for **7b**, enhancement of basicity in this instance resulted in a slight diminution of diuretic activity while substantially diminishing antihypertensive activity.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM390 NMR spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were determined using a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise.

2-(1,1-Dimethylethyl)-5-ethoxyoxazole (3). To a vigorously stirred slurry of P_2O_5 (163.8 g, 1.15 mol) in $CHCl_3$ (600 mL) maintained under an N_2 atmosphere was added slowly a solution of ethyl *N*-(2,2-dimethyl-1-oxopropyl)glycinate[4] (107.8 g, 0.576 mol) in $CHCl_3$ (350 mL). After the addition was completed, the reaction mixture was stirred and heated at reflux under N_2 for 14 h. The cooled reaction mixture was treated with 20% NaOH (800 mL), vigorously stirred for 0.5 h, and allowed to separate into two phases. After the aqueous phase was discarded, the organic phase was washed with H_2O and saturated brine, dried ($MgSO_4$), and filtered. Distillation of the filtrate provided **3** as a pale yellow oil (64 g, 66%): bp 58–64 °C (0.7 mmHg); NMR ($CDCl_3$) 1.30 (9 H, s, *t*-C_4H_9), 1.40 (3 H, t, CH_2CH_3), 4.07 (2 H, q, OCH_2), 5.90 ppm (H-4, s). Anal. ($C_9H_{15}NO_2$) H, N; C: calcd, 63.88; found, 64.49.

4-Cyano-6-(1,1-dimethylethyl)-3-pyridinol (5). A neat mixture of **3** (17 g, 0.1 mol) and acrylonitrile (6.1 g, 0.11 mol) was stirred with heating at 70–75 °C for 16 h. The resulting dark mixture was cooled to 20 °C and chromatographed on silica gel (600 g). Elution with 1% MeOH in $CHCl_3$ (4.35 L) yielded recovered **3** (10.7 g, 63% recovery). Continued elution with the same eluant (300 mL) afforded a mixture of **3** and **5** (3.2 g). Further elution (2.5 L) gave the desired product as a solid (6.5 g, 37%), mp 185–195 °C. Two crystallizations of the latter from MeOH–H_2O (1:1; v/v) provided an analytical sample of **5** as colorless crystals (4.5 g, 26%): mp 201–202 °C; NMR (Me_2SO-d_6) 1.23 (9 H, s, *t*-C_4H_9), 7.63 (H-5, s), 8.45 ppm (H-2, s). Anal. ($C_{10}H_{12}N_2O$) C, H, N.

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Alternatively, unreacted **3** could be recovered by distillation, e.g., by heating the reaction mixture at 80 °C (0.5 mmHg). In this way (11.1 g, 65.6 mmol) of **3** was recovered. The residue was triturated with hexane (30 mL) to give cyanopyridinol **5** (3.5 g, 19.9%), mp 192–197 °C.

4-(Aminomethyl)-6-(1,1-dimethylethyl)-3-pyridinol Dihydrochloride (6). A solution of **5** (5.7 g, 32 mmol) in MeOH–12 N HCl (30:1, v/v, 310 mL) was hydrogenated over 10% Pd/C (1 g) at 25 °C and 40–45 psi pressure. The reaction mixture was then filtered, and the collected catalyst was washed with EtOH. Evaporation (in vacuo) of the combined filtrate and washings yielded **6** (7.9 g, 98%), mp 304–306 °C dec. Crystallization from EtOH–Et_2O–H_2O (100:100:4, v/v) afforded an analytical sample of **6** as colorless crystals: mp 304–306 °C dec; NMR (Me_2SO-d_6) 1.47 (9 H, s, *t*-C_4H_9), 4.23 (2 H, CH_2N, br s), 8.17 (H-5, s), 8.45 ppm (H-2, s). Anal. ($C_{10}H_{16}N_2O$·2HCl) C, H, N.

4-(Aminomethyl)-6-(1,1-dimethylethyl)-2-iodo-3-pyridinol (7a). A solution of ICl (2.68 g, 20 mmol) in 4 N HCl (15 mL) was added to a solution of **6** (5.06 g, 20 mmol) in H_2O (30 mL). The resulting solution was kept at 20–25 °C for 18 h, diluted with H_2O to a volume of 100 mL, and then treated with 15 N NH_4OH (12 mL). The resulting precipitate was collected, washed with H_2O, and air-dried to give crude **7a** (4.8 g, 78%), mp 162–165 °C. Crystallization from 50% EtOH provided an analytical sample of **7a** as pale tan crystals: mp 170–171 °C; NMR (Me_2SO-d_6) 1.19 (9 H, s, *t*-C_4H_9), 3.90 (2 H, CH_2N, s), 6.92 ppm (H-5, s). Anal. ($C_{10}H_{15}IN_2O$) C, H, N.

4-(Aminomethyl)-6-(1,1-dimethylethyl)-2-iodo-3-pyridinol Dihydrochloride (7b). To a solution of **7a** (4.8 g, 16 mmol) in EtOH (50 mL) was added 12 N HCl (3 mL). The resulting solution was diluted slowly with Et_2O (150 mL) and then cooled to 0 °C. The precipitate was collected, washed with Et_2O, and air-dried to afford **7b**·2HCl (5.4 g, 91%), mp 177–179 °C dec. Crystallization from Et_2O–EtOH–H_2O (125:50:2; v/v) provided an analytical sample as colorless needles: mp 178–179 °C dec. Anal. ($C_{10}H_{15}IN_2O$·2HCl) C, H, N.

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Synthesis and Study of the Potential Antiallergic Activity of Some Pyrazole Derivatives

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The synthesis and study of the oral antiallergic activity of a series of monopyrazole derivatives (**2–14**) considered as analogues of active bispyrazole **1** are described. None of the compounds showed significant inhibition of the rat passive cutaneous anaphylaxis (PCA), with the exception of the already known 5-aminoindazole (**2**). The activity of this compound is, however, lower than that of compound **1**.

The discovery of the significant and prolonged antiallergic activity of bispyrazole **1** prompted us to investigate some related compounds in order to ascertain the relative importance of the pyrazole rings in relation to the an-

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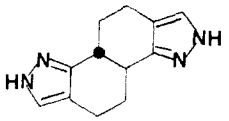
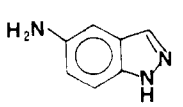


1



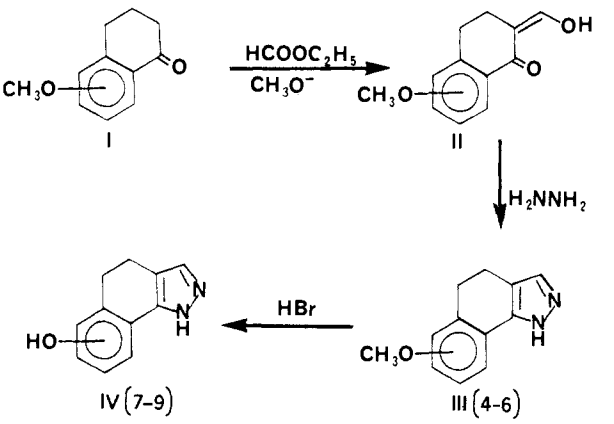
2

tiallergic activity of this new agent.[2] We have previously shown that anti-PCA activity is completely lost when both pyrazole N-H hydrogens in 1 are substituted by methyl or phenyl groups.[2] However, we have not been able to synthesize a derivative of 1 with a free N-H hydrogen in only one of the pyrazole rings. In order to circumvent this problem, we decided to prepare and study a series of monopyrazoles structurally related to 1. In doing so we were forced to depart from the characteristic "bis functionality" of 1 which is also typical of disodium chromoglycate (DSCG) and other very potent antiallergic compounds.[3] However, the significant activity discovered for the commercially available monopyrazole **2**, coupled to the fact that symmetry is not a prerequisite for anti-PCA activity,[4] suggested that a series of monopyrazoles structurally related to 1 was worth exploring. Compounds **3–14** (Table I) were designed and synthesized. Their synthesis and anti-PCA activity are the subject of the present publication.

Chemistry. There are several partial structures of 1 that one can select for a monopyrazole series. The availability of starting materials plus the possibility of attaching different substituents in the aromatic ring were the determining factors in choosing the present series of monopyrazole derivatives. The corresponding starting ketones are commercially available with the exception of 6,7-diethyl-1-tetralone, which was prepared by the method of Buckle et al.[5] The ketones were treated with ethyl formate in dry pyridine or benzene utilizing sodium methoxide as catalyst, to afford the corresponding hydroxymethylene ketones. These intermediates without further purification were treated with hydrazine hydrate in refluxing methanol or ethanol to afford the final products. The phenolic compounds **7–9** were obtained from their methoxy precursors by hydrolysis with 48% HBr.[6] The general synthetic sequence is illustrated for the methoxy and hydroxy derivatives (**4–9**) in Scheme I. Compounds **6** and **10** were obtained as hydrochloride salts. The yields and physical properties of all the monopyrazoles prepared are shown in Table I.

Biological Activity and Discussion. The biological assay was performed as reported previously for compound 1.[2] All the compounds were given orally at a single dose of 200 mg/kg. Anti-PCA activity was measured 1 and 3 h after oral administration. When compared to the 77 and 55% inhibition produced by compound 1 (see Figure 1), the monopyrazoles synthesized showed no significant inhibition of the PCA reaction in rats either at 1 or 3 h after administration. With the methoxy-substituted compounds, only the 6- and 8-isomers (compounds **4** and **6**) show some degree of activity against the PCA reaction 1 h after oral administration with inhibition values of 15 and 32%, respectively. After 3 h, however, the activity of the 7-isomer (**5**) begins to approximate that of the other isomers after 1 h (27%), but still the level of activity is rather low to allow any sort of correlation. Surprisingly, with the corresponding hydroxyl compounds the anti-PCA activity is even lower, and after 3 h one of the isomers (**9**) tends to become a weak potentiator of the PCA reaction. The rest of the compounds can likewise be regarded as inactive, with the exception of **2** (54%, 3 h). Compound **2** shows the type of prolonged activity characteristic of 1. It is interesting that it becomes a better inhibitor with time and thus represents a new "core" structure upon which one can design a potentially interesting structure–activity study.

Scheme I



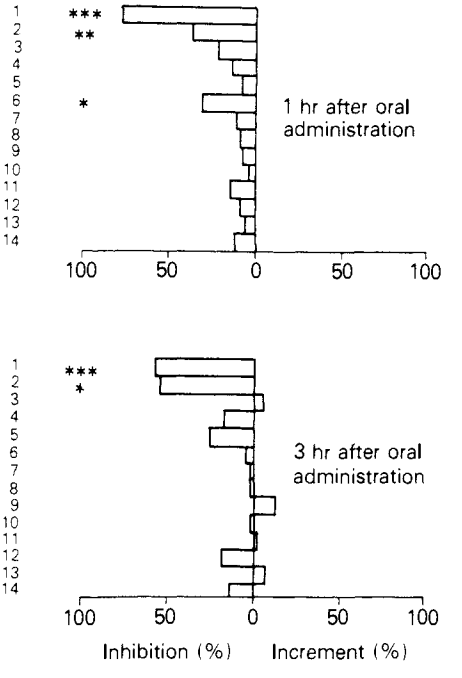


Figure 1. Inhibition of rat reaginic PCA reaction induced by compounds **1–14** per os 1 and 3 h before antigen challenge.

Experimental Section

General. All chemical reagents are commercially available.

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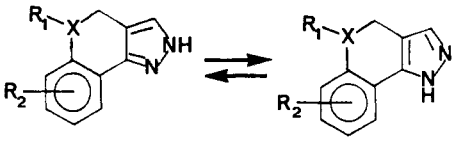
Table I. Pyrazole Derivatives



3—14

no.	X	R_1	R_2	yield, %	crystn solvent	mp, °C (lit.)	formula	anal.
3	CH	H	H	82	pet. ether	120-121 (123)[a]	$C_{11}H_{10}N_2$	
4	CH	H	6-OMe	50	acetone-pet. ether	130-131	$C_{12}H_{12}N_2O$	C, H, N
5	CH	H	7-OMe	60	benzene-pet. ether	160-161 (162-163.5)[b]	$C_{12}H_{12}N_2O$	
6	CH	H	8-OMe	40[c]	EtOH-Et_2O	217-221	$C_{12}H_{13}ClN_2O$	C, H, N
7	CH	H	6-OH	98	Et_2O	196.5-197	$C_{11}H_{10}N_2O$	C, H, N
8	CH	H	7-OH	80	MeCN	206-207 (198-203)[b]	$C_{11}H_{10}N_2O$	
9	CH	H	8-OH	80	acetone-benzene	215-216	$C_{11}H_{10}N_2O$	C, H, N
10	CH	H	7,8-Et_2	60[d]	EtOH-Et_2O	175-178	$C_{15}H_{19}ClN_2$	C, H, N
11	CH	Me	H	95	$CHCl_3$-hexane	124-125	$C_{12}H_{12}N_2$	C, H, N
12	$(CH_2)_2$		H	44	MeCN	108-110	$C_{12}H_{12}N_2$	C, H, N
13	O		H	54	benzene	169-170	$C_{10}H_8N_2O$	C, H, N
14	S		H	47	EtOH	165-166 (168.5-170)[e]	$C_{10}H_8N_2S$	

[a] K. von Auwers and C. Wiegand, *J. Prakt. Chem.*, 134, 82 (1932). [b] Reference 6. [c] Refers to the free base. [d] Refers to the HCl salt. [e] K. Ramalingan, G. X. Thyvelikakath, K. D. Berlin, R. W. Chestnut, R. A. Brown, N. N. Durham, S. E. Ealick, and D. V. D. Helm, *J. Med. Chem.*, 20, 847 (1977).

They were purchased either from E. Merck or Aldrich Chemical Co. Melting points were determined by means of an Electrothermal capillary melting point apparatus and are uncorrected. A Perkin-Elmer Model 727 infrared spectrophotometer was employed for IR spectra using Nujol mulls. A Varian Associates Model EM-360 analytical NMR spectrometer was used for NMR spectra of either deuteriochloroform or Me_2SO-d_6 solutions with internal tetramethylsilane (δ 0.00) at ambient temperature. Mass spectra were obtained in a Hitachi Perkin Elmer RMU-6H instrument at 70 eV. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. All compounds gave analytical results for C, H, and N within ±0.4% of the theoretical values.

Biological Method. All compounds were administered orally as microsuspensions in 2% hydroxyethylcellulose (Cellosize) to animals under light ether anesthesia. Reaginic serum was obtained in mice immunized with proteins in alumina gel.[7] The PCA test was performed in rats.[8] Sprague–Dawley rats that weighed 120–140 g were injected with 0.1-mL serum dilutions at six intradermal sites and challenged iv 48 h later with 1 mg of antigen plus 2 mg of Evans blue per kilogram of body weight in 0.15 N NaCl. Thirty minutes after challenge the animals were sacrificed and the diameter of the skin reactions was measured on the inverted skin. Percent inhibition was calculated with the formula: % = $100(1 - a/b)$, where a is the sum of the reaction diameters in the treated animals and b the sum or the reaction diameters in the control animals.[9] Each variable was tested in groups of five rats.

Syntheses. Reference to known compounds are found in Table I. The general method of synthesis is exemplified for compound **6**.

4,5-Dihydro-8-methoxy-1*H*-benz[*g*]indazole Hydrochloride (6). A mixture of 3.5 g (20 mmol) of 7-methoxy-1-tetralone, 1.62 g (30 mmol) of freshly prepared $NaOCH_3$, 8.1 mL (100 mmol) of ethyl formate, and 90 mL of dry pyridine was stirred under nitrogen at room temperature for 18 h. After the mixture was adjusted to a pH between 5 and 6 with the aid of 50 mL of AcOH and 430 mL of water, it was extracted with benzene several times. The benzene layers were thoroughly washed with water and then were extracted with 2% KOH solution. The basic extracts were washed with ether and then, after reacidification with AcOH, they were extracted again with benzene. The benzene extracts were dried (Na_2SO_4) and reduced to dryness to give 3.8 g (93%) of crude hydroxymethylene ketone. To this material, without further purification, was added 2 mL (ca. 0.05 mol) of hydrazine hydrate and 30 mL of ethanol, and the mixture was refluxed for 6 h. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform and washed with water. The organic layer was dried (Na_2SO_4) and then reduced to dryness to afford 1.5 g (40%) of an oil, which solidified on standing. This solid was dissolved in ether and ethereal hydrogen chloride was added until precipitation ceased. The solid was filtered and recrystallized from ethanol–ether to afford **6** as light brown crystals: mp 217–221 °C; IR (Nujol) 3100, 2790, 1620, 1490 cm^{-1}; NMR (Me_2SO-d_6) δ 2.85 (br s, 4), 3.85 (s, 3), 7.5 (m, 4), 12.0 (br s, 1). Anal. ($C_{12}H_{13}ClN_2O$) C, H, N.

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