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Studies on *v*-Triazoles. 7. Antiallergic 9-Oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazoles[1]

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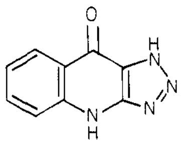
A series of the title compounds was prepared by cyclization of the appropriate 5-(aryloxy)-*v*-triazole-4-carboxylic acids and evaluated for antiallergic activity by the rat passive cutaneous anaphylaxis (PCA) screen. The most potent compounds were 6-(mesyloxy)-9-oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazole and its 5-methyl homologue, which were some tenfold more potent than disodium cromoglycate. Dialkyl derivatives, especially those substituted at C-5 and C-6 or C-6 and C-7, and 6-methoxy compounds were also among the more potent compounds. One compound, 6,7-dimethyl-9-oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazole, was further evaluated and shown to be a potent inhibitor of rat PCA when given orally.

The introduction of disodium cromoglycate (DSCG) in 1967 as an effective treatment for asthma[2] has stimulated considerable research aimed at the identification of other compound types having a similar mode of action.[3] In particular, this effort has centered on overcoming the lack of oral activity shown by DSCG. For some years we have been interested in compounds containing the 2-nitro-1,3-dicarbonyl moiety, which are potent inhibitors of the passive cutaneous anaphylaxis (PCA) reaction in the rat,[4] but more recently, using the same biological system, we have identified new classes of antiallergic compounds containing the *v*-triazole nucleus. The discovery that some triazoloquinolines, 1,[5] showed activity led to a more potent series based on 9-oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazole (6),[6] on which we now report our results.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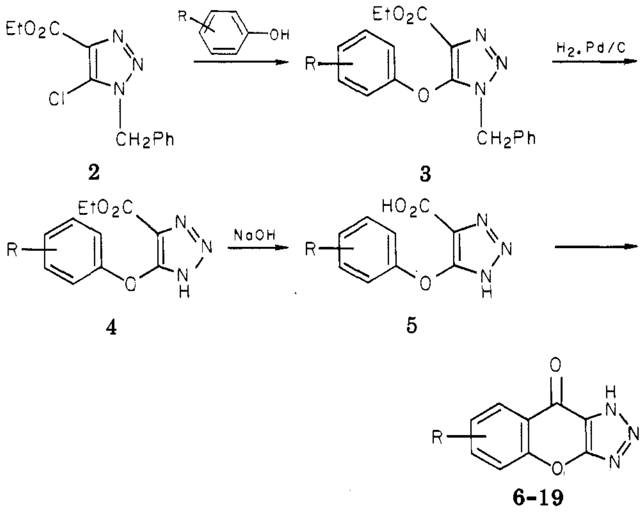
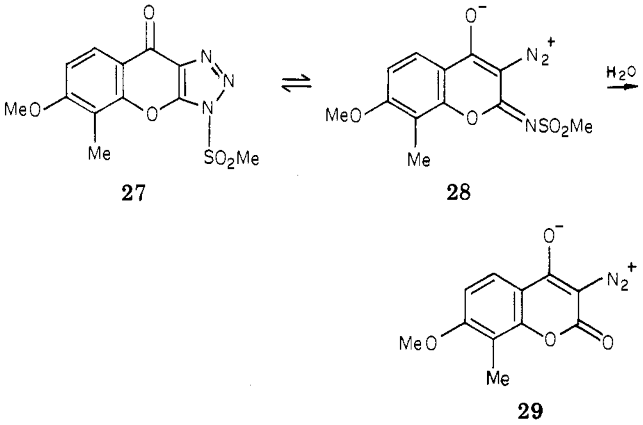
Chemistry. The synthetic route to the majority of the target compounds is outlined in Scheme I. Ethyl 1-benzyl-5-chloro-*v*-triazole-4-carboxylate (2)[6,7] was reacted with phenoxide ion in *N*,*N*-dimethylformamide to give the (aryloxy)triazoles 3, which were converted to the debenzylated derivatives 4 by high-pressure catalytic hydrogenolysis at 100 °C. Alkaline hydrolysis of 4 yielded the corresponding acids 5, which were cyclized to the required tricyclic derivatives 6 with either polyphosphoric acid or phosphoric oxide in methanesulfonic acid. Details of the synthetic work relating to compounds 6–16 are published elsewhere.[6]

Scheme I



Scheme II



Compounds 17–19 were similarly prepared from the corresponding triazolecarboxylic acids with the phosphoric oxide in methanesulfonic acid procedure (method A), but in the case of compound 17, which was synthesized on a larger scale, the diazocoumarin oxide 29 (Scheme II) was also isolated. Compound 29 presumably arises from the intermediate mesylate 27 by cleavage to the diazo compound 28 and subsequent hydrolysis on aqueous workup. Similar cleavages of triazoles substituted on nitrogen by electron-withdrawing groups are well known.[8]

Dealkylation of the ethers 9, 10, and 17–19 with thiolate anion (method B)[9] gave the respective phenols 20–24 (Scheme III) in reasonable yield. Alkaline mesylation (method C) of 20 and 22 resulted in exclusive attack at the hydroxy group[10] to give 25 and 26, respectively. The

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(1) Part 6: Buckle, D. R.; Rockell, C. J. M. *J. Chem. Res., Synop.* **1982**, 292.

(2) Howell, J. B. L.; Altounyan, R. E. C. *Lancet* **1967**, *2*, 539.

(3) See, for example, Bell, S. C.; Capetola, R. J.; Ritchie, D. M. *Annu. Rep. Med. Chem.* **1979**, *14*, 51. Devlin, J. P. *Ibid.* **1980**, *15*, 59. Lunt, E. *Prog. Pharm. Res.* **1982**, *4*, 41.

(4) 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.

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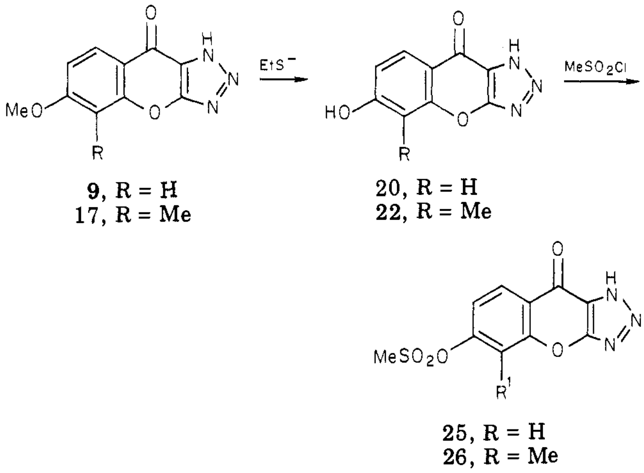
(6) Buckle, D. R.; Outred, D. J.; Rockell, C. J. M. *J. Heterocyl. Chem.* **1981**, *18*, 1117.

(7) Hoover, J. R. E.; Day, A. R. *J. Am. Chem. Soc.* **1956**, *78*, 5832.

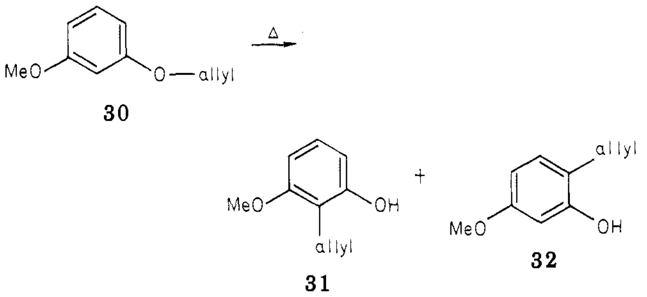
(8) Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 82. See also the nitration of 6 in which similar diazocoumarin oxides are formed, Buckle, D. R. *J. Heterocyl. Chem.* **1982**, *19*, 129.

(9) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.

Scheme III



Scheme IV



assignment of these derivatives as O rather than N substituted was evident from their ^{1}H NMR spectra. Thus, compound **26**, for example, showed a marked downfield shift of the aromatic protons relative to the parent phenol **22**, the C-7 proton signal moving from δ 6.97 to 7.53 and the C-8 proton signal moving from δ 7.90 to 8.18. In addition, the C-5 methyl signal was shifted 0.21 ppm downfield on mesylation.

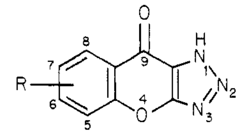
The starting phenols **31** and **32** required for the synthesis of **18** and **19**, respectively, were prepared by Claisen rearrangement of the allyl ether **30** (Scheme IV)[11] and were separated by liquid chromatography on silica. The allyl groups were subsequently converted to propyl during the hydrogenolytic cleavage of the *N*-benzyl groups.

Results and Discussion

A feature of many compounds with activity of the DSCG type is the presence of an acidic functionality, usually linked by ethylenic or aromatic conjugation to a carbonyl group. Frequently this acidic function is a carboxy group, although other groups, such as tetrazole[12] and the 2-nitro-1,3-dicarbonyl fragment,[4] are effective. The acidity of *v*-triazoles is well known, and the fact that this acidity is potentiated by carbonyl substituents at C-4 and/or C-5[13] led us, by analogy with existing structures, to investigate tricyclic triazoles, and in particular those based on the benzopyranotriazole **6**. Table I lists the compounds studied and their potencies in the rat PCA test.

The parent compound **6** was approximately equipotent with DSCG in our test system, but the dialkylated derivatives **11–14** were noticeably more potent. The other multiple alkylated derivatives studied, **15** and **16**, were equipotent with the parent **6**, whereas the only monoalkylated derivative, **7**, was of reduced potency.

Table I. Inhibition of Rat PCA by 9-Oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazoles



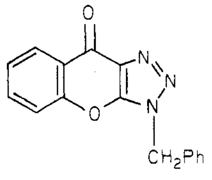
no.	R	act. in rat PCA test: ED$_{50}$,[a] mg/kg iv
6	H	1.4 (1.1–1.8)
7	7-Me	5.0 (4.1–5.8)
8	7-OMe	1.7 (0.9–5.2)
9	6-OMe	0.3 (0.03–0.6)
10	8-OMe	3.5 (1.9–22.5)
11	5,6-Me$_2$	0.3 (0.05–0.6)
12	6,7-Me$_2$	0.4 (0.3–0.5)
13	7,8-Me$_2$	0.6 (0.4–0.9)
14	6,7-[-(CH$_2$)$_4$-]	0.6 (0.3–0.8)
15	7,8-[-(CH$_2$)$_4$-]	2.1 (1.6–3.0)
16	5,6,8-Me$_3$	1.2 (0.8–1.6)
17	5-Me, 6-OMe	0.4 (0.3–0.5)
18	5-*n*-Pr, 6-OMe	1.0 (0.8–1.5)
19	5-*n*-Pr, 8-OMe	>10
20	6-OH	1.8 (1.4–2.4)
21	8-OH	1.7 (1.4–2.1)
22	5-Me, 6-OH	2.2 (1.8–2.7)
23	5-*n*-Pr, 6-OH	1.1 (0.8–1.4)
24	5-*n*-Pr, 8-OH	7.0 (6.2–7.8)
25	6-OSO$_2$Me	0.2 (0.2–0.3)
26	5-Me, 6-OSO$_2$Me	0.2 (0.1–0.4)
	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.

The potencies of the methoxylated compounds **8–10** were noticeably position dependent, with the preferred substitutions being 6 > 7 $\geq$ 8. This preference was endorsed in the two *n*-propyl homologues **18** and **19**. Cleavage of the methoxy groups to give the phenolic compounds, while having little effect in the C-8 series (cf. compounds **10** and **21**), resulted in a reduction of potency in the C-6 series (cf. compounds **9** and **20**; **17** and **22**). Potency was restored on mesylation, as in compounds **25** and **26**, which gave some of the most potent compounds.

Compound **12** was further investigated and shown to be orally active with an approximate ED$_{50}$ of 1 mg/kg.

The *N*-benzyl compound **30**[6] was inactive at doses up to 100 mg/kg (subcutaneously), suggesting the need for a free triazole N-H.



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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. Where represented by elemental symbols, the analyses of these elements fall within ±0.4% of the calculated values. Analytical TLC was carried out on Eastman Chromatogram sheets of silica gel with fluorescent indicator; the sheets were eluted with chloroform, alone

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(11) White, W. N.; Slater, C. D. *J. Org. Chem.* **1961**, *26*, 3631.

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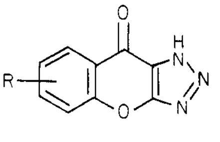
Table II. 9-Oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazoles



no.	R	mp,[a] °C	recrystn solvent	formula	anal.	yield, %	method[b]
17	5-Me, 6-OMe	268-270	EtOH	$C_{11}H_9N_3O_2$	C, H, N	72	A
18	5-*n*-Pr, 6-OMe	220-222	EtOH-H_2O	$C_{13}H_{13}N_3O_3$	C, H, N	46	A
19	5-*n*-Pr, 8-OMe	229-231	EtOH	$C_{13}H_{13}N_3O_3$	C, H, N	70	A
20	6-OH	300	DMF-H_2O	$C_9H_5N_3O_3$	C, N; H[c]	85	B
21	8-OH	256-258	MeOH	$C_9H_5N_3O_3$	C, H, N	53	B
22	5-Me, 6-OH	292-293	EtOAc-EtOH	$C_{10}H_7N_3O_3$	C, H, N	99	B
23	5-*n*-Pr, 6-OH	283-284	EtOH	$C_{12}H_{11}N_3O_3$	C, H, N	66	B
24	5-*n*-Pr, 8-OH	208-209	EtOAc	$C_{12}H_{11}N_3O_3$	C, H, N	95	B
25	6-OSO_2Me	230-231	MeOH	$C_{10}H_7N_3O_5S$	C, H, N, S	55	C
26	5-Me, 6-OSO_2Me	211-212	EtOH	$C_{11}H_9N_3O_5S$	C, H, N	77	C

[a] All melting points were accompanied by decomposition. [b] See text and Experimental Section. [c] H: calcd, 2.48; found, 3.14; M^+ 203.0337.

or with 5–20% methanol, and spots were visualized under UV light (254 nm) and with iodine.

Ethyl 1-Benzyl-5-(3-methoxy-2-methylphenoxy)-*v*-triazole-4-carboxylate. To a stirred solution of 3-methoxy-2-methylphenol (13.8 g, 0.1 mol) in dry DMF (100 mL) was added a 50% dispersion of NaH in mineral oil (4.8 g, 0.1 mol), and the solution was stirred for 1 h at room temperature to ensure formation of the sodium salt. To this salt was added **2** (26.6 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 EtOAc and water. The organic phase was washed with dilute aqueous NaOH and brine and dried ($MgSO_4$). Evaporation of the solvent gave an oil, which was chromatographed on SiO_2 by elution with chloroform to give 30.8 g (84%) of the title compound as an oil, which was not further purified: IR ν_{max} (film) 1722 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.03 (3 H, t, J = 7 Hz, ester CH_3), 2.18 (3 H, s, aromatic CH_3), 3.85 (3 H, s, OCH_3), 4.11 (2 H, q, J = 7 Hz, ester CH_2), 5.37 (2 H, s, benzyl CH_2), 5.89 (1 H, d, J = 8.5 Hz, C-4 H), 6.59 (1 H, d, J = 8.5 Hz, C-6 H), 6.88 (1 H, t, J = 8.5 Hz, C-5 H), 7.29 (5 H, s, Ph).

Ethyl 5-(3-Methoxy-2-methylphenoxy)-1*H*-*v*-triazole-4-carboxylate. A solution of the above ester (30 g, 0.082 mol) in EtOH (400 mL) was hydrogenated at 96 °C and 1000 psi over 10% palladium on charcoal (0.3 g) until the reaction was complete (2–3 h). The catalyst was removed from the cooled solution by filtration, and the filtrate was evaporated to an oil, which crystallized after chromatography on SiO_2 with chloroform. Recrystallization from toluene–petroleum ether (bp 60–80 °C) gave 20.6 g (91%) of the title ester: mp 107–108 °C; IR ν_{max} (mull) 3150 (broad, N-H), 1705 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz, ester CH_3), 2.12 (3 H, s, aromatic CH_3), 3.81 (3 H, s, OCH_3), 4.32 (2 H, q, J = 7 Hz, ester CH_2), 6.63 (2 H, distorted d, C-4 and C-6 H), 7.09 (1 H, m, C-5 H), 10.3 (1 H, broad, exchangeable, N-H). Anal. ($C_{13}H_{15}N_3O_4$) C, H, N.

5-(3-Methoxy-2-methylphenoxy)-1*H*-*v*-triazole-4-carboxylic Acid. Hydrolysis of the above ester (19.4 g, 0.07 mol) with 1.25 M aqueous NaOH (220 mL) at 70–80 °C for 3 h gave, on cooling and acidification, 12.9 g (74%) of the title acid. Recrystallization from EtOAc–petroleum ether (bp 60–80 °C) gave material of mp 129 °C (dec) after initial loss of water of crystallization at ca. 90 °C: IR ν_{max} (mull) 1685 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (3 H, s, aromatic CH_3), 3.82 (3 H, s, OCH_3), 6.52 (1 H, d, J = 8.5 Hz), 6.76 (1 H, d, J = 8.5 Hz), 7.12 (1 H, t, J = 8.5 Hz, C-5 H). Anal. ($C_{11}H_{11}N_3O_4 \cdot 0.75H_2O$) C, H, N.

Ethyl 5-(2-Allyl-5-methoxyphenoxy)-1-benzyl-*v*-triazole-4-carboxylate. Reaction of the phenol **32** (15.41 g, 0.094 mol) with **2** (27.80 g, 0.094 mol) as described above afforded 32.54 g (88%) of the title ester, mp [toluene–petroleum ether (bp 40–60 °C)] 55–56 °C. Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

5-(5-Methoxy-2-*n*-propylphenoxy)-1*H*-*v*-triazole-4-carboxylic Acid. Hydrogenation of the above ester (30.00 g) as previously described gave 22.7 g (98%) of the ethyl ester of the title compound, which hydrolyzed under alkaline conditions to furnish 19.79 g (98%) of the carboxylic acid, mp [ethyl acetate–petroleum ether (bp 40–60 °C)] 113–114 °C dec. Anal. ($C_{13}H_{15}N_3O_4$) C, H, N.

5-(3-Methoxy-2-*n*-propylphenoxy)-1*H*-*v*-triazole-4-carboxylic Acid. In a similar manner, the isomeric phenol **31** (13.32 g, 0.08 mol) was reacted with ethyl 5-chloro-1-(4-methoxybenzyl)-*v*-triazole-4-carboxylate[14] (24.0 g, 0.08 mol) to give 21.58 g (64%) of ethyl 5-(2-allyl-3-methoxyphenoxy)-1-(4-methoxybenzyl)-*v*-triazole-4-carboxylate, mp [ethanol–petroleum ether (bp 60–80 °C)] 109–110 °C. Anal. ($C_{23}H_{25}N_3O_5$) C, H, N. Hydrogenolysis of this ester (1.0 g) in ethanol (300 mL) as described above furnished 0.53 g (63%) of the ethyl ester of the title compound, mp 97–99 °C, after chromatography on SiO_2, gradient eluting with chloroform to 9:1 chloroform–methanol. Anal. ($C_{15}H_{19}N_3O_4$) C, H, N. Alkaline hydrolysis of this ester gave 88% of the title acid, mp (aqueous EtOH) 146–147 °C dec. Anal. ($C_{13}H_{15}N_3O_4$) C, H, N.

6-Methoxy-5-methyl-9-oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazole (17). Method A. Phosphoric oxide (240 g) was added to vigorously stirred 98% methanesulfonic acid (600 mL) at 80 °C (oil bath temperature), and the mixture was stirred until homogeneous (1 h). Powdered 5-(3-methoxy-2-methylphenoxy)-1*H*-*v*-triazole-4-carboxylic acid (32.30 g, 0.13 mol) was added, and the mixture was stirred for 90 min at 80 °C, after which the mixture was cooled and poured into cold water. After 16 h the precipitated product was collected by filtration, washed well with water, and recrystallized from EtOH to give the triazole **17** (19.80 g, 66%): mp 268–270 °C dec; IR ν_{max} (mull) 3300 (broad, N-H), 1638 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.26 (3 H, s, aromatic CH_3), 3.97 (3 H, s, OCH_3), 7.12 (1 H, d, J = 9 Hz, C-7 H), 8.02 (1 H, d, J = 9 Hz, C-8 H), 16.5 (1 H, broad, exchangeable N-H). Anal. ($C_{11}H_9N_3O_3$) C, H, N. Evaporation of the ethanolic mother liquors afforded 3.4 g of solid shown by TLC ($CHCl_3$, 10% MeOH) to be a mixture of **17** and a faster (R_f ~0.8) material. Chromatography on SiO_2 eluting with chloroform gave 1.32 g of a white crystalline solid, mp 203 °C (from EtOH), shown to be 3-diazo-7-methoxy-8-methylcoumarin 4-oxide (**29**): IR ν_{max} (mull) 2180 (N_2^+ 1720 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.28 (3 H, s, aromatic CH_3), 3.98 (3 H, s, OCH_3), 6.83 (1 H, d, J = 9 Hz, C-6 H), 7.90 (1 H, d, J = 9 Hz, C-5 H). Anal. ($C_{11}H_8N_2O_4$) C, H, N.

Further elution with 30% MeOH in chloroform resulted in an additional 1.92 g (6%) of compound **17**.

6-Hydroxy-5-methyl-9-oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazole (22). Method B. A 50% dispersion of NaH in mineral oil (1.92 g, 0.04 mol) was added to a solution of ethanethiol (2.55 g, 3.01 mL 0.04 mol) in dry DMF (50 mL), and the mixture was stirred for 15 min. To this solution was added the triazole **17** (1.27 g, 0.0055 mol) and the total stirred at 115 °C (oil bath temperature) for 90 min. After the mixture was cooled, the solvent was removed in vacuo, and the residue was dissolved in water and washed once

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

with ether. Acidification and cooling of the aqueous phase resulted in the slow precipitation of the phenol **22**, which was separated and recrystallized from EtOAc–EtOH to yield 1.18 g (99%) of white crystalline solid: mp 292–293 °C dec; IR ν_{max} (mull), 3170 (OH), 2600 (broad, N-H), 1645 (C=O) cm^{-1}; ^{1}H NMR (Me$_2$SO-d_6) δ 2.29 (3 H, s, aromatic CH$_3$), 6.97 (1 H, d, J = 9 Hz, C-7 H), 7.90 (1 H, d, J = 9 Hz, C-8 H), 11.0 (1 H, exchangeable OH). Anal. (C$_{10}$H$_7$N$_3$O$_3$) C, H, N.

6-(Mesyloxy)-5-methyl-9-oxo-1*H*,9*H*-benzopyrano[2,3-*d*]-*v*-triazole (26). Method C. Anhydrous potassium carbonate (5.52 g, 0.04 mol) was added to a solution of the triazole **22** (4.34 g, 0.02 mol) in dry DMF (100 mL), and the mixture was stirred during the slow addition of a solution of methanesulfonyl chloride (3.20 g, 0.028 mol) in dry DMF (10 mL). The resulting mixture was stirred for 18 h at 20 °C, and the solvent removed in vacuo. Water was added and the pH was brought to 1 with hydrochloric acid. The precipitated product was washed with water and dried. Recrystallization from ethanol gave, after drying in vacuo at 80 °C, compound **26** (4.51 g, 77%): mp 211–212 °C; IR ν_{max} (mull) 2600 (broad, N-H), 1670 (C=O) cm^{-1}; ^{1}H NMR (Me$_2$SO-d_6) δ 2.50 (3 H, s, aromatic CH$_3$), 3.58 (3 H, s, S-CH$_3$), 4.3 (1 H, broad exchangeable, N-H), 7.53 (1 H, d, J = 9 Hz, C-7 H), 8.18 (1 H, d, J = 9 Hz, C-8 H). Anal. (C$_{11}$H$_9$N$_3$O$_5$S) 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 of compounds were adjusted so that for most compounds three different doses produced an inhibition of between 20 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. The median effective dose associated confidence limits were then estimated as the doses corresponding to a response of 50%, as calculated from the equations of the regression line and the 95% confidence limits of the mean response to any given dose.[16]

Acknowledgment. The authors express their thanks to D. M. Rose for the statistical analyses.

Registry No. 2, 75020-50-7; **2** (4′-OMe), 75020-42-7; **3** (R = 2-Me, 3-OMe), 83705-30-0; **3** (R = 2-allyl, 5-OMe), 83394-21-2; **3** (R = 2-allyl, 3-OMe)(4′-OMe), 83402-44-2; **4** (R = 2-Me, 3-OMe), 83705-31-1; **4** (R = 2-Pr, 5-OMe), 83394-22-3; **4** (R = 2-Pr, 3-OMe), 83394-13-2; **5** (R = 2-Me, 3-OMe), 83705-32-2; **5** (R = 2-Pr, 5-OMe), 83394-23-4; **5** (R = 2-Pr, 3-OMe), 83394-14-3; **6**, 75020-20-1; **7**, 75020-23-4; **8**, 75020-27-8; **9**, 79572-28-4; **10**, 79572-29-5; **11**, 75020-31-4; **12**, 75020-35-8; **13**, 75020-36-9; **14**, 83705-35-5; **15**, 83705-36-6; **16**, 75020-40-5; **17**, 83705-33-3; **18**, 83394-15-4; **19**, 83394-24-5; **20**, 79572-30-8; **21**, 83394-05-2; **22**, 79572-25-1; **23**, 83394-16-5; **24**, 83394-25-6; **25**, 83710-14-9; **26**, 79572-24-0; **29**, 83705-34-4; **31**, 6738-38-1; **32**, 13677-76-4; 3-methoxy-2-methylphenol, 6971-52-4; 3-methoxy-2-methylphenol sodium salt, 42840-22-2.

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Conformational Effects on the Activity of Drugs. 10.[1] Synthesis, Conformation, and Pharmacological Properties of 1-(2,5-Dimethoxyphenyl)-2-aminoethanols and Their Morpholine Analogues[2]

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In order to obtain a better understanding of the effects that structural parameters have on the changes of adrenergic activity when 1-aryl-2-aminoethanol derivatives are converted into their corresponding 2-arylmorpholine cyclic analogues, we synthesized 1-(2,5-dimethoxyphenyl)-2-aminoethanol derivatives **5–7** and their morpholine analogues **8–10**. The preferred conformation of amino alcohols and their cyclic analogues have been determined through an ^{1}H NMR and IR study. Compounds **5** and **6** showed both α-stimulating and α-blocking activity on rat vas deferens, the effect depending on the concentration employed; on the same isolated tissue, *N*-isopropyl derivative **7** and the morpholine analogues **8–10** exhibited only α-blocking activity. As for the β-adrenergic activity, only the open-chain compound **7** possessed a moderate blocking effect on isolated guinea pig atria. The results of this work seem to indicate that the changes of pharmacological activity involved in the transformation of the adrenergic drugs into their morpholine analogues are influenced more by characteristic features of the aromatic moiety than by the ethanolamine or propanolamine structure of the drugs.

Morpholine analogues of adrenergic drugs have proved to be a useful tool for studying the conformational aspects of the activity of these drugs at the molecular level.[3–7] In previous works on this series,[4–7] we described the synthesis and the pharmacological properties of morpholine derivatives **2** and **4**, which are conformationally restrained analogues of INPEA (**1**) and methoxamine (**3**), respectively. In compounds **2** and **4**, the ethanolamine portion of the corresponding open-chain compounds **1** and **3** is incorporated in the morpholine ring, in the same preferred conformation as in the open-chain parent compounds.

The comparative pharmacological studies of INPEA (**1**), a well-known β-blocking drug,[8,9] and of its morpholine

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(1) For paper 9, see Balsamo, A.; Barili, P. L.; Gagliardi, M.; Lapucci, A.; Macchia, B.; Macchia, F. *Eur. J. Med. Chem.* **1982**, *17*, 285.

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