g, were selected at random from animal pools for use in the protection tests. Techniques for establishing mouse infections and maintenance of cultures will not be further described here.

Fresh stock solutions of the antibiotics were prepared at the beginning of each experiment and diluted so that the desired dose was contained in 0.2 mL when administered subcutaneously or in 0.5 mL when administered by oral intubation. The drug was administered immediately after the infecting dose and daily for 4 consecutive days thereafter. The test animals were observed for 3 additional days. Evaluation of antibiotic activity was based on the median protective dose (CD_{50}) as determined in groups of 10 animals challenged with 100 × LD_{50} of the microorganism. Calculation of the CD_{50} was by the method of Spearman and Karber.[17]

The procedures for testing antibiotics in *Plasmodium berghei* infected mice were different from those employed for the rest of the bacteria and have also been described previously.[18] The *Bacteroides fragilis* abscess model is similar to that described by Walker, Nitzan, and Wilkins.[19] The infection is produced by the subcutaneous injection of a *B. fragilis* culture grown in a semisolid medium, which results in the development of palpable subcutaneous abscesses. A human clinical isolate of *B. fragilis* was grown anaerobically on Schaedler Agar at 37 °C for 72 h. Six isolated colonies were harvested with a sterile loop and a cell suspension made in 2.0 mL of prereduced BHI broth. A 0.5-mL aliquot of this suspension was used to inoculate serum vials of prereduced BHI semisolid medium (BHI broth plus 0.25% agar). The vials were incubated anaerobically at 37 °C for 20 h. After incubation, the number of viable cells was determined by plate count, and 0.5 mL of culture was used to inoculate mice subcutaneously under the loose skin of the groin on the left side of the mouse. Untreated animals develop palpable subcutaneous abscesses in 4–7 days. Drug solutions were prepared in distilled water and administered in a 0.2-mL subcutaneous dose. Infected animals received one dose 4 h postinfection and two doses daily for 2 days on the side opposite the infected site. Mice were examined 7 days after infection for the presence or absence of abscesses, evident by palpation. The median protective dose (CD_{50}), i.e., the amount of drug required to protect 50% of the animals from abscess formation, was calculated from the 7-day data.

Pharmacology. Blood and abscess levels of pirlimycin and clindamycin in *B. fragilis* infected mice were determined by microbiological assay. Mice were infected with *B. fragilis* as previously described. Seven days postinfection, groups of five mice each were dosed with 200 mg/kg of pirlimycin or clindamycin and sacrified at various time intervals following dosage. Blood samples were collected by cardiac puncture, and abscesses were excised. These materials were assayed for antibiotic activity by standard microbiological methods.

Excretion of bioactivity via the urine of rats given a single subcutaneous or oral dose of pirlimycin or clindamycin was determined by standard microbiological methods. Animals were housed in individual metabolism cages for collection of urine.

Registry No. 1, 18323-44-9; **2**, 22965-79-3; **3a**, 98-98-6; **3b**, 59-67-6; **3c**, 55-22-1; **3d**, 4021-07-2; **3e**·HCl, 79415-18-2; **3f**, 87999-87-9; **3g**, 83282-39-7; **3h**, 42205-74-3; **3i**, 8799-88-0; **3j**, 87999-89-1; **3k**, 770-08-1; **3l**, 934-60-1; **3m**, 4080-48-2; **4e**, 88015-20-7; **5a**, 78788-61-1; **5b**, 78788-62-2; **5c**, 78788-63-3; **5d**, 87999-90-4; **5e**, 78788-60-0; **5f**, 87999-91-5; **5g**, 78788-74-6; **5h**, 87999-92-6; **5i**, 87999-93-7; **5j**, 87999-94-8; **5k**, 78788-66-6; **5l**, 87999-95-9; **5m**, 87999-96-0; **6a**, 88154-62-5; **6b**, 87999-97-1; **6c**, 87999-98-2; **6d**, 87999-99-3; **6e**·HCl, 80081-63-6; **6f**, 88000-00-4; **6g**, 79464-95-2; **6h**, 88000-01-5; **6i**, 88000-02-6; **6k**, 88080-01-7; **6l**, 88000-03-7; **6m**, 88000-04-8; **7a**, 78822-42-1; **7b**, 88000-05-9; **7d**, 88080-02-8; **7e**·HCl, 78822-40-9; **7f**, 88080-03-9; **7g**, 78788-73-5; **7h**, 88080-04-0; **7i**, 88080-05-1; **7j**, 88000-06-0; **7k**, 88080-06-2; **7l**, 88080-07-3; **7m**, 88080-08-4; **8**, 88080-09-5; **9**, 88080-10-8; **10**, 88000-07-1; **11**, 88080-11-9; **12**·HCl, 88000-08-2; **13**, 88000-09-3; **14**·HCl, 88080-12-0; **7e**, 79548-73-5; **15**, 88000-10-6; **16**, 88000-11-7; **16** (*N*-Cbz derivative), 88015-21-8; **17**, 88000-12-8; **18**, 88015-22-9; **19**, 88000-13-9; **20**, 88000-14-0; 2-bromo-4-ethylpyridine, 54453-91-7.

(17) Spearman, C.; Karber, G. "Statistical Methods in Biological Assays", 2nd ed.; Hafner: New York, 1964; pp 523–530.
(18) Lewis, C. *J. Parasitol.* **1968**, 169–170.
(19) Walker, C. B.; Nitzan, D.; Wilkins, T. D. *Antimicrob. Agents Chemother.* **1977**, 435–440.
(20) We thank R. C. Thomas for the preparation of this compound.

Notes

Studies on 1,2,3-Triazoles. 10.[1] Synthesis and Antiallergic Properties of 9-Oxo-1*H*,9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazoles and Their *S*-Oxides

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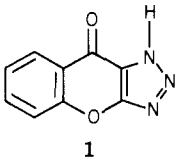
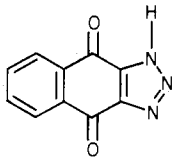
Received June 15, 1983

Selected derivatives of 9-oxo-1*H*,9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole, a new heterocyclic ring system, and their *S*-oxides have been prepared and evaluated for antiallergic activity in the rat passive cutaneous anaphylaxis screen. Several of the compounds show intravenous potencies similar to or greater than that of disodium cromoglycate, the most potent being 6,7-dimethyl-9-oxo-1*H*,9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole and its 4,4-dioxide.

Derivatives of benzopyrano[2,3-*d*]-1,2,3-triazole (**1**) and



1



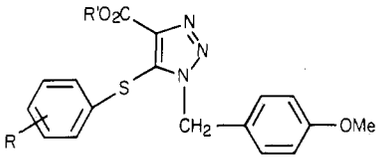
2

the related naphtho[2,3-*d*]-1,2,3-triazole (**2**) have recently been shown to be potent inhibitors of the IgE-mediated passive cutaneous anaphylaxis (PCA) reaction in the rat,[1,2] and one compound, BRL 22321A, the sodium salt of the 6,7-dimethyl derivative of **2**, has undergone extensive pharmacological evaluation.[3] Of particular interest was

(1) Part 9. Buckle, D. R.; Smith, H.; Spicer, B. A.; Tedder, J. M. *J. Med. Chem.* **1983**, *26*, 714.
(2) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1983**, *26*, 251.

0022-2623/84/1827-0223$01.50/0

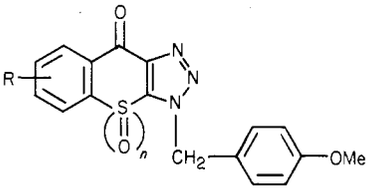
Table I. 5-(Arylthio)-1-(4-methoxybenzyl)-1,2,3-triazole-4-carboxylic Acids and Esters



no.	R	R¹	mp, °C (crystn solvent)	formula	anal.	yield, %
4	H	Et	60-61 (Et_2O-PE)[a]	$C_{19}H_{19}N_3O_3S$	C, H, N, S	71
5	4-Me	Et	60-61 (EtOH-PE)[a]	$C_{20}H_{21}N_3O_3S$	C, H, N, S	68
6	3,4-Me_2	Et	98-100 (EtOH)	$C_{21}H_{23}N_3O_3S$	C, H, N, S	82
7	4-OMe	Et	95-96 (EtOH-PE)[a,b]	$C_{20}H_{21}N_3O_4S$	C, H, N, S	74
8	H	H	118-120[c] (AcOEt)	$C_{17}H_{15}N_3O_3S$	C, H, N	100
9	4-Me	H	154-155[c] (AcOEt)	$C_{18}H_{17}N_3O_3S$	C, H, N, S	100
10	3,4-Me_2	H	98-100[c] (AcOEt)	$C_{19}H_{19}N_3O_3S$	C, H, N, S	100
11	4-OMe	H	141-142 (AcOEt)	$C_{18}H_{17}N_3O_4S$	C, H, N, S	96

[a] PE = petroleum ether; fraction of bp 60-80 °C. [b] See ref 5. [c] Melted with decomposition.

Table II. 3-(4-Methoxybenzyl)-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazoles and Their *S*-Oxides



no.	R	*n*	mp,[a] °C (crystn solvent)	formula	anal.	yield, %	method[b]
14	H	0	160 (EtOH)	$C_{17}H_{13}N_3O_2S$	C, H, N, S	40	A
15	7-Me	0	193-194 (EtOH-$CHCl_3$)	$C_{18}H_{15}N_3O_2S$	C, H, N, S	59	A
16	6,7-Me_2	0	220-222 (EtOH-$CHCl_3$)	$C_{19}H_{17}N_3O_2S$	C, H, N, S	58[c]	A
17	7,8-Me_2	0	192-193 (EtOH-$CHCl_3$)	$C_{19}H_{17}N_3O_2S$	C, H, N, S	58[c]	A
23	H	1	177-178 (EtOH-$CHCl_3$)	$C_{17}H_{13}N_3O_3S$	C, H, N, S	61[d]	D
25	H	2	158-159 (EtOH-$CHCl_3$)	$C_{17}H_{13}N_3O_4S$	C, H, N, S	59	E
26	7-Me	2	160-161 (EtOH)	$C_{18}H_{15}N_3O_4S$	C, H, N, S	60	E
27	6,7-Me_2	2	193-194 (EtOH-$CHCl_3$)	$C_{19}H_{17}N_3O_4S$	C, H, N, S	91	E
28	7,8-Me_2	2	152-153 (EtOH)	$C_{19}H_{17}N_3O_4S$	C, H, N, S	67	E

[a] Melting point with decomposition. [b] See text and Experimental Section. [c] Yield of mixed isomers 16 and 17. [d] 34% of the sulfone 25 was also formed.

the smooth muscle relaxant activity exhibited by BRL 22321A, which has resulted in its selection for clinical study.[3] Encouraged by the potency of these tricyclic triazoles in the rat PCA reaction, we have investigated the related benzothiopyrano[2,3-*d*]-1,2,3-triazoles **18–22** and their *S*-oxides **24** and **29–32**, which represent a novel heterocyclic class.[4] This paper describes the synthesis and activity of these compounds.

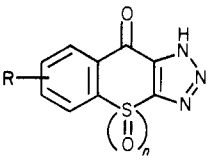
Chemistry. The facile nucleophilic displacement reactions of ethyl 5-chloro-1-(4-methoxybenzyl)-1,2,3-triazole-4-carboxylate (**3**) have established this compound as a versatile intermediate for the synthesis of various vicinal triazoles.[5] In particular, the reaction of **3** with 4-methoxybenzenethiol has been shown to furnish ethyl 5-(arylthio)-1-(4-methoxybenzyl)-1,2,3-triazole-4-carboxylate (**7**) in good yield.[5] Extending this reaction to other benzenethiols (Scheme I) leads to uniformly good yields of the corresponding triazoles **4–6**, the alkaline hydrolysis of which results in nearly quantitative yields of the parent carboxylic acids **8–11** (Table I). The cyclization of these acids may be effected either directly or by the prior removal of the *N*-(4-methoxybenzyl) substituent. In general, the direct cyclization is preferred, since the presence of the N-substituent facilitates the reaction by allowing activation of the carboxylic acid as its acid chloride. Thus, reaction of **8–10** with oxalyl chloride, followed by cyclization in the presence of aluminum chloride (method A), gave moderate yields of the tricyclic products **14–17** (Table II). The asymmetrically substituted phenylthio derivative **10** gave a mixture of the two possible products **16** and **17**, which could be readily separated.

Treatment of these N-protected triazoles **14–17** with hot trifluoroacetic acid (method B)[5] resulted in the clean removal of the 4-methoxybenzyl groups to give the N-unsubstituted triazoles **18–21** in good yield (Table III). The most advantageous route to the 7-methoxy derivative **21** utilized the alternative cyclization procedure. Thus, **7** was converted to the unprotected triazole **12** by reaction with trifluoroacetic acid and subsequently hydrolyzed to the acid **13**.[5] Heating **13** in a solution of phosphoric oxide in methanesulfonic acid (method C) then gave the tricyclic product **22** in relatively low yield.

Oxidation to the *S*-oxides was accomplished by utilizing the *N*-(4-methoxybenzyl) intermediates **14–17**. Reaction of the parent compound **14** with *m*-chloroperbenzoic acid (Scheme II, method D) afforded both the sulfoxide **23** (61%) and the sulfone **25** (34%), which were readily separated chromatographically. When potassium permanganate in warm (≃50 °C) acetic acid (method E) was used, compounds **14–17** were smoothly oxidized to their sulfones **25–28** in good yield (Table II). Deprotection of the sulfones **25–28** with trifluoroacetic acid gave reasonable yields of the N-substituted derivatives **29–32** (Table III), although a similar reaction with the sulfoxide **23** resulted

(3) Spicer, B. A.; Clarke, G. D.; Harling, E. J.; Hassall, P. A.; Ross, J. W.; Smith, H.; Taylor, J. F. *Agents Actions* **1983**, *13*, 301.
(4) Buckle, D. R. European Patent 59 606, 1982.
(5) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 627.

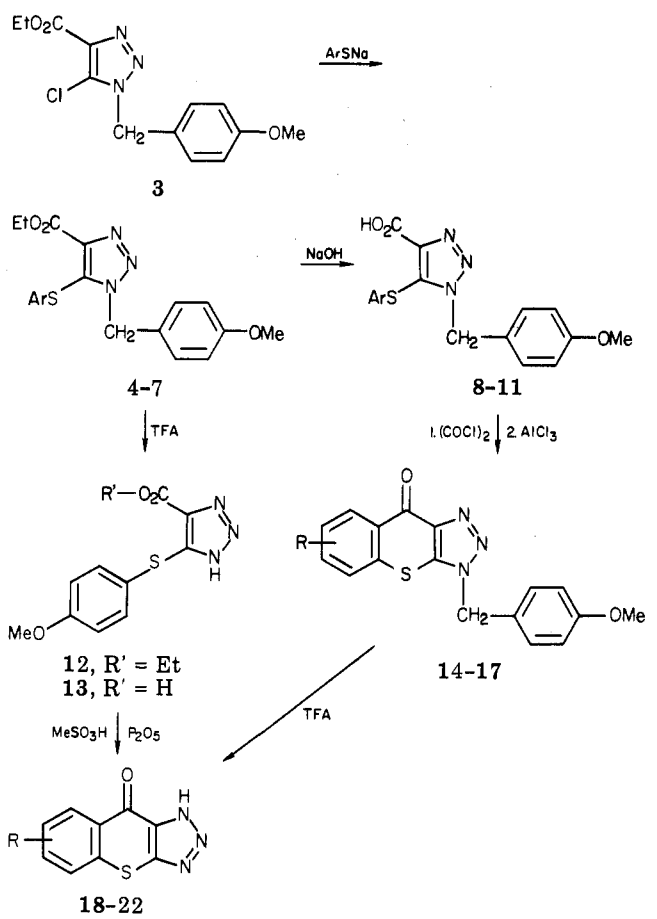
Table III. 9-Oxo-1*H*,9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazoles and Their *S*-Oxides



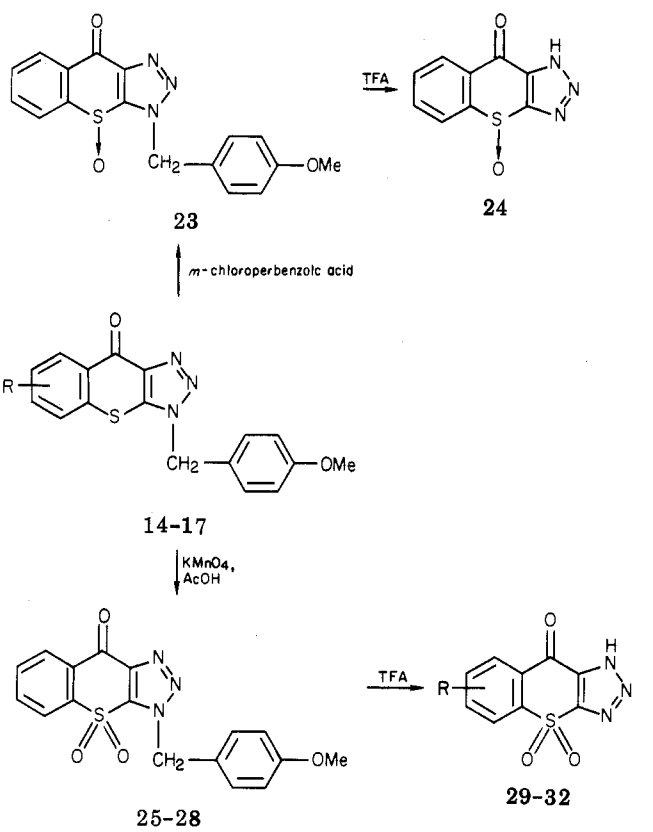
no.	R	*n*	mp,[a] °C (crystn solvent)	formula	anal.	yield, %	method[b]	act. in rat PCA test: ED_{50},[c] mg/kg iv
18	H	0	272-274 (MeOH)	$C_9H_5N_3OS$	C, H, N	71	B	1.43 (0.91-1.95)
19	7-Me	0	270-272 (EtOH)	$C_{10}H_7N_3OS \cdot 0.2H_2O$	C, H, N, S	98	B	11.37 (9.83-13.39)
20	6,7-Me_2	0	274-276 (EtOH-DMF-H_2O)	$C_{11}H_9N_3OS$	C, H, N, S	72	B	0.43 (0.34-0.53)
21	7,8-Me_2	0	283-285 (EtOH-$CHCl_3$)	$C_{11}H_9N_3OS$	C, H, N, S	100	B	3.18 (2.50-4.19)
22	7-OMe	0	275-277 (EtOH-DMF)	$C_{10}H_7N_3O_2S \cdot 0.25H_2O$	C, H, N, S	9.5	C	1.59 (1.16-2.43)
24	H	1	174 (EtOH)	$C_9H_5N_3O_2S \cdot 0.25H_2O$	C, H, N[d]	36	B	1.23 (0.66-4.14)
29	H	2	236-238 (EtOH-H_2O)	$C_9H_5N_3O_3S \cdot 0.5H_2O$	C, H, N	77	B	6.14 (4.91-7.80)
30	7-Me	2	254-255 (EtOH)	$C_{10}H_7N_3O_3S$	C, H, N, S	72	B	5.88 (4.57-8.30)
31	6,7-Me_2	2	262-263 (EtOH)	$C_{11}H_9N_3O_3S$	C, H, N, S	67	B	0.60 (0.36-0.89)
32	7,8-Me_2	2	271-272 (EtOH-H_2O)	$C_{11}H_9N_3O_3S$	C, H, N	100	B	>1[e]

[a] All melting points occurred with decomposition. [b] See text and Experimental Section. [c] Calculated from the line of best fit; figures in parentheses represent the 95% confidence limits of the regression line at 50% inhibition. DSCG = 2.0 (1.5-2.9). [d] N: calcd, 18.78; found, 18.35. [e] Insufficient compound available for complete evaluation.

Scheme I



Scheme II



in a much reduced yield (36%) of the desired triazole **24**.

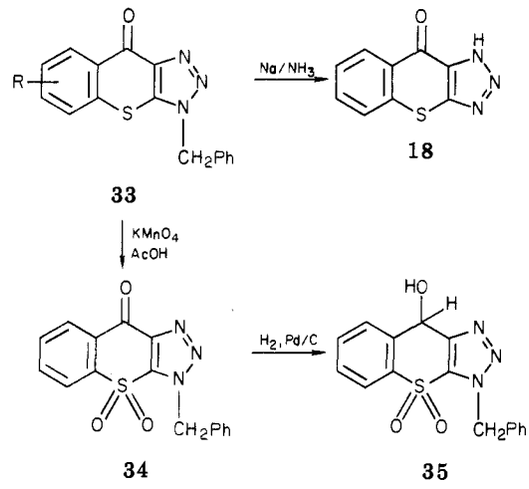
The thiopyranotriazole **18** was also prepared by debenzylation of the *N*-benzyl compound **33** with sodium in liquid ammonia (Scheme III), but the yield was poor. Moreover, in an attempt to prepare the corresponding sulfone **29** by hydrogenolysis of its *N*-benzyl derivative **34**, only the hydroxy sulfone **35** was isolated. This latter reaction reinforces our earlier observation in the benzopyranotriazole series[6] concerning the high stability of the *N*-benzyl bond in these tricyclic derivatives.

Results and Discussion

In an earlier publication[1] it was shown that derivatives of the naphthotriazole **2** were noticeably more potent at

(6) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M. *J. Heterocycl. Chem.* **1981**, *18*, 1117.

Scheme III



inhibiting the rat PCA reaction than similarly substituted derivatives of the related benzopyranotriazole 1 and that, typically, the parent compounds and the 6,7-dimethyl derivatives act as suitable markers for the comparison of potency across the series. When this comparison is made with the benzothiopyranotriazole series, it is evident that there is no potency enhancement relative to the benzopyranotriazoles [parent ED_{50} = 1.4 (1.1–1.8) mg/kg iv; 6,7-dimethyl ED_{50} = 0.04 (0.03–0.04) mg/kg iv].[1] Furthermore, oxidation of compound **18** to the sulfoxide **24** and sulfone **29** did not effect an improvement in potency. Similarly, the potency of the 6,7-dimethyl derivative **20** was not enhanced on oxidation to the sulfone **31** (Table III).

The absence of improvement demonstrated by these compounds has resulted in the synthesis of only a representative group of analogues, with the result that meaningful structure–activity discussions are not possible. Not surprisingly, however, there does appear to be a similarity in potency of the unoxidized derivatives **18–22** to that of similarly substituted benzopyranotriazoles.[2]

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 recorded on a Varian Cary 219 spectrophotometer. Where represented by elemental symbols, the analyses of these elements fall within ±0.4% of the calculated values.

5-(Arylthio)-1-(4-methoxybenzyl)-1,2,3-triazole-4-carboxylates (4–7, Table I). To a stirred solution of the thiophenol (0.1 mol) in dry DMF (250 mL) was added a 50% dispersion of NaH in mineral oil (4.8 g, 0.1 mol), and the mixture was stirred for 1 h at room temperature to ensure formation of the sodium salt. To this salt was added finely powdered ethyl 5-chloro-1-(4-methoxybenzyl)-1,2,3-triazole-4-carboxylate[5] (29.55 g, 0.1 mol) in a single portion, and the mixture was stirred at 70–80 °C for 24 h. After the mixture was cooled, the solvent was removed in vacuo, and the residue was partitioned between AcOEt and water. The organic phase was washed with dilute aqueous NaOH and brine and dried ($MgSO_4$). Evaporation of the solvent gave crude **4–7**, which was purified by recrystallization or, in the case of **4**, by chromatography on SiO_2 by elution with chloroform and then recrystallization.

5-(Arylthio)-1-(4-methoxybenzyl)-1,2,3-triazole-4-carboxylic Acids (8–11, Table I). Hydrolysis of the above esters **4–7** (0.1 mol) with 1.25 M aqueous NaOH (170 mL) at 85 °C for 3 h gave, on cooling and acidification, near quantitative yields of the corresponding acids **8–11**. Recrystallization from AcOEt afforded material of analytical purity.

3-(4-Methoxybenzyl)-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole (14). Method A. A mixture of the carboxylic acid **8** (0.05 mol) and oxalyl chloride (14.1 g, 0.11 mol) in dry CH_2Cl_2 (150 mL) was treated with a catalytic amount of DMF and then stirred at ambient temperature for 1–2 h. The resulting clear solution was evaporated in vacuo to remove excess oxalyl chloride, and the residual acid chloride (ν_{max} 1760 cm^{-1}) was redissolved in dry CH_2Cl_2 (200 mL) and cooled to 0 °C. Anhydrous $AlCl_3$ (25.64 g, 0.177 mol) was added in portions to the stirred solution over 30 min, and the mixture was stirred for a further 3 h at 0 °C. After dilution with ice–water, the product was extracted with $CHCl_3$, and the extracts were washed with water and brine. The dried ($MgSO_4$) extracts were evaporated to yield an oil, which, on chromatography on SiO_2 eluting with $CHCl_3$ and recrystallization from EtOH, gave the triazole **14** (8.08 g, 40%): mp 160 °C dec; IR ν_{max} (mull) 1660 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (3 H, s, OCH_3), 5.61 (2 H, s, CH_2), 7.11 (4 H, AB q, J = 8.5 Hz, $\Delta\nu$ = 25 Hz, benzyl aromatics), 7.54 (3 H, m, C-5, C-6, and C-7 H), 8.68 (1 H, m, C-8H); UV λ_{max} (EtOH) 237 nm (ϵ 35 000), 242 (34 700), 332 (7200). Anal. ($C_{17}H_{13}N_3O_2S$) C, H, N, S.

Compounds **15–17** were similarly prepared, except that for the two isomers **16** and **17** the former was isolated by fractional recrystallization of the crude material from ethanol–chloroform and the latter by chromatography of the enriched recrystallization mother liquors on SiO_2 eluting with CH_2Cl_2 when it eluted as the faster running isomer.

9-Oxo-1*H*,9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole (18). Method B. A solution of the (4-methoxybenzyl)triazole **14** (0.96 g) in trifluoroacetic acid (50 mL) was stirred at 60–65 °C (oil bath temperature) for 5 h, when HPLC monitoring showed complete reaction. The solvent was removed in vacuo, and the residue was triturated with water, filtered, and dried. Chromatography on SiO_2, eluting first with $CHCl_3$ and then with 10% MeOH–$CHCl_3$, gave the triazole **18** (0.43 g, 71%): mp (MeOH) 272–274 °C dec; IR ν_{max} (mull) 2600 (broad, NH), 1620 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.80 (3 H, complex m, C-5, C-6, and C-7 H), 8.53 (1 H, dd, C-8 H). Anal. ($C_9H_5N_3OS$) C, H, N.

Similarly prepared were compounds **19–21** and **24–32** (Table III), the time course of the reaction being followed by HPLC, reaction times of 3–6 h being usual.

9-Oxo-7-methoxy-1*H*,9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole (22). Method C. Phosphorus pentoxide (60 g) was added to vigorously stirred 98% methanesulfonic acid (150 g) at 80 °C (oil bath temperature), and the mixture was stirred for 1 h until homogeneous. Powdered 5-[(4-methoxyphenyl)thio]-1*H*-1,2,3-triazole-4-carboxylic acid[5] (7.78 g, 0.031 mol) was added in one portion, and the mixture was stirred at 103 °C for 24 h, after which the cooled mixture was diluted with ice water (600 mL). After 90 min the solid was filtered, washed well with water, and dried. Chromatography on SiO_2, eluting with $CHCl_3$, gave the product **22** (0.68 g, 9.5%) as a pale yellow solid: mp (EtOH–DMF) 275–277 °C dec; IR ν_{max} (mull) 2400 (broad, NH), 1622 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.89 (3 H, s, OCH_3), 7.41 (1 H, dd, J = 3 and 8.5 Hz, C-6 H), 7.90 (1 H, d, J = 8.5 Hz, C-5 H), 7.82 (1 H, d, J = 3 Hz, C-8 H). Anal. ($C_{10}H_7N_3O_2S$·0.25H_2O) C, H, N, S.

Oxidation of 3-(4-Methoxybenzyl)-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole (14). (a) With *m*-Chloroperbenzoic Acid. Method D. To a stirred solution of **14** (1.615 g, 5 mmol) in $CHCl_3$ (125 mL) at 0 °C was added a solution of ≃85% *m*-chloroperbenzoic acid (1.015 g, 5 mmol) in $CHCl_3$ (20 mL), and the mixture was stirred at room temperature. After 3 days, an additional 0.25 g of peracid was added, and the reaction was left for an additional 3 days. The solvent was removed in vacuo, and the residue was chromatographed on SiO_2, eluting with CH_2Cl_2, to give 3-(4-methoxybenzyl)-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole 4,4-dioxide (**25**; 0.60 g, 34%): mp (EtOH–$CHCl_3$) 157–158 °C; IR ν_{max} (mull) 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.79 (3 H, s, OCH_3), 5.83 (2 H , s, CH_2), 7.21 (4 H, AB q, J = 9.7 Hz, $\Delta\nu$ = 57 Hz, benzyl aromatics), 7.95 (3 H, m, C-5, C-6, and C-7 H), 8.45 (1 H, m, C-8 H). Anal. ($C_{17}H_{13}N_3O_4S$) C, H, N, S.

Further elution with CH_2Cl_2 gave 3-(4-methoxybenzyl)-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole 4-oxide (**23**; 1.04 g, 61%): mp (EtOH–$CHCl_3$) 177–178 °C; IR ν_{max} (mull) 1693 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (3 H, s, OCH_3), 5.71 (1 H, d, J = 15 Hz), 6.04 (1 H, d, J = 15 Hz), 7.18 (4 H, AB q, J = 9 Hz, $\Delta\nu$ = 51 Hz, benzyl aromatics), 7.89 (3 H, complex m, C-5, C-6, and

C-7 H), 8.50 (1 H, complex m, C-8 H). Anal. ($C_{17}H_{13}N_3O_3S$) C, H, N, S.

(b) With $KMnO_4$. Method E. A solution of potassium permanganate (5.6 g, 35 mmol) in water (60 mL) was added in five portions over 2.5 h to a stirred solution of **14** (2.2 g, 6.8 mmol) in glacial AcOH (150 mL) at 30–40 °C, when TLC indicated that the oxidation was complete. The resulting mixture was poured into water (500 mL) and decolorized by the dropwise addition of 30% H_2O_2. The resulting white precipitate was filtered off, washed well with water, and dried to give the sulfone **25** (1.43 g, 59%), identical with that prepared in method D above.

Compounds **26–28** (Table II) were similarly prepared, although the amount of oxidant was tailored to the individual compounds.

3-Benzyl-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole (33). Reaction of thiophenol (7.44 g, 68 mmol) with ethyl 1-benzyl-5-chloro-1,2,3-triazole-4-carboxylate[6,7] (18.00 g, 68 mmol) as described for compounds **4–7** afforded ethyl 1-benzyl-5-(phenylthio)-1,2,3-triazole-4-carboxylate (16.00 g, 70%): mp (petroleum ether, bp 60–80 °C) 45–47 °C; IR ν_{max} (mull) 1720 (C=O) cm^{-1}. Anal. ($C_{18}H_{17}N_3O_2S$) C, H, N, S.

Hydrolysis of this ester (16.00 g) with 2.5 M aqueous NaOH at 90–100 °C for 2 h gave the corresponding carboxylic acid (12.00 g, 82%): mp (EtOH) 78 °C; IR ν_{max} (mull) 3510, 3400, 2500 (broad OH), 1700 (C=O) cm^{-1}. Anal. ($C_{16}H_{13}N_3O_2S \cdot H_2O$) C, H, N, S.

Reaction of this acid (12.00 g, 39 mmol) with thionyl chloride (110 mL) at reflux over 90 min gave the acyl chloride, which was isolated by evaporation of the excess reagent in vacuo. After dissolution in dry CH_2Cl_2 (150 mL), anhydrous $AlCl_3$ (16 g) was added portionwise with stirring at ambient temperature, and stirring was continued for an additional 3 h before pouring into ice–water. Extraction with $CHCl_3$ gave crude **33** after drying ($MgSO_4$) and evaporation. Recrystallization from EtOH–H_2O gave pure **33** (9.0 g, 80%): mp 189–190 °C; IR ν_{max} (mull) 1645 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.77 (2 H, s, CH_2), 7.43 (5 H, s, benzyl aromatics), 7.70 (3 H, m, C-5, C-6, and C-7 H), 8.79 (1 H, m, C-8 H). Anal. ($C_{16}H_{11}N_3OS$) C, H, N, S.

Reduction of 3-Benzyl-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole (33). Sodium was added in small pieces over 45 min to a solution of **33** (1.00 g) in liquid ammonia (50 mL) until a permanent blue color was obtained, and ammonium chloride was then added. Evaporation of the ammonia and extraction of the residue with water gave a solution, which on acidification gave 0.33 g of impure **18**. Chromatography of SiO_2, eluting with $CHCl_3$ and then 10% MeOH–$CHCl_3$, then afforded a low yield of material identical with that prepared by method B above.

3-Benzyl-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole 4,4-Dioxide (34). Oxidation of **33** (3.00 g) with potassium permanganate as described in method E gave, after chromatography on SiO_2 eluting with $CHCl_3$–petroleum ether (bp 40–60 °C) (3:1), the sulfone **34** (2.03 g, 61%): mp 164 °C; IR ν_{max} (mull) 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (2 H, s, CH_2), 7.39 (5 H, m, Ph), 7.94 (3 H, m, C-5, C-6, and C-7 H), 8.42 (1 H, m, C-8 H). Anal. ($C_{16}H_{11}N_3O_3S$) C, H, N, S.

Catalytic Reduction of 3-Benzyl-9-oxo-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole 4,4-Dioxide (34). A solution of the sulfone **34** (0.50 g) in EtOH (200 mL) containing DMF (100 mL) was hydrogenated over 5% palladium on charcoal (0.1 g) at 1000 psi and 100 °C for 1 h, after which time no **34** remained. Filtration and evaporation of the filtrate in vacuo resulted in a white solid, which on recrystallization from EtOH gave 3-benzyl-9-hydroxy-9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazole 4,4-dioxide (**35**; 0.35 g, 97%): mp 161 °C; IR ν_{max} (mull) 3270 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.70 (1 H, s, exchangeable, OH), 5.81 (2 H, s, CH_2) 6.03 (1 H, s, C-9 H), 7.70 (9 H, m, aromatics). Anal. ($C_{16}H_{13}N_3O_3S$) C, H, N, S.

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Rat Passive Cutaneous Anaphylaxis. This was carried out in a similar manner to that previously described.[8] Charles Rivers Sprague–Dawley male rats of 250–300-g body weight were given 0.1 mL each of six twofold serial dilutions of antiserum raised in rats to ovalbumin[8] in 0.9% saline, injected intradermally into separate sites on their shaved backs. Seventy-two hours later, the animals were challenged by intravenous injection of 0.3 mL of a 1% solution of ovalbumin in phosphate-buffered saline mixed with 0.2 mL of a 5% solution of pontamine sky-blue in isotonic saline. The rats were killed after 20 min, and the diameter of the blue wheals at the antibody injection sites were measured on the outer surface of the skin. The starting dilution of the serum was adjusted so that there was no response, after challenge, at the injection site of the highest dilution and a maximal response at the lowest dilution. Typically, six twofold serial dilutions of the serum from 1:4 to 1:128 were used.

Compounds were tested for their ability to reduce the diameter of the wheals at the four intradermal sites, which in control groups gave less than maximal response. Each dose of the compound was administered intravenously in groups of six animals immediately before an intravenous challenge of ovalbumin. Control groups were given the same volume of carrier fluid immediately prior to challenge. The doses for each compound were adjusted so that for most compounds three different doses produced an inhibition of between 30 and 70%.

The results were calculated as follows: percentage inhibition of PCA = $100(1 - a/b)$, where a is the sum of the diameters of the wheals produced in the test animal at the four sites of antibody dilutions, which in control animals gave less than maximum response, and b is the mean sum of the diameters of the wheals produced in the control group of animals at the antibody sites, which gave less than maximum response. A typical variation in a control group of six animals gave an standard error of the mean (SEM) of ±6%. Regression lines were fitted to each data set plotted against the log 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.[9]

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Registry No. **3**, 75020-42-7; **4**, 84158-58-7; **5**, 84158-64-5; **6**, 84158-74-7; **7**, 81581-06-8; **8**, 84158-59-8; **8** acid chloride, 87598-43-4; **9**, 84158-65-6; **9** acid chloride, 87598-44-5; **10**, 84158-75-8; **10** acid chloride, 87598-45-6; **11**, 87598-46-7; **13**, 81581-13-7; **14**, 87598-47-8; **15**, 87598-48-9; **16**, 87598-49-0; **17**, 87598-50-3; **18**, 84158-61-2; **19**, 84158-67-8; **20**, 84158-77-0; **21**, 84158-81-6; **22**, 84158-80-5; **23**, 87598-51-4; **24**, 84158-84-9; **25**, 87598-52-5; **26**, 87598-53-6; **27**, 87598-54-7; **28**, 87598-55-8; **29**, 84158-63-4; **30**, 84158-69-0; **31**, 84158-79-2; **32**, 84158-83-8; **33**, 87598-56-9; **34**, 87598-57-0; **35**, 87598-58-1; ethyl 1-benzyl-5-chloro-1,2,3-triazole-4-carboxylate, 75020-50-7; ethyl 1-benzyl-5-(phenythio)-1,2,3-triazole-4-carboxylate, 84158-70-3; 1-benzyl-5-(phenythio)-1,2,3-triazole-4-carboxylic acid, 84158-71-4; 1-benzyl-5-(phenylthio)-1,2,3-triazole-4-carbonyl chloride, 87598-59-2; thiophenol, 108-98-5; 4-methylthiophenol, 106-45-6; 3,4-dimethylthiophenol, 18800-53-8; 4-methoxythiophenol, 696-63-9.

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