(experiment 1) or with (experiment 2) ethylene glycol at a 1% concentration (v/v). On days indicated, all animals were placed in individual metabolism cages for collection of urine between 0800 and 1400 h. Urinary oxalic acid was determined as its dichloroethyl ester by electron-capture gas chromatography according to the procedure of Tocco and co-workers.[28]

Acknowledgment. The authors thank the late Dr. R. E. Zwickey and his collaborators for the determination of acute LD_{50} values in mice, Dr. M. Hite and his colleagues for the Ames test results, and Mrs. T. H. Brunner and Mary Zook for manuscript preparation.

Registry No. 1, 18594-05-3; 2, 77529-35-2; 3, 77529-36-3; 4, 70262-86-1; 5, 84863-74-1; 6, 77529-37-4; 7, 84863-75-2; 8, 84863-76-3; 9, 23981-48-8; 10, 83098-20-8; 11, 84863-77-4; 12, 19813-81-1; 13, 77529-38-5; 14, 29677-27-8; 15, 84863-78-5; 16, 77529-39-6; 17, 84863-79-6; 18, 84863-80-9; 19, 72337-51-0; 20, 83098-21-9; 21, 24675-44-3; 22, 84863-81-0; 23, 83011-65-8; 24, 83011-64-7; 25, 77529-40-9; 26, 19813-83-3; 27, 84863-82-1; 28, 83098-22-0; 29, 83098-23-1; 30, 84863-83-2; 31, 84863-84-3; 32, 80653-66-3; 33, 84863-85-4; 34, 84863-86-5; 35, 78742-98-0; 36, 78742-99-1; 37, 84863-87-6; 38, 20287-70-1; 39, 78743-00-7; 40·HCl, 78764-56-4; 41, 78764-57-5; 42, 78782-93-1; 43, 78743-02-9; 44, 78743-01-8; 45·HCl, 78743-03-0; 46, 78743-04-1; 47, 80653-68-5; 48·HCl, 39067-05-5; 49·HCl, 80653-67-4; 50, 80653-70-9; 51, 80653-71-0; 52, 84863-88-7; 53, 78743-05-2; 54, 17969-37-8; 55, 84863-89-8; 56, 78742-96-8; 57, 17969-36-7; 58, 78743-06-3; 59, 84863-90-1; 60, 78743-08-5; 61, 78743-10-9; 62, 78743-09-6; 63, 78743-07-4; 64, 84863-91-2; 65, 78764-58-6; 66, 31112-96-6; 67, 31112-95-5; 68, 80653-72-1; 69, 80653-73-2; 70, 80653-74-3; 71, 84863-92-3; 72, 84863-93-4; 73, 84863-94-5; 74, 84863-95-6; 75, 84863-96-7; 76, 84863-97-8; 77, 84863-98-9; 78, 84863-99-0; 79, 84864-00-6; 80, 77529-41-0; 81, 84864-01-7; 82, 84864-02-8; 83, 77529-42-1; 84, 77529-43-2; 85, 84864-03-9; 86, 84864-04-0; 87, 84864-05-1; 88, 77529-44-3; 89, 77529-45-4; 90, 83116-17-0; 91, 83098-26-4; 92, 80458-70-4; 93, 80458-71-5; 94, 84864-06-2; 95, 84864-07-3; 96, 5347-00-2; 97, 3464-18-4; 98, 3464-15-1; 99, 83011-68-1; 100·$C_{12}H_{23}N$, 84864-09-5; 101, 83098-27-5; 102, 83098-28-6; 103, 79669-71-9; 104, 84864-10-8; 105, 78743-11-0; 106, 78743-12-1; 107, 84864-11-9; 108, 78742-97-9; 109, 78743-13-2; 110, 78764-60-0; 111, 78764-59-7; 112, 78743-15-4; 113, 84864-12-0; 114, 78743-16-5; 115, 78743-14-3; 116, 78743-17-6; 117, 78764-61-1; 118, 80653-76-5; 119, 80653-77-6; 120, 80653-75-4; 121, 80653-78-7; 122, 80653-79-8; 123, 84864-13-1; 124, 84864-14-2; 125, 84864-15-3; 126·HBr, 84864-16-4; 127, 84864-17-5; 128, 78443-35-3; GAO, 9028-71-1; diethyl oxalate, 95-92-1; *N*-dodecanenitrile, 2437-25-4; ethyl 3-cyano-2-hydroxytridec-2-enoate, 84864-18-6; 3-phenylpropionitrile, 645-59-0; ethyl 3-cyano-2-hydroxy-4-phenylbut-2-enoate, 84864-19-7; 3,4-dichlorothiobenzamide, 22179-73-3; ethyl 4-chloroacetoacetate, 638-07-3; 4-acetyl-4′-bromo[1,1′-biphenyl], 5731-01-1; methyl([1,1′-biphenyl]-4-yl)acetate, 59793-29-2; *N*-methyl-2-([1,1′-biphenyl]-4-yl)acetamide, 84864-20-0; *p*-bromoacetophenone, 99-90-1; 2-phenylindole, 948-65-2; 1-(4-acetylphenyl)-2-phenylindole, 84864-21-1; 2-acetyl-6-hydroxynaphthalene, 10441-41-5; 3,4-dihydro-2*H*-1,5-benzodioxepin-3-spirooxirane, 27612-42-6; 2-acetyl-6-[(3-hydroxy-3,4-dihydro-2*H*-1,5-benzodioxepin-3-yl)methoxy]naphthalene, 83098-19-5; (6,7-dichloro-2-cyclopentyl-2-methyl-1-oxoindan-5-yl)acetic acid, 71500-84-0; methyl(6,7-dichloro-2-cyclopentyl-2-methyl-1-oxoindan-5-yl)acetate, 83011-63-6; 2-[(6,7-dichloro-2-cyclopentyl-2-methyl-1-oxoindan-5-yl)oxy]acetamide, 83011-64-7; (±)-*cis*-2-[(6,7-dichloro-2-cyclopentyl-1-hydroxy-2-methylindan-5-yl)-oxy]acetamide, 84864-22-2; (±)-*trans*-2-[(6,7-dichloro-2-cyclopentyl-1-hydroxy-2-methylindan-5-yl)oxy]acetamide, 84864-23-3; 4-acetylbiphenyl, 92-91-1; 3-([1,1′-biphenyl]-4-yl)-3-oxopropionaldehyde sodium salt, 84864-24-4; 3-([1,1′-biphenyl]-4-yl)-3-oxopropionaldehyde oxime, 84864-25-5; 3-([1,1′-biphenyl]-4-yl)-3-oxopropionamide, 84864-26-6; 4-phenylpiperidine, 771-99-3; ethyl bromoacetate, 105-36-2; ethyl(4-phenyl-1-piperidyl)acetate, 84864-27-7; ethyl 3-amino-2-thioxopropanoate, 84864-28-8; 1-(4-bromophenyl)ethanone, 99-90-1; 2-[4-(4-bromophenyl)thiazol-2-yl]acetamide, 17969-16-3; 3-hydroxy-10,11-dihydro-5*H*-5-oxodibenzo[*a*,*d*]cycloheptene, 17910-77-9; 3-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, 84864-29-9.

(28) Tocco, D. J.; Duncan, A. E. W.; Noll, R. M.; Duggan, D. E. *Anal. Biochem.* **1979**, *94*, 470.
(29) Foucaud, A.; Person, H.; Duclos, M. *Bull. Soc. Chim. Fr.* **1965**, 2552.
(30) Fairfull, A. E. S.; Lowe, J. L.; Peak, D. A. *J. Chem. Soc.* **1952**, 742.
(31) Hepworth, W.; Gilbert, G. J. U.S. Patent 3749787, 1973; *Chem. Abstr.* **1968**, *68*, 68976*g*.

Studies on *v*-Triazoles. 9.[1] Antiallergic 4,9-Dihydro-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazoles

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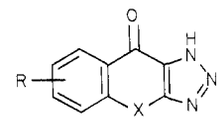
A short series of the title compounds was prepared and evaluated for antiallergic activity in the rat passive cutaneous anaphylaxis screen. All but the two N-methylated derivatives were active in this screen by the intravenous route, the most potent being the symmetrical dimethyl compound, 4,9-dihydro-6,7-dimethyl-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazole, and its 5-nitro derivative. The latter two compounds were noticeably more potent than disodium cromoglycate, and one of these, the unnitrated material, was selected for further evaluation as a potential antiasthmatic drug.

In a previous paper in this series,[2] we reported the antiallergic activity of a novel series of benzopyranotriazoles of type **1** that resulted from our studies on the triazoloquinolines **2**.[3] As part of this program, we also investigated the analogous 4,9-dihydro-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazoles **3** which constitute a potent class of antiallergic compounds as assessed by their ability to inhibit the IgE-mediated passive cutaneous anaphylaxis (PCA) reaction in the rat. This paper describes the synthesis and activity of these compounds.



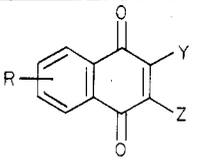
1, X = O
2, X = NH
3, X = CO

Chemistry. Several methods are available for the synthesis of simple naphthotriazoles **3**, the method of

(1) Part 8. Tedder, J. M.; Buckle, D. R. *J. Chem. Res., Synop.* **1983**, 12.
(2) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1983**, *26*, 251.
(3) D. R. Buckle, *J. Chem. Res., Synop.* **1980**, 308.

0022-2623/83/1826-0714$01.50/0

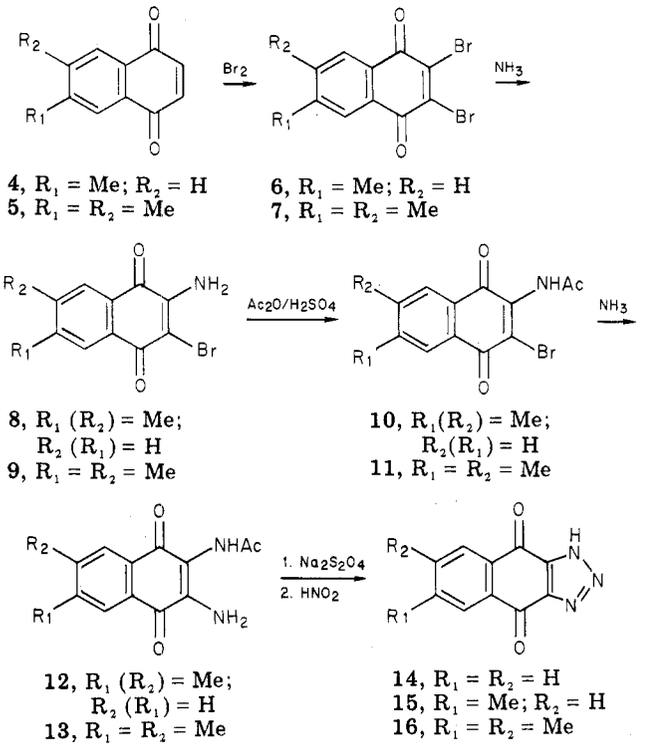
Table I. Halo and Amino Quinone Intermediates



compd	R	Y	Z	mp, °C	formula	anal.	yield, %
6	6-Me	Br	Br	194 (EtOH)	$C_{11}H_6Br_2O_2$	C, H	69
7	6,7-Me_2	Br	Br	237-238 ($CHCl_3$)	$C_{12}H_8Br_2O_2$	C, H	79
8	6(7)-Me	NH_2	Br	173 (AcOH)	$C_{11}H_9BrNO_2$	C, H, N	75
9	6,7-Me_2	NH_2	Br	228 (AcOH)	$C_{12}H_{10}BrNO_2$	C, H, N	86
10	6(7)-Me	NHAc	Br	192-193	$C_{13}H_{10}BrNO_3$	H, N, Br; C[a]	70
11	6,7-Me_2	NHAc	Br	252 ($CHCl_3$-PE)[b]	$C_{14}H_{12}BrNO_3$	C, H, N	67
12	6(7)-Me	NHAc	NH_2	200-201 (EtOH)	$C_{13}H_{12}N_2O_3$	C, H, N	40
13	6,7-Me_2	NHAc	NH_2	217-218 (EtOH)	$C_{14}H_{14}N_2O_3$	C, H, N	77

[a] C: calcd, 50.67; found, 49.51. [b] PE = petroleum ether; fraction of bp 60-80 °C.

Scheme I



4, R_1 = Me; R_2 = H
5, R_1 = R_2 = Me

6, R_1 = Me; R_2 = H
7, R_1 = R_2 = Me

8, R_1 (R_2) = Me; R_2 (R_1) = H
9, R_1 = R_2 = Me

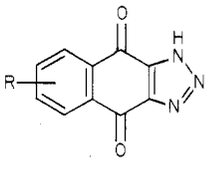
10, R_1(R_2) = Me; R_2(R_1) = H
11, R_1 = R_2 = Me

12, R_1 (R_2) = Me; R_2 (R_1) = H
13, R_1 = R_2 = Me

14, R_1 = R_2 = H
15, R_1 = Me; R_2 = H
16, R_1 = R_2 = Me

choice being largely dependent on the position and type of substitution. The parent compound, **14**, was prepared from 2,3-dichloronaphthoquinone by the method of Fieser and Martin,[4] and an analogous procedure was used for the 6-methyl and 6,7-dimethyl homologues, **15** and **16**, respectively. Thus, bromination of the naphthoquinones **4** and **5** (Scheme I) afforded the respective 2,3-dibromo derivatives **6** and **7** in reasonable yield (Table I). Amination of these with gaseous ammonia in hot nitrobenzene or *N,N*-dimethylformamide resulted in the displacement of one halogen atom to give the corresponding bromoamines **8** and **9**. No attempt was made to determine the selectivity of halogen displacement in the asymmetric bromo compound **6** or to rigorously purify or determine the structure of the major isomer. Acylation of **8** and **9** with acetic anhydride containing catalytic amounts of sulfuric acid gave the amides **10** and **11**, which were then sufficiently activated to undergo displacement of the second halogen with ammonia in hot nitrobenzene to give **12** and **13**. *N,N*-Dimethylformamide was not a suitable

Table II. 4,9-Dihydro-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazoles



compd	R	act. in rat PCA test: ED_{50},[a] mg/kg iv
14	H	0.26 (0.20-0.33)
15	6-Me	0.15 (0.11-0.20)
16	6,7-Me_2	0.037 (0.032-0.043)
20	5-NO_2	0.12 (0.08-0.19)
21	6-NO_2	*b*
22	5-OH	0.19 (0.15-0.26)
23	5-OMe	0.60 (0.38-1.15)
24	5-SMe	0.64 (0.48-1.06)
25	5-SEt	0.71 (0.51-1.01)
26	6-OH	0.41 (0.34-0.49)
27	6-OMe	0.12 (0.05-0.22)
28	6-OAc	0.41 (0.08-0.67)
29	5-SOMe	0.10 (0.07-0.13)
30	5-SO_2Me	1.52 (1.21-1.98)
31	6,7-Me_2, 5-NO_2	0.06 (0.01-0.11)
DSCG		2.0 (1.5-2.9)

[a] Calculated from the line of best fit; figures in parentheses represent the 95% confidence limits of the regression line at 50% inhibition. [b] Insufficient compound available for complete evaluation (see text).

alternative solvent for this second displacement due to the formation of complex products. Diazotization of the amino amides **12** and **13** was facilitated by prior reduction to the hydroquinone with sodium dithionite, as found by Fieser and Martin[4] for the unsubstituted compound **14**, and led to moderate yields of the naphthotriazoles **14–16** (Table II).

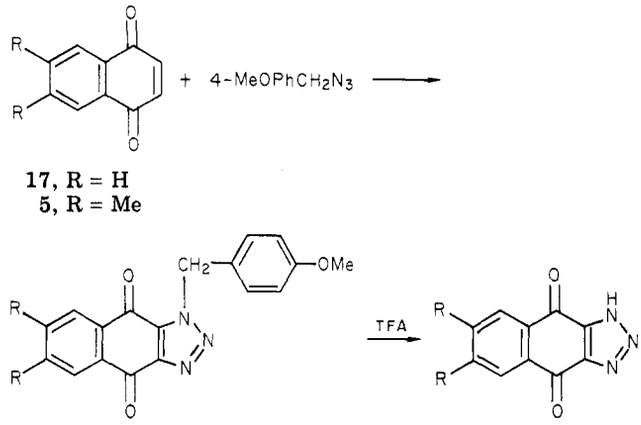
A preferred procedure for the parent and alkyl derivatives, which avoids the lengthy amination process, is shown in Scheme II. 1,3-Dipolar addition of 4-methoxybenzyl azide to naphthoquinone **17** results in formation of the 4-methoxybenzyl derivative **18** which may be readily debenzylated with hot trifluoroacetic acid[5] to give the N-unsubstituted triazole **14**. Similarly, the dimethyl homologue **5** may be converted via the 4-methoxybenzyl derivative **19** into **15**.

Nitration of the parent triazole **14** resulted in a 9:1 mixture of the 5- and 6-nitro derivatives **20** and **21**, respectively (Scheme III), from which the major isomer, **20**,

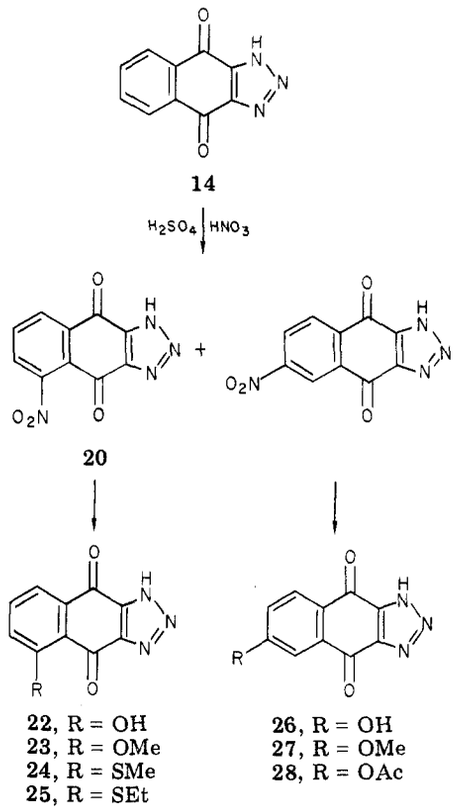
(4) Fieser, L. F.; Martin, E. L. *J. Am. Chem. Soc.* **1935**, *57*, 1844.

(5) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 627.

Scheme II



Scheme III

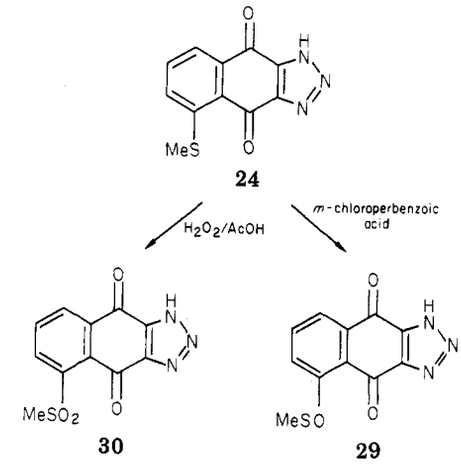


could be isolated by fractional recrystallization. The minor isomer, **21**, was only isolated pure in low yield. A similar nitration of the dimethylnaphthotriazole **16** gave the 5-nitro derivative **31** in good yield.

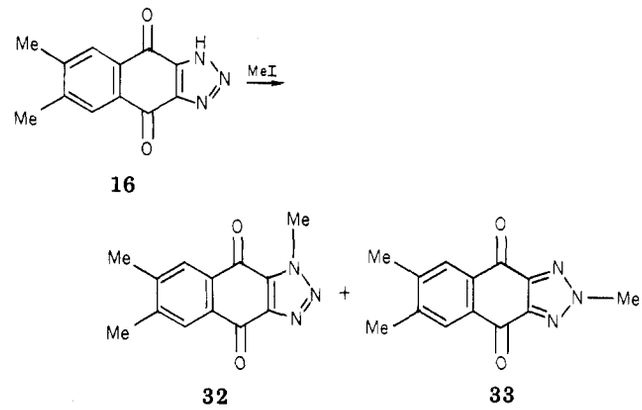
The facile nucleophilic displacement reactions of **20** and **21** have been described recently,[1] and these have proved of value in the synthesis of hydroxy, alkyloxy, and alkylthio derivatives of **14**. Thus, reaction of **20** with aldoximate anion[6] resulted in a clean displacement of the nitro group and formation of the hydroxy derivative **22**. An analogous reaction with methoxide anion afforded the corresponding methoxy compound **23**. Similarly, reaction of **20** with methyl thiolate and ethyl thiolate anions gave the corresponding alkylthio derivatives **24** and **25**, respectively. The nitro derivative **21** underwent a similar displacement with methoxide anion to give **27**, but the low availability of pure

(6) Knudsen, R. N.; Snyder, H. R. *J. Org. Chem.* **1974**, *39*, 3343.

Scheme IV



Scheme V



21 limited the usefulness of this reaction.

A more ready access to derivatives oxygenated at C-6 was suggested by the observation that anthraquinone is converted, presumably via the sulfate, into its 2-hydroxy derivative on photolysis in concentrated sulfuric acid.[7] Thus, photolysis of the unsubstituted triazole **14** under essentially similar conditions afforded the 6-hydroxy derivative **26** in moderate yield, the identity of the product being confirmed by its spectral and analytical characteristics.

Reaction of **26** with acetic anhydride at room temperature proceeded to give the acetoxy derivative **28** in moderate yield, no evidence being found for N-acetylation.[8]

Oxidation of the sulfide **24** to the derivatives **29** and **30** was readily achieved as shown in Scheme IV. Thus, oxidation at room temperature with *m*-chloroperbenzoic acid gave the methylsulfinyl derivative **29** in good yield. More vigorous oxidation with hydrogen peroxide in hot acetic acid resulted in formation of the sulfone **30**.

The isomeric *N*-methyl compounds **32** and **33** were simply prepared by direct alkylation of compound **16** with methyl iodide under alkaline conditions and were formed in the respective ratio of 2:1 (Scheme V). Chromatographic separation furnished pure samples of each isomer, which were readily distinguishable by their ^{1}H NMR spectra, the unsymmetrical isomer **32** showing a difference in chemical shift between the C-5 and C-8 proton signals of 0.12 Hz.

(7) Broadbent, A. D.; Stewart, J. M. *J. Chem. Soc., Chem. Commun.* **1980**, 676.

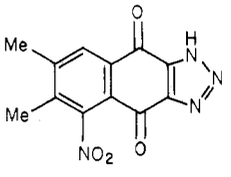
(8) Cf. Buckle, D. R.; Rockell, C. J. M.; Oliver, R. S. *J. Heterocycl. Chem.* **1982**, *19*, 1147.

Results and Discussion

Many compounds of diverse structure have been shown to possess antiallergic activity of the type shown by disodium cromoglycate (DSCG), and relative potencies have usually been assessed by their ability to inhibit rat passive cutaneous anaphylaxis (PCA). Salient features of many of these compounds are an acidic function and the presence of a carbonyl group attached to an aromatic ring, often as part of a bi- or tricyclic system.[9] It has recently been shown that two tricyclic systems containing the acidic v-triazole moiety, the benzopyranotriazoles **1**[2] and the triazoloquinolines **2**,[3] can provide compounds with this activity. We have now demonstrated that the related naphthotriazoles **3** are also active. The naphthotriazoles provided the most potent compounds in that similarly substituted compounds were the most potent in this series. For example, for the parent compounds, the intravenous doses producing 50% inhibition of the rat PCA test were 0.26 mg/kg (0.20–0.33)[10] for the naphthotriazole **14** and 1.4 mg/kg (1.1–1.8) for the equivalent benzopyranotriazole **1** (R = H) and 4.9 mg/kg (3.8–6.3) for the triazoloquinoline **2** (R = H). The additional carbonyl group of the naphthotriazoles should increase the acidity of the triazole moiety, and this may contribute to the increase in potency. Of the compounds investigated in this series, substitution at C-5 produced compounds with activity noticeably dependent on the nature of the substituent. Thus, the hydroxy derivative **22** was of equal potency to the parent **14**, whereas the nitro and methylsulfinyl compounds, **20** and **29**, respectively, were of slightly increased potency. The methoxy (**23**), methylthio (**24**), and ethylthio (**25**) compounds were weaker than the unsubstituted compound (**14**), and weaker still was the sulfone (**30**), which was the least potent of all the compounds studied.

In those compounds substituted at C-6, only marginal differences in potency were found for the range of substituents studied, most compounds being similar to the parent compound **14**.

In common with many of the systems that we have studied,[2,11] the symmetrical dimethyl homologue **16** was one of the most potent compounds, being equaled only by its nitration product **31**.



31

The *N*-methyl derivative **32** and **33**, in which the acidity of the triazole ring is removed, were inactive when given subcutaneously at doses up to 50 mg/kg.

From this series, compound **16** (BRL 22321A) was selected for further evaluation and was shown to be as equally potent as an inhibitor of rat PCA by both the subcutaneous and oral routes (ED_{50} = 0.2 mg/kg). The results of a more detailed assessment of this compound are described elsewhere.[12]

(9) See Lunt, E. In "Critical Reports in Applied Chemistry—Progress in Pharmaceutical Research"; Wooldridge, K. R. H., Ed.; Blackwell Scientific Publications: Oxford, 1982; Vol. 4, p 41.

(10) The numbers in parentheses represent the 95% confidence limits of the line of best fit; see Experimental Section.

(11) See Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Smith, R. J.; Spicer, B. A. *J. Med. Chem.* **1977**, *20*, 1059, and references cited therein.

Experimental Section

Melting points were determined with a Büchi melting point apparatus and are recorded uncorrected. The structures of all compounds were consistent with their IR and NMR spectra, which were determined with a Perkin-Elmer 197 spectrophotometer and a Varian EM 390 90-MHz spectrometer, respectively. UV spectra were carried out by using a Varian Cary 219 spectrophotometer. Where represented by elemental symbols, the analyses of these elements fall within ±0.4% of the calculated values.

Intermediate 2,3-Disubstituted 1,4-Naphthoquinones. 2,3-Dibromo-6,7-dimethyl-1,4-naphthoquinone (7). Bromine (16.0 g, 0.1 mol) was added dropwise over 5 h to a stirred solution of 6,7-dimethyl-1,4-naphthoquinone (**5**;[13] 9.13 g, 0.05 mol) in CH_2Cl_2 (100 mL), during which time hydrogen bromide was evolved. After the solution was stirred overnight, N_2 was blown through the mixture, and the dark yellow precipitate was filtered off and washed with CH_2Cl_2. Recrystallization from $CHCl_3$, afforded 13.6 g (79%) of the dibromo derivative **7**, mp 237–238 °C. Anal. ($C_{12}H_8Br_2O_2$) C, H.

2-Amino-3-bromo-6,7-dimethyl-1,4-naphthoquinone (9). Dry NH_3 was passed through a refluxing solution of **7** (10.00 g, 29 mmol) in dry $PhNO_2$ (65 mL) for 30 min, and the orange solid that separated on cooling was filtered off and washed with petroleum ether (bp 40–60 °C). Trituration of this solid with water removed ammonium bromide to give 6.96 g (86%) of **9**, mp (AcOH) 228 °C. Anal. ($C_{12}H_{10}BrNO_2$) C, H, N.

2-Acetamido-3-bromo-6,7-dimethyl-1,4-naphthoquinone (11). To a solution of **9** (10.00 g, 35.7 mmol) in acetic anhydride (100 mL) was added concentrated H_2SO_4 (0.25–0.5 mL). The yellow acetyl derivative that rapidly separated was isolated after ~15 min and was recrystallized from chloroform–petroleum ether (bp 40–60 °C) to give 7.75 g (67%) of title compound **11**, mp 225 °C. Anal. ($C_{14}H_{12}BrNO_3$) C, H, N.

2-Acetamido-3-amino-6,7-dimethyl-1,4-naphthoquinone (13). Dry NH_3 was passed through a stirred, refluxing solution of **11** (7.50 g, 23.3 mmol) in dry $PhNO_2$ (50 mL) for 1 h, and the mixture was cooled. The red solid that separated was filtered off and then washed well with ether–petroleum ether (bp 40–60 °C) and then water to give 4.46 g (77%) of **13**, mp 212–216 °C. Recrystallization from EtOH raised the melting point to 218 °C. Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

2-Acetamido-3-amino-6(7)-methyl-1,4-naphthoquinone (12). This was prepared from 6-methyl-1,4-naphthoquinone (**4**)[14] in an analogous manner to the 6,7-dimethyl homologue **13** described above (see Table I).

Naphtho[2,3-*d*]-*v*-triazoles. Compounds **22–25** and **27** were prepared by the procedure previously described.[1]

4,9-Dihydro-4,9-dioxo-1-(4-methoxybenzyl)naphtho[2,3-*d*]-*v*-triazole (18). 1,4-Naphthoquinone (1.20 g, 7.5 mmol) and 4-methoxybenzyl azide[5] (0.40 g, 2.5 mmol) were dissolved in EtOAc (50 mL), and the mixture was heated at reflux for 5 h. After standing overnight, the mixture was shaken with a solution of $FeCl_3$ (0.5 g) in 0.2 M HCl (50 mL), and the organic phase was separated, washed with water, and dried ($MgSO_4$). Evaporation gave a crude solid, which was chromatographed on SiO_2 eluting with EtOAc–petroleum ether (bp 60–80 °C) (1:10). Naphthoquinone (0.71 g) was eluted first, followed by **18** (0.43 g, 55% based on the azide): mp (EtOAc) 194 °C; IR ν_{max} (mull) 1690 (C=O) cm^{-1}; UV λ_{max} (EtOH) 228 nm (ϵ 43 600), 244 (52 100), 266 (29 100), 330 (1700); ^1H NMR ($CDCl_3$) δ 3.80 (3 H, s, OMe), 5.96 (2 H, s, CH_2), 7.20 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 54 Hz), 7.8 (2 H, m, C-6 H and C-7 H), 8.3 (2 H, m, C-5 H and C-8 H). Anal. ($C_{18}H_{13}N_3O_3$) C, H, N.

4,9-Dihydro-6,7-dimethyl-4,9-dioxo-1-(4-methoxybenzyl)-naphtho[2,3-*d*]-*v*-triazole (19). Reaction of 6,7-dimethyl-1,4-naphthoquinone (**5**;[13] 2.0 g, 10.8 mmol) with 4-methoxybenzyl azide[5] (0.49 g, 3.0 mmol) in EtOAc (50 mL) as described for compound **18** above afforded the triazole **19** (0.44 g, 42% based on the azide): mp (EtOAc) 178–179 °C; IR ν_{max} (mull) 1695, 1680

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(C=O) cm^{-1}; UV λ_{max} (EtOH) 226 nm (ϵ 25 800), 257 (41 000), 279 inf (39 700), 342 (1200); ^1H NMR ($CDCl_3$) δ 2.37 (6 H, s, Me), 3.75 (3 H, s, OMe), 5.90 (2 H, s, CH_2), 7.17 (4 H, AB q, J = 8.7 Hz, $\Delta\nu$ = 37 Hz), 7.92 (1 H, s), 8.03 (1 H, s). Anal. ($C_{20}H_{17}N_3O_3$) C, H, N.

4,9-Dihydro-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazole (14). A. From 2-Acetamido-3-amino-1,4-naphthoquinone. Reduction and diazotization of 2-acetamido-3-amino-1,4-naphthoquinone (10.1 g, 44 mmol) as described by Fieser and Martin[4] gave, on repeated runs, yields of ca. 5.64 g (59%) of the naphthoquinone **14** as its monohydrate: mp (aqueous acetone) 250 °C dec (lit.[4] mp 240–245 °C); IR ν_{max} (mull) 3520, 3320, 2650 (broad), 1685, 1590, 1580, 1502 cm^{-1}; UV λ_{max} (EtOH) 246 nm (ϵ 53 600), 270 (20 500), 330 (3900); ^1H NMR (Me_2SO-d_6) δ 7.35 (3 H, broad exchangeable NH + H_2O), 8.1 (4 H, m, aromatics). Drying in vacuo at 100 °C gave anhydrous material. Anal. ($C_{10}H_5N_3O_2$) C, H, N.

B. From 4,9-Dihydro-4,9-dioxo-1-(4-methoxybenzyl)-naphtho[2,3-*d*]-*v*-triazole (18). A solution of the *N*-(4-methoxybenzyl)triazole **18** (25 mg, 0.078 mmol) in CF_3CO_2H (2 mL) was heated to 50 °C for 5 h and evaporated to dryness under reduced pressure. Ethyl acetate (5 mL) and 1 M aqueous NaOH (5 mL) were added to the residue, and the organic phase was discarded. The aqueous phase was acidified to pH 1 with HCl, and the product was extracted into EtOAc. Evaporation of the dried ($MgSO_4$) extract gave 14 mg (90%) of the triazole **14**, mp (aqueous acetone) 250 °C dec, identical with that prepared by method A above.

4,9-Dihydro-6,7-dimethyl-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazole (16). A. From 2-Acetamido-3-amino-6,7-dimethyl-1,4-naphthoquinone (13). A solution of sodium dithionite (2.50 g, 14.4 mmol) in water (10 mL) was added to a stirred suspension of **13** (1.68 g, 6.5 mmol) in water (150 mL), and the mixture was stirred for 1 h. The white hydroquinone that precipitated was collected, dissolved in 2 M HCl (50 mL), and cooled to 0 °C. A cold solution of $NaNO_2$ (2.00 g, 25.3 mmol) in water (20 mL) was added over 2 h, and the resulting suspension was stirred overnight at room temperature. Filtration of the separated solid afforded 1.34 g (84%) of the triazole **16**, mp (aqueous acetone) 262 °C dec. Drying at 107 °C in vacuo gave the anhydrous material: IR ν_{max} (mull) 3120, 1695, 1675, 1595 cm^{-1}; UV λ_{max} (EtOH) 255 nm (ϵ 70 000), 283 (20 200), 338 (4100); ^1H NMR (Me_2SO-d_6) δ 2.22 (6 H, s, Me), 7.56 (2 H, s, aromatics), one low-field broad exchangeable proton. Anal. ($C_{12}H_9N_3O_2$) C, H, N.

B. From 4,9-Dihydro-6,7-dimethyl-4,9-dioxo-1-(4-methoxybenzyl)naphtho[2,3-*d*]-*v*-triazole (19). A solution of the triazole **19** (155 mg, 0.45 mmol) in CF_3CO_2H (5 mL) was maintained at 25 °C for 8 h, and an equal volume of water was added. The precipitated solid was removed by filtration and discarded. Addition of a large volume of water (30 mL) yielded a further precipitate, which after isolation and recrystallization from aqueous acetone gave 64 mg (61%) of **16** identical with that prepared by method A above.

4,9-Dihydro-4,9-dioxo-6-methyl-1*H*-naphtho[2,3-*d*]-*v*-triazole (15). 2-Acetamido-3-amino-6(7)-methyl-1,4-naphthoquinone (**12**; 6.80 g) was diazotized as described for compound **16** to yield 5.54 g (84%) of the triazole **15** as a monohydrate: mp (aqueous Me_2CO) 235 °C dec; IR ν_{max} (mull) 3500, 2650 (broad), 1690, 1675, 1595, 1505 cm^{-1}; ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.54 (3 H, s, Me), 7.60 (1 H, dd, J = 2 and 8 Hz, C-7 H), 8.09 (1 H, d, $J \simeq$ 2 Hz, C-5 H), 8.17 (1 H, d, J = 8 Hz, C-8 H), 11.0 (3 H, broad exchangeable NH + H_2O). Anal. ($C_{11}H_7N_3O_2 \cdot H_2O$) C, H, N.

Nitration of 4,9-Dihydro-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazole (14). The naphthotriazole **14** (5.00 g, 25 mmol) was dissolved in a mixture of concentrated H_2SO_4 (25 mL) and fuming HNO_3 (50 mL, d 1.52), and the resulting solution was heated so that the internal temperature rose to 90–100 °C, care being taken that the exothermic reaction did not become excessive. After 10 min at this temperature, the reactants were poured onto ice (250 g). When all the ice had melted, the bright yellow solid was filtered off and washed with water. Drying in vacuo afforded 4.46 g (74%) of a mixture of 5-nitro (**20**) and 6-nitro (**21**) derivatives in the ratio of 9:1, respectively (by NMR and HPLC). Multiple recrystallizations from aqueous acetone yielded 0.64 g of pure 5-nitro derivative **20** as a yellow solid: mp 244–246 °C dec; IR ν_{max} (mull) 3425 (broad), 2600 (broad), 1700, 1600, 1540, 1505 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 6.5 (3 H, broad exchangeable NH + H_2O), 8.15 (1 H, dd, J = 2 and 8 Hz, C-8 H), 8.30 (1 H, t, J = 8 Hz , C-7 H), 8.63 (1 H, dd, J = 2 and 8 Hz, C-6 H). Anhydrous material was formed on drying in vacuo at 100 °C. Anal. ($C_{10}H_4N_4O_4$) C, H, N.

The minor isomer was isolated from the enriched recrystallization liquors by chromatography on SiO_2, gradient eluting with EtOAc–MeOH. Recrystallization from MeOH gave pure **21**: mp 253–254 °C dec; IR ν_{max} (mull) 3225 (broad), 1700, 1607, 1600, 1540 cm^{-1}; NMR (Me_2CO-d_6) δ 6.5 (3 H, broad exchangeable NH + H_2O), 8.60 (1 H, d, J = 9 Hz, C-8 H), 8.85 (1 H, dd, J = 2 and 9 Hz, C-7 H), 9.00 (1 H, d, J = 2 Hz, C-5 H). Anhydrous material was obtained on drying in vacuo at 100 °C. Anal. ($C_{10}H_4N_4O_4$) C, H, N.

4,9-Dihydro-4,9-dioxo-6-hydroxy-1*H*-naphtho[2,3-*d*]-*v*-triazole (26). A solution of the parent naphthotriazole **14** (1.80 g, 8.3 mmol) in 98% H_2SO_4 (700 mL) was photolyzed for 40 h under N_2 by using a medium-pressure Hg lamp (Hanovia, quartz reactor). The resulting solution was poured onto crushed ice (3 kg), and the product was extracted into EtOAc. The extracts were washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to yield 1.30 g of a mixture of unchanged **14** and 6-hydroxy derivative **26** in a 1:1 ratio. (Optimal conversion occurred after ~80 h of photolysis when the ratio of **14** to **26** reached around 3:7, but shorter reaction times allowed for a greater through-put to **26**.) The crude mixture was chromatographed on Al_2O_3 (100 g, Merck 1097), eluting first with MeOH and then with MeOH–H_2O–NH_4OH (90:8:2), when compounds **14** and **26** were sequentially eluted as their ammonium salts. Acidification gave 0.59 g (42%; 70% on the basis of unrecovered **14**) of **26**: mp (aqueous Me_2CO) 285 °C dec; IR ν_{max} (mull) 3500–2300, 1680, 1595, 1570 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 7.30 (1 H, dd, J = 2.0 and 9.0 Hz, C-7 H), 7.73 (1 H, d, J = 2.0 Hz, C-5 H), 8.17 (1 H, d, J = 9.0 Hz, C-8 H), ~8.0 (2 H, broad exchangeable NH + OH). Anal. ($C_{10}H_5N_3O_3 \cdot H_2O$) C, H, N.

6-Acetoxy-4,9-dihydro-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazole (28). A solution of compound **26** (430 mg, 2 mmol) in Ac_2O (10 mL) was stirred for 30 min, and the white precipitate that formed was filtered off and dried in vacuo. Further product was isolated from the filtrate by hydrolysis of the anhydride and extraction ($CHCl_3$), and the combined material was recrystallized from MeOH to give 280 mg (55%) of **28**: mp 177–179 °C; IR ν_{max} (mull) 3550, 3440, 2650 (broad), 1750, 1695, 1600 cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 2.38 (3 H, s, CH_3), 7.65 (1 H, dd, J = 3 and 8 Hz, C-7 H), 8.00 (1 H, d, J = 3 Hz, C-5 H), 8.35 (1 H, d, J = 8 Hz, C-8 H), 7.5–8.5 (1 H, broad exchangeable NH). Anal. ($C_{12}H_7N_3O_4$) C, H; N: calcd, 16.34; found, 15.92.

4,9-Dihydro-4,9-dioxo-5-(methylsulfinyl)-1*H*-naphtho[2,3-*d*]-*v*-triazole (29). *m*-Chloroperbenzoic acid (400 mg, ~2 mmol, 80–90% purity) was added in small portions over 4 h to a stirred solution of **24** (500 mg, 2.04 mmol) in $CHCl_3$ (200 mL). The mixture was stirred for a further 30 min after the completion of the addition and evaporated to dryness. Extraction of the residue with CH_2Cl_2 (3 × 50 mL) left crude sulfoxide **29**, which on recrystallization from H_2O gave 405 mg (76%) of the product as red crystals: mp 262 °C dec; IR ν_{max} (mull) 2600 (broad), 1695, 1690, 1575 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.87 (3 H, s, CH_3), 8.20 (1 H, t, J = 8 Hz, C-7 H), 8.33 (1 H, dd, J = 3 and 8 Hz, C-6 H), 8.57 (1 H, dd, J = 3 and 8 Hz, C-8 H). Anal. ($C_{11}H_7N_3O_3S \cdot 0.5H_2O$) C, H, N.

4,9-Dihydro-4,9-dioxo-5-(methylsulfonyl)-1*H*-naphtho[2,3-*d*]-*v*-triazole (30). The sulfide **24** (500 mg, 2.04 mmol) was added to a solution of 30% H_2O_2 (2 mL) in glacial AcOH (50 mL), and the mixture was heated at 100 °C for 2 h. The cooled product was diluted with water, and the precipitated material was filtered off and washed with water. Recrystallization from ethanol afforded 330 mg (58%) of the title compound as a yellow solid: mp 273 °C dec; IR ν_{max} (mull) 3400, 3250, 1710, 1690 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.67 (3 H, s, CH_3), 8.17 (1 H, t, J = 7.5 Hz, C-7 H), 8.6 (2 H, d, J = 7.5 Hz, C-6 H and C-8 H). Anal. ($C_{11}H_7N_3O_4S$) C, H, N.

4,9-Dihydro-6,7-dimethyl-4,9-dioxo-5-nitro-1*H*-naphtho[2,3-*d*]-*v*-triazole (31). A mixture of **16** (0.40 g, 1.8 mmol), concentrated H_2SO_4 (4 mL), and fuming HNO_3 (8 mL, d 1.52) was heated for 10 min at 95 °C, care being taken not to let the

exothermic reaction become too vigorous. After cooling, the mixture was poured onto ice (200 g) and then allowed to stand overnight. The precipitated solid was filtered off, washed well with cold water, and dried to give 0.38 g (80%) of the 5-nitro derivative **31**: mp (EtOH) 263–266 °C dec; IR ν_{max} (mull) 3500, 3430, 1690 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.24 (3 H, s, Me), 2.55 (3 H, s, Me), 8.18 (1 H, s, aromatic), one midfield, broad exchangeable proton. Anal. ($C_{12}H_8N_4O_4$) C, H, N.

Methylation of 4,9-Dihydro-6,7-dimethyl-4,9-dioxo-1*H*-naphtho[2,3-*d*]-*v*-triazole (16). Anhydrous K_2CO_3 (1.60 g, 11.6 mmol) was added to a solution of **16** (1.135 g, 5 mmol) and MeI (0.5 mL) in dry Me_2NCHO (25 mL), and the mixture was stirred for 1 h at 20 °C. Dilution with water afforded a buff-colored precipitate, which was separated, washed with water, and dried in vacuo over P_2O_5 to give 1.02 g (84%) of N^1-methyl (**32**) and N^2-methyl (**33**) isomers in the ratio 2:1 (from NMR). Chromatography on SiO_2 eluting with $CHCl_3$ gave first the white N-2 isomer **33**: mp ($CHCl_3$–petroleum ether, bp 40–60 °C) 224 °C; IR ν_{max} (mull) 1690, 1685 (shoulder), 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (6 H, s, C-CH_3), 4.42 (3 H, s, N-CH_3), 8.03 (2 H, s, aromatics). Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

Further elution gave the pale yellow N-1 isomer **32**: mp ($CHCl_3$–petroleum ether, bp 40–60 °C) 238 °C; IR ν_{max} (mull) 1695 (shoulder) 1685, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (6 H, s, C-CH_3), 4.45 (3 H, s, N-CH_3), 7.90 (1 H, s, aromatic), 8.02 (1 H, s, aromatic). Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

Rat Passive Cutaneous Anaphylaxis. This was carried out by the procedure previously described,[15] except that Charles Rivers' Sprague–Dawley male rats were used. Each dose of a compound was given intravenously to six animals at the time of antigen challenge, the doses being adjusted so that for most compounds three different doses produced an inhibition of between 30 and 70%. The variation in a control group of six animals gave an SEM of about 6%, and inhibitions greater than 20% were usually significant. Regression lines were fitted to each data set plotted against the $\log_{10}$ dose, and the median effective dose associated confidence limits were then estimated as the doses corresponding to a 50% response, as calculated from the equations of the regression line and the 95% confidence limits of the mean response to any given dose.[16]

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Registry No. **4**, 605-93-6; **5**, 2202-79-1; **6**, 72364-92-2; **7**, 41791-77-9; **8**, 72367-94-3; **9**, 6944-78-1; **10**, 72367-95-4; **11**, 72364-90-0; **12**, 72367-96-5; **13**, 18691-24-2; **14**, 3915-98-8; **15**, 72364-93-3; **16**, 72364-91-1; **17**, 130-15-4; **18**, 79707-02-1; **19**, 79707-03-2; **20**, 72364-96-6; **21**, 72365-05-0; **22**, 80841-91-4; **23**, 84731-20-4; **24**, 84731-21-5; **25**, 84731-22-6; **26**, 80841-85-6; **27**, 72364-95-5; **28**, 84731-23-7; **29**, 84731-24-8; **30**, 84731-25-9; **31**, 72364-98-8; **32**, 84731-26-0; **33**, 84731-27-1; 4-$MeOPhCH_2N_3$, 70978-37-9; **12** (R_1, R_2 = H), 13755-96-9.

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Structure–Activity Correlations for a Series of Antiallergy Agents. 2. Geometric and Electronic Characterization of Some Oxamic and Dioxamic Acids[1]

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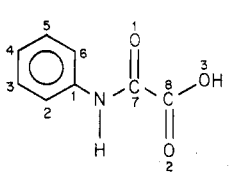
Hartree-Fock self-consistent field calculations using the ab initio molecular fragment technique have been performed on some phenyloxamic and *m*-phenylenedioxamic acids, which exhibit markedly different activities in the rat passive cutaneous anaphylaxis (PCA) assay. Attention is focused upon structural features that are most likely to affect the drug–receptor interactions, such as the preferred molecular geometry, the electronic charge distribution, and the nature of the higher occupied (HOMO) and lower unoccupied (LUMO) molecular orbitals. Judging from the regions of high density in HOMOs and LUMOs, the benzene ring would preferably act as an electron acceptor, while the oxamic acid moiety would serve best as an electron donor. Factors affecting the relative PCA activities of oxamic and dioxamic acids are discussed.

A number of oxamic and dioxamic acids, resembling structures **1** and **2**, have been shown to inhibit the allergic



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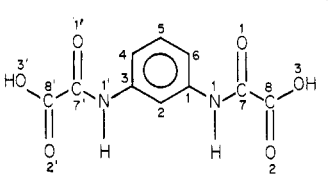

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response that follows antigen–antibody reaction on sensitized mast cells.[1,3] Although the site of action has not been identified unequivocally, an agent with a similar spectrum of biological effects (cromolyn sodium) has been observed to associate reversibly with the mast cell.[4,5] Since no penetration of cromolyn sodium into the interior cell was detected, it appears that the entity with which the drugs interact may be located on, or within, the cellular membrane. In any case, the drugs ultimately block release of the mediators of the allergic reaction from the triggered mast cell. Activity of this type may be measured in a

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