Bicyclic Pyrazolines, Potential Central Nervous System Depressants and Antiinflammatory Agents

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The synthesis and CNS activity of a series of 34 substituted bicyclic pyrazolines are described. Ten of these compounds were also screened for antiinflammatory activity. One of the compounds (15) exhibited significant antiinflammatory activity in the carrageenan-induced edema test.

The initial compound of this new series of substituted bicyclic pyrazolines (1) exhibited a modest CNS depressant profile when given to rats by the ip route. We prepared a series of analogues of 1 which were expected to show enhanced CNS depressant activity. Some of these products were also screened for antiinflammatory activity.

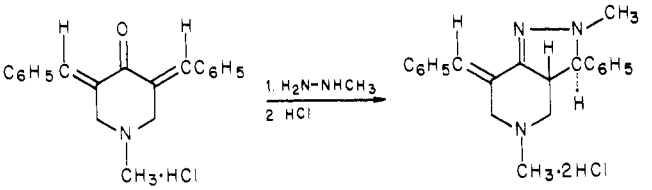
Compound 1 was obtained by the interaction of 3,5-dibenzylidene-1-methyl-4-piperidone (A) with methylhydrazine (Scheme I).[1] The structural assignment of 1 was based on the IR (absence of CO and NH bands) and NMR spectral data. Shift reagent and decoupling experiments in $CDCl_3$ showed that the protons of the pyrazoline ring are *trans* coupled (J = 13 Hz). The shift-reagent study also showed the benzylidene proton and the =N- linkage in a cis conformation. The above reaction appears to give predominantly a single isomer, since the TLC study of the mother liquor of the product indicated the presence of an additional quantity of 1, some unreacted ketone, and probably a small amount of an isomeric pyrazoline or pyrazole. The intermediate A was obtained by heating 1-methyl-4-piperidone and excess benzaldehyde in a mixture of ethanol and concentrated hydrochloric acid. Most of the compounds shown in Table I were prepared by utilizing the appropriate 4-piperidone (or cyclohexanone), benzaldehyde, and hydrazine in the above reaction procedure.

The yields listed in Table I were obtained by heating the dibenzylidene compounds with the substituted hydrazine in methanol for a period of 4–5 h. During the subsequent preparation of an additional quantity of **15a**, we moderated the reaction conditions and found that the yield was increased from 63 to 72% by allowing the reaction to take place at room temperature using a larger volume of methanol.

Some of the compounds shown in Table I were readily purified as dihydrochloride salts. Compound 1 was highly soluble (>10%) in water, whereas the dihydrochloride salt of the *N*-propyl analogue **15a** when added to water initially became gummy and changed to a water-insoluble granular monohydrochloride salt. Because **15a** showed a low order of toxicity and antiinflammatory activity similar to phenylbutazone in the carrageenan-induced edema test by the oral route, we attempted to prepare crystalline water-soluble salts of this material. The phosphoric acid salt **15** was obtained as a crystalline, water-soluble salt and showed about the same antiinflammatory activity as **15a**.

Structure–Activity Relationships. Compounds of this series were screened for CNS activity, and the results are shown in Table I. Structural modifications of 1, wherein the R (CH_3) group was replaced by a higher alkyl or aralkyl group (**3–6**), the R′ (CH_3) group was replaced by a higher alkyl (**14–16**), aralkyl (**17**), hydroxyalkyl (**18**), trifluoroethyl (**19**), acetyl (**20**), or dimethylaminopropyl (**22**), and the phenyl group was replaced by 2-, 3-, or 4-chlorophenyl or 4-methoxyphenyl, yielded less active products. Several derivatives of the most active CNS depressant compound (**7**) were prepared; however, these

Scheme I



A 1

materials (**8–13**) also showed decreased depressant activity. The decrease in the degree of biological activity may be partially due to the decreased water solubility of these analogues. Although **7** showed good depressant activity at 12.5 mg/kg ip, an oral dose of 100 mg/kg was necessary to cause a depressant effect. The dimethylaminoethyl compound **21** had a low therapeutic ratio (active at 25 mg/kg and toxic at 100 mg/kg ip). Seven compounds (**28–34**) were derived from 2,6-dibenzylidenecyclohexanone. Because **30** exhibited a moderate CNS depressant profile, the diethylamino, piperidino, morpholino, and 4-methylpiperazino analogues **31–34** were prepared and were found less active than **30**.

Ten compounds (**1**, **5**, **6**, **15**, **16**, **18**, **19**, **26**, **27**, and **33**) were screened for antiinflammatory activity in the carrageenan-induced edema test at 150 mg/kg po in the rat. Compound **15** compared favorably with phenylbutazone in this test (47 and 51% inhibition, respectively), was considerably less toxic in mice (LD_{50}, po: **15**, 5400 mg/kg; phenylbutazone, 1200 mg/kg), and was not ulcerogenic in rats at doses of 150, 300, and 600 mg/kg po (eight rats per dose).

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer IR-621 spectrometer and the NMR spectra with a Varian XL-100(15) spectrometer using Me_4Si as an internal standard. All analyses obtained were within 0.4% of the theoretical values. Most of the piperidones and the methylhydrazine used in this work were purchased from Aldrich Chemical Co. The other substituted hydrazines were prepared according to literature methods.

3,5-Dibenzylidene-1-methyl-4-piperidone Hydrochloride (A). A stirred solution of 57.0 g (0.5 mol) of 1-methyl-4-piperidone, 110.0 g (1.0 mol) of benzaldehyde, and 400 mL of EtOH was cooled and treated portionwise with 200 mL of concentrated HCl while maintaining the temperature below 30 °C. The pale-yellow solution was refluxed for 4 h and cooled. The yellow solid was filtered and dried: wt 91.5 g; mp 242–244 °C. The filtrate was concentrated to about 50% of the original volume to give an additional 29.0 g of product: mp 242–244 °C; total yield 73%. The compound can be recrystallized from DMF: mp 242–244 °C (reported[2] mp 234–240 and 243.5–244.5 °C); IR (Nujol) 1670 (CO), 1600, and 1580 cm^{-1} (C_6H_5CH=C). A shift-reagent study showed the carbonyl and phenyl groups in a trans configuration.

The above procedure is more convenient than the literature method[2] using gaseous HCl. Most of the compounds listed in Table II and 2,6-dibenzylidenecyclohexanone (intermediate for **28–34**) were prepared according to the above procedure. The

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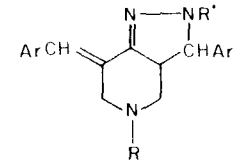
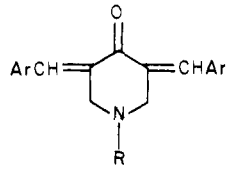
Table I. Substituted Bicyclic Pyrazolines



compd	R	R'	Ar	mp, °C	yield, %	formula	recrystn solvent[a]	depressant act.[b] ED, mg/kg, ip
1	CH_3	CH_3	C_6H_5	157-159[c]	80	$C_{21}H_{23}N_3 \cdot 2HCl \cdot H_2O$	A	50
2	CH_3	H	C_6H_5	162-164[c]	78	$C_{20}H_{21}N_3 \cdot 2HCl \cdot 0.5H_2O$	B	50
3	C_2H_5	CH_3	C_6H_5	153-155[c]	65	$C_{22}H_{25}N_3 \cdot 2HCl \cdot H_2O$	A	200
4	$(CH_2)_3CH_3$	CH_3	C_6H_5	112-114[c]	53	$C_{24}H_{29}N_3 \cdot 2HCl \cdot H_2O$	A	100
5	$CH_2C_6H_5$	CH_3	C_6H_5	160-162[c]	65	$C_{27}H_{27}N_3 \cdot 2HCl$	A	100
6	$(CH_2)_2C_6H_5$	CH_3	C_6H_5	129-131	25	$C_{28}H_{29}N_3 \cdot 2HCl \cdot H_2O$	A	100
7	H	CH_3	C_6H_5	214-216	58	$C_{20}H_{21}N_3 \cdot HCl$	C	12.5
8	$COCH_3$	CH_3	C_6H_5	118-120	48	$C_{22}H_{23}N_3O$[d]	D	100
9	COC_2H_5	CH_3	C_6H_5	95-97	43	$C_{23}H_{25}N_3O$	D	200
10	$CONH_2$	CH_3	C_6H_5	191-193	54	$C_{21}H_{22}N_4O$[e]	E	>200
11	$CONHCH_3$	CH_3	C_6H_5	170-172[c]	80	$C_{22}H_{24}N_4O \cdot HCl$	A	>200
12	$C(NH_2)=NH$	CH_3	C_6H_5	212-214	51	$C_{21}H_{23}N_5 \cdot HCl$	A	200
13	$(CH_2)_2COCH_3$	CH_3	C_6H_5	185-187[c]	64	$C_{24}H_{27}N_3O \cdot HCl$	A	>200
14	CH_3	C_2H_5	C_6H_5	156-158[c]	35	$C_{22}H_{25}N_3 \cdot 2HCl \cdot 2H_2O$	A	>200
15	CH_3	$(CH_2)_2CH_3$	C_6H_5	125-128	53	$C_{23}H_{27}N_3 \cdot H_3PO_4 \cdot H_2O$[f]	E	100
16	CH_3	$(CH_2)_3CH_3$	C_6H_5	140-142[c]	62	$C_{24}H_{29}N_3 \cdot 2HCl$	A	>200
17	CH_3	$(CH_2)_3C_6H_5$	C_6H_5	182-184	71	$C_{28}H_{29}N_3 \cdot HCl$	E	>200
18	CH_3	$(CH_2)_2OH$	C_6H_5	142-144[c]	47	$C_{22}H_{25}N_3O \cdot 2HCl \cdot H_2O$	A	200
19	CH_3	CH_2CF_3	C_6H_5	185-187[c]	45	$C_{22}H_{22}F_3N_3 \cdot 2HCl \cdot 0.5H_2O$	A	100
20	CH_3	$COCH_3$	C_6H_5	251-253[c]	44	$C_{22}H_{23}N_3O \cdot HCl$[g]	A	200
21	CH_3	$(CH_2)_2N(CH_3)_2$	C_6H_5	132-135	64	$C_{24}H_{30}N_4 \cdot 2HCl \cdot H_2O$[h]	F	25
22	CH_3	$(CH_2)_2N(CH_3)_2$	C_6H_5	174-176[c]	55	$C_{25}H_{32}N_4 \cdot 2HCl$[h]	G	100
23	$(CH_2)_2C_6H_5$	$(CH_2)_3N(CH_3)_2$	C_6H_5	128-130[c]	50	$C_{32}H_{38}N_4 \cdot 2C_4H_4O_4 \cdot 0.5H_2O$[i,j]	A	>200
24	CH_3	CH_3	2-ClC_6H_4	198-200	65	$C_{21}H_{21}Cl_2N_3 \cdot HCl$	C	>200
25	CH_3	CH_3	3-ClC_6H_4	163-165[c]	71	$C_{21}H_{21}Cl_2N_3 \cdot 2HCl$	A	>200
26	CH_3	CH_3	4-ClC_6H_4	132-134[c]	62	$C_{21}H_{21}Cl_2N_3 \cdot 2HCl \cdot H_2O$	A	>200
27	CH_3	CH_3	4-$OCH_3C_6H_4$	142-144[c]	51	$C_{23}H_{27}N_3O_2 \cdot 2HCl \cdot H_2O$	A	>200
28	*k*	CH_3	C_6H_5	107-109	82	$C_{21}H_{22}N_2$	E	>200
29	*k*	$(CH_2)_2N(CH_3)_2$	C_6H_5	137-139	34	$C_{24}H_{29}N_3 \cdot C_4H_4O_4 \cdot H_2O$[h,i]	A	100
30	*k*	$(CH_2)_3N(CH_3)_2$	C_6H_5	177-179	68	$C_{25}H_{31}N_3 \cdot C_2H_2O_4$[i]	H	50
31	*k*	$(CH_2)_3N(C_2H_5)_2$	C_6H_5	104-106	45	$C_{27}H_{35}N_3 \cdot C_4H_4O_4$[h,i]	A	100
32	*k*	$(CH_2)_3NC_5H_{10}$[l]	C_6H_5	146-148	45	$C_{28}H_{35}N_3 \cdot C_4H_4O_4$[h,i]	A	200
33	*k*	$(CH_2)_3NC_4H_8O$[l]	C_6H_5	152-154	53	$C_{27}H_{33}N_3O \cdot HCl \cdot 0.5H_2O$[j]	A	100
34	*k*	$(CH_2)_3NC_4H_8NCH_3$[l]	C_6H_5	179-181	57	$C_{28}H_{36}N_4 \cdot 2C_4H_4O_4$[h,i]	H	200
meprobamate								50

[a] A = MeOH-Et_2O; B = $CHCl_3$ (suspension); C = EtOH; D = $(i\text{-Pr})_2O$; E = CH_3CN; F = CH_3CN-Et_2O; G = CH_3CN-EtOAc; H = DMF-CH_3CN. [b] All compounds were administered as 5% solutions of dispersions (containing two drops of Tween 80) in water at doses of 200, 100, and 50 mg/kg to young adult female rats. Compounds showing activity at 50 mg/kg were also tested at 25 and 12.5 mg/kg. The ED values are the lowest doses showing decreased motor activity in 2/2 rats. [c] Melts with decomposition. [d] The HCl salt (mp 128-130 °C, from MeOH-Et_2O) became gummy when suspended in water and could not be dispersed satisfactorily to permit biological evaluation. [e] The HCl salt (mp 156-158 °C, from MeOH-Et_2O) when suspended in water hydrolyzes to the free base. [f] Melting points of the hydrochloride salts and free base are given in the Experimental Section. [g] Melting point of base, 174-176 °C (from CH_3CN). [h] Initially purified by crystallization of the dioxalic acid salts from DMF-CH_3CN: 21, mp 201-203 °C; 22, mp 148-151 °C; 29, mp 157-159 °C; 31, mp 145-147 °C; 32, mp 172-174 °C; 34, mp 204-206 °C. [i] $C_4H_4O_4$-maleic acid and $C_2H_2O_4$-oxalic acid. These products did not form crystalline hydrochloride salts. [j] Material was initially purified by crystallization of the base from CH_3CN: 23, mp 100-102 °C; 33, mp 98-100 °C. [k] In the above general formula, NR is replaced by $-CH_2-$. [l] NC_5H_{10} = piperidino; NC_4H_8O = morpholine; NC_4H_8N = piperazino.

Table II. 3,5-Diarylidene-4-piperidones



no.	R	Ar	mp, °C[a]	yield, %	formula
A	CH_3	C_6H_5	242–244	73	$C_{20}H_{19}NO\cdot HCl$
B	C_2H_5	C_6H_5	234–236	59	$C_{21}H_{21}NO\cdot HCl$
C	$(CH_2)_3CH_3$	C_6H_5	212–214	33	$C_{23}H_{25}NO\cdot HCl$
D	$CH_2C_6H_5$	C_6H_5	216–218	36	$C_{26}H_{23}NO\cdot HCl$
E	$(CH_2)_2C_6H_5$	C_6H_5	225–227	43	$C_{27}H_{25}NO\cdot HCl$
F	H	C_6H_5	273–275[b]	88	$C_{19}H_{17}NO\cdot HCl$
G	CH_3	3-ClC_6H_4	237–239	43	$C_{20}H_{17}Cl_2NO\cdot HCl$
H	CH_3	4-ClC_6H_4	256–258	17	$C_{20}H_{17}Cl_2NO\cdot HCl$
I	CH_3	4-$OCH_3C_6H_4$	230–232	54	$C_{22}H_{23}NO_3\cdot HCl$

[a] Melt with decomposition. Crystallized from DMF–CH_3CN, except A, B, F (EtOH trituration), and C (DMF). [b] Mp 276–277 °C: G. M. Kuettel and S. M. McElvain, *J. Am. Chem. Soc.*, **53**, 2692 (1931).

synthesis of G and I were carried out using KOH in place of HCl according to a procedure described for the preparation of the *o*-chlorobenzylidene analogue[2] (intermediate for **24**).

7-Benzylidene-3,3a,4,5,6,7-hexahydro-2,5-dimethyl-3-phenyl-2*H*-pyrazolo[4,3-*c*]pyridine Dihydrochloride (1). A suspension of 10.0 g (0.03 mol) of A in 100 mL of MeOH was treated with 1.5 g (0.03 mol) of methylhydrazine and heated, and the resulting solution was refluxed for 4 h. The solvent was removed on a rotary evaporator, and the crystalline yellow residue (12.6 g, mp 102–105 °C) was dissolved in 100 mL of CH_3CN and treated with 4.6 mL of 6.7 N HCl in EtOH. The crystalline dihydrochloride separated after several minutes. The mixture was allowed to stand at room temperature for 3 h, filtered, washed with CH_3CN and Et_2O, and dried in a desiccator to give 11.3 g of yellow product, mp 154–156 °C (dec). This material was suspended in 100 mL of MeOH and warmed slightly to obtain a solution, and the solution was diluted to 400 mL with Et_2O to give 10.0 g (80%) of pale-yellow crystals: mp 157–159 °C (dec); IR (Nujol) 1620 (conj C=N–), 1575 cm^{-1} (C_6H_5CH=C); NMR (Me_2SO-d_6) δ 2.72 (2-Me), 2.85 (5-Me), 3.56 (CH_2), 3.92 (1 H), 4.35 (=CCH_2N), 7.30, 7.42 ($2C_6H_5$, =CH), 12.85 (N + H exchanged), 7.10 (3 H, exchanged). The free base melts at 101–103 °C (from CH_3CN).

Compounds **8** and **9** were prepared from the free base of **7** and the acyl chloride in benzene in the presence of 1 equiv of Et_3N (mixture was refluxed for 3 h); **10** was prepared from the free base of **7** and KCNO in aqueous acetic acid at room temperature for 12 h; **11** was prepared from the free base of **7** and excess CH_3NCO in benzene at reflux for 4 h; **12** was prepared from **7** and excess cyanamide in EtOH after refluxing for 24 h; and **13** was prepared from the free base of **7** and 1 equiv of methyl vinyl ketone in DMF and allowing the solution to stand for 12 h at room temperature.

7-Benzylidene-3,3a,4,5,6,7-hexahydro-5-methyl-3-phenyl-2-propyl-2*H*-pyrazolo[4,3-*c*]pyridine Phosphate (**15**) **and Dihydrochloride** (**15a**). A stirred suspension of 125.0 g (0.38 mol) of A in 1.25 L of MeOH was treated with 30.0 g (0.40 mol) of *n*-propylhydrazine[3] and heated, and the resulting solution was refluxed for 5 h. The solvent was removed on a rotary evaporator and the red gummy residue was triturated with 400 mL of Et_2O. The solvent was removed as above, and the residue was stirred vigorously with 900 mL of H_2O and 450 mL of Et_2O for 4 h. The pale-yellow crystalline monohydrochloride salt was filtered and washed with 120 mL of cold H_2O and Et_2O: yield 92.5 g (63%); mp 170–172 °C. Anal. ($C_{23}H_{27}N_3\cdot HCl$) C, H, N, Cl.

Alternatively, 10.0 g (0.03 mol) of A in 200 mL of MeOH was warmed to 35 °C, and the resulting solution was treated with a solution of 3.0 g (0.04 mol) of *n*-propylhydrazine in 20 mL of MeOH. After standing at room temperature for 24 h, the solvent was removed on a rotary evaporator and the amorphous residue was stirred with 50 mL of water and 100 mL of Et_2O. The mixture was cooled and filtered to give 8.4 g (72%) of the pale-yellow crystalline monohydrochloride, mp 170–172 °C.

The above material (92.5 g) was converted to the free base by treatment of a stirred suspension in 1 L of H_2O and 1 L of Et_2O with 33 g of K_2CO_3 (portionwise). After two clear layers were obtained, the organic phase was separated, and the aqueous phase was extracted with 400 mL of Et_2O (three times). The organic phases were combined and dried ($MgSO_4$), and the solvent was evaporated to give 79.0 g of pale-yellow solid, mp 106–109 °C. After crystallization from 500 mL of CH_3CN, the pale-yellow base weighed 70.0 g (53%), mp 110–112 °C.

The H_3PO_4 salt **15** was prepared by treatment of a stirred suspension of 50.0 g of the base in 500 mL of EtOH with a solution of 18.4 g of 85% H_3PO_4 in 300 mL of EtOH. After a solution was obtained, the solvent was removed on a rotary evaporator to give a pale-yellow foamlike residue. The latter (75.0 g) was dissolved in 850 mL of CH_3CN (warmed to 50 °C), cooled, and seeded. After cooling overnight, the pale-yellow solid was filtered, washed with 200 mL of cold CH_3CN, and dried in vacuo to give 63.5 g (52%) of pale-yellow solid, mp 125–128 °C (sinters at 85 °C).

Although **15** is highly soluble in H_2O, a 10 and a 2% solution in H_2O began to precipitate the free base after 20 and 90 min, respectively. A 2% solution, when treated with a drop of 10% H_3PO_4, remains clear for several days.

The dihydrochloride salt **15a** was prepared by treatment of a suspension of 14.8 g of the above base in 120 mL of CH_3CN with 14.1 mL of 6.1 N HCl in EtOH to give a pale-yellow solution. The crystalline salt rapidly separated from solution. After cooling overnight, the product was filtered and dried: wt 17.4 g (49%); mp 125–127 °C (dec). Recrystallization of this material from 125 mL of MeOH–875 mL of Et_2O gave 15.8 g (45%) of pale-yellow solid, mp 128–130 °C (dec). Anal. ($C_{23}H_{27}N_3\cdot 2HCl\cdot H_2O$) C, H, N, Cl.

Treatment of the aqueous phase from which the 79 g of the monohydrochloride was isolated with excess K_2CO_3, followed by extraction with ether and evaporation of the solvent, gave 36.5 g of residue. The latter was crystallized from 180 mL of CH_3CN to give an additional 4.5 g of base, mp 109–111 °C. A TLC study of the filtrate indicated the presence of the free base of the starting ketone A, additional product, and unidentified material, presumably an isomeric pyrazoline or pyrazole.

Compound **20** was prepared from the free base of **2** and acetyl chloride in benzene solution in the presence of 1 equiv of Et_3N. The mixture was refluxed for 2 h.

Compound **21** was obtained by interaction of the free base of **18** with tosyl chloride in pyridine at 4–5 °C to give the tosylate ester in 57% yield, mp 131–133 °C (from CH_3CN). The latter was suspended in benzene and treated with excess Me_2NH, allowed to stand at room temperature for 2 days, and then refluxed for 6 h.

***N*-(3-Hydrazinopropyl)morpholine.** Interaction of 40.0 g (0.20 mol) of *N*-(3-chloropropyl)morpholine hydrochloride and 30 mL of N_2H_4 (anhydrous) in 160 mL of EtOH according to a procedure described by Nagrody and Morris[4] gave 17.7 g (56%) of product as a colorless hygroscopic oil, bp 115–117 °C (1 mm). Anal. ($C_7H_{17}N_3O$) C, H, N.

7-Benzylidene-3,3a,4,5,6,7-hexahydro-2-[3-(4-morpholinyl)propyl]-3-phenyl-2*H*-indazole Hydrochloride (**33**). A

stirred suspension of 70.4 g (0.25 mol) of 2,6-dibenzylidenecyclohexanone[5] in 640 mL of MeOH was treated with 41.6 g (0.26 mol) of the above substituted hydrazine and warmed, and the resulting solution was refluxed for 4 h. The solvent was removed on a rotary evaporator and the residual solid was crystallized from 500 mL of CH_3CN to give 72.2 g of pale-yellow base, mp 106–108 °C. Anal. ($C_{27}H_{33}N_3O$) C, H, N.

A stirred suspension of the above base in 360 mL of CH_3CN was treated with 32 mL of 5.6 N HCl in EtOH, and the resulting solution was diluted with 1.8 L of Et_2O to give 72.2 g (62%) of colorless solid, mp 148–151 °C. Recrystallization of this material from 350 mL of MeOH–3.5 L of Et_2O gave 62.0 g (53%) of colorless product, mp 152–154 °C.

Carrageenan-Induced Edema Test and Results. The procedure described by Millonig and Yiakas[6] was used to test agents for antiedema activity. The test compounds were dissolved or suspended in water or 1% aqueous sodium carboxymethylcellulose in a volume of 1 mL and administered orally to adult Charles River Sprague-Dawley rats (seven per group) 2 h prior to injection (footpad) of 0.05 mL of a 1% solution of carrageenan in pyrogen-free saline. Three hours after the injection of carrageenan, the rats were killed, and the paws were removed and weighed. The contralateral paw served as the control. The percentage of inhibition of edema was observed for the following compounds at a dose of 150 mg/kg: 1 (22% inhibition), **5** (0%), **6** (32%), **15** (47%), **16** (26%), **18** (41%), **19** (27%), **26** (17%), **27** (29%), **33** (30%), phenylbutazone (51%).

Ulcerogenic Test. Male Sprague-Dawley rats were deprived of food pellets but allowed free access to water containing 5% dextrose for 48 h before oral administration (via gavage) of the test compound. The compound was dissolved or suspended in water and administered orally to eight rats at each dose. After dosing (six h), the animals were sacrificed, and their stomachs were excised and examined grossly for hyperemia, fresh or tarry blood, and erosions (hemorrhagic or nonhemorrhagic) in the rumen and glandular portions.

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References and Notes

(1) For review articles on the chemistry of pyrazolines, see C. H. Jarboe, *Chem. Heterocycl. Compd.*, **22**, 177–278 (1967); T. L. Jacobs, *Heterocycl. Compd.*, **5**, 45–161 (1957).
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Synthesis and Preliminary Biological Studies of 4- and 5-[2-Hydroxy-3-(isopropylamino)propoxy]benzimidazoles: Selective β_2 Adrenergic Blocking Agents

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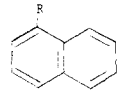
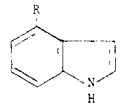
Benzimidazoles carrying the 2-hydroxy-3-(isopropylamino)propoxy side chain at either the C-4 or C-5 ring positions were synthesized and investigated for β-adrenergic blocking activity. Both compounds demonstrated β_2 selectivity when evaluated in guinea pig atrial and tracheal preparations. The C-4 isomer was 17 times more selective toward tracheal tissue, and its overall potency was roughly comparable to that of propranolol. β_2 selectivity of the C-5 isomer was minimal, with a potency about one-hundredth that of propranolol.

Many heterocyclic analogues of propranolol (**1**) have



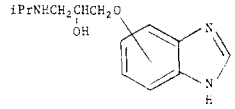
1



2

R = iPrNHCH$_2$CHCH$_2$O– (OH)

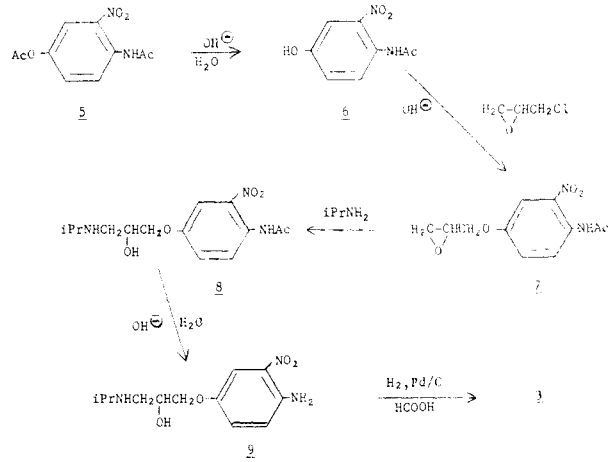
been prepared and some found highly active as β-adrenergic blocking agents.[1-4] Perhaps the most successful drug so far to emerge from these studies is pindolol (**2**), which possesses an indole nucleus and is at least ten times more potent than propranolol.[1,5,6] Despite the close structural resemblance between the indole and benzimidazole ring systems, the benzimidazole analogues **3** and **4** were conspicuously absent from the literature at the beginning of this study.



3 side chain at C-5

4 side chain at C-4

Scheme I



The purpose of this report is to describe the synthesis and initial biological evaluation of two benzimidazole

