1.0 (t, 3 H), 1.7 (m, 2 H), 3.3 (m, 2 H), 6.5–7.5 (m, 3 H), 8.2 (dd, 1 H).

Antigen-Induced Release of Histamine from Rat Mast Cells (RMC).[8] The effect of test compounds on antigen-induced release of histamine (AIR) from passively sensitized rat mast cells was determined according to the procedure of Khandwala et al.[8] Washed RMC were passively sensitized with rat antiovalbumin serum in vitro, washed, and challenged with ovalbumin to cause release of histamine. Test compounds were added simultaneously with the antigen. Both spontaneous histamine release in the absence of antigen and AIR are expressed as percent of total extractable histamine in the cells. The compound activity is expressed as percent inhibition of AIR or as the I_{50} value (concentration of the test compound required to inhibit AIR by 50%). Test compounds were dissolved in Me_2SO (final concentration of Me_2SO was 0.17% and did not affect AIR).

Passive Cutaneous Anaphylaxis in the Rat (PCA). The effect of compounds on IgE-mediated cutaneous wheal formation in the rat was determined by a modification of the method of Watanabe and Ovary.[9] Antiserum for these studies was prepared according to the following immunization protocol. Male Sprague–Dawley rats (approximately 250 g) were injected intramuscularly on days 0, 2, and 4 with 10 μg of ovalbumin and 20 mg of aluminum hydroxide (Amphojel) in 1 mL of saline. On day 0 each rat also was given 10^9 *Bordatella pertussia* organisms by the intraperitoneal route. Rats were exsanguinated on day 8, and the serum was collected by the usual methods.

The method for passive cutaneous anaphylaxis was as follows. Naive rats were sensitized at dorsal sites by intradermal injection of the syngeneic IgE antiovalbumin antiserum (1:20 dilution). After a latency period of 48 h to allow cytophilic antibodies to bind to the cutaneous mast cells, groups of four rats were given either vehicle (1% methylcellulose, 3 mL) or graded doses of compound (1 dose/group). Rats were challenged intravenously with antigen (4 mg of ovalbumin) in 1% Evans blue dye 10 min after oral administration of test compound. Thirty minutes after antigen challenge the rats were sacrificed by cervical dislocation, the dorsal skins reflected, and blued wheal areas measured. Mean values ± SE for wheal areas in control and drug-treated groups were determined and compared statistically by using the Student's t test.

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Registry No. **1a**, 90042-19-6; **1b**, 80708-30-1; **1c**, 90042-26-5; **1d**, 90042-23-2; **1e**, 90042-21-0; **1f**, 90042-22-1; **1g**, 92473-50-2; **1h**, 90042-20-9; **1i**, 90042-24-3; **1j**, 90042-25-4; **1k**, 90042-29-8; **1l**, 80708-31-2; **1m**, 92473-51-3; **1n**, 90042-33-4; **1o**, 90042-30-1; **1p**, 90042-39-0; **1q**, 90042-28-7; **1r**, 90042-34-5; **1s**, 80708-34-5; **1t**, 80708-35-6; **1u**, 80708-33-4; **1v**, 90042-37-8; **1w**, 90042-38-9; **1x**, 90042-35-6; **1y**, 90042-36-7; **5c**, 95-54-5; **5d**, 4760-34-3; **5e**, 623-08-5; **5f**, 18358-63-9; **5g**, 35203-49-7; **5h**, 5961-59-1; **6**, 79-37-8; **7a**, 92473-52-4; **7b**, 92473-53-5; **7c**, 15804-19-0; **7d**, 20934-51-4; **7e**, 92473-54-6; **7f**, 92473-55-7; **7g**, 92473-56-8; **7h**, 80776-49-4; **8j**, 92489-89-9; **9a**, 80708-29-8; **9b**, 92473-57-9; **9c**, 92473-58-0; **9d**, 92473-59-1; **9e**, 92473-60-4; **9f**, 92489-90-2; **9g**, 87885-14-1; **10** (R = H), 88-73-3; **12a**, 55432-58-1; **13a**, 92473-61-5; **14a**, 92473-62-6; H_2NNHCO_2Et, 4114-31-2; $ClCOCO_2Me$, 5781-53-3; n-$C_3H_7NH_2$, 107-10-8.

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