# Tetrahydro-2-benzoxepins: A Novel Family of Hypotensives

Ruth E. TenBrink, John M. McCall,* Donald T. Pals, Robert B. McCall, John Orley, Steve J. Humphrey, and Michael G. Wendling

*The Upjohn Company, Research Laboratories, Kalamazoo, Michigan 49001.* *Received July 28, 1980*

A novel series of 1-(alkylamino)-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepins shows hypotensive activity. A typical example is 1-[2-(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]-4-(4-fluorophenyl)piperazine. This compound is an $\alpha$ blocker with peripheral and central activities.

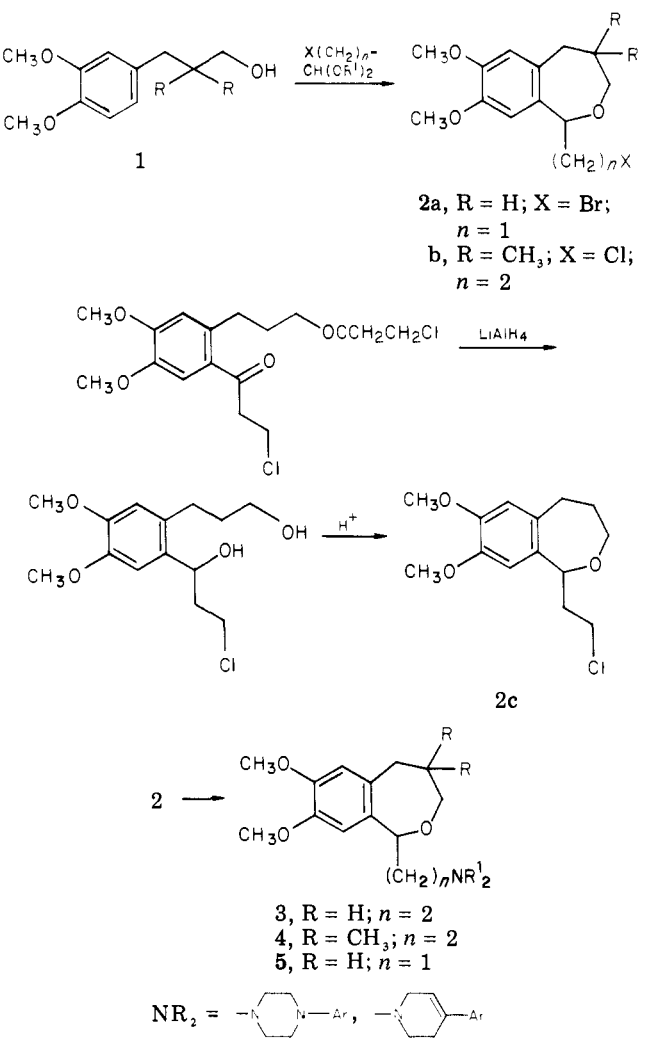
We have investigated a series of 1-(alkylamino)-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepins. In the rat, many of these compounds are orally active hypotensive agents. One member of this series, 1-[2-(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]-4-(4-fluorophenyl)-piperazine (**3a**), is an $\alpha$ blocker which resembles prazosin[1] in its mechanism of action. Benzoxepin **3a** has both peripheral and central activities.

**Chemistry.** The syntheses which we have developed for 1-(haloalkyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepins (**2a–c**) are shown in Scheme I. In general, the benzoxepin ring forms reluctantly, but these new methods which rely either on condensation reactions with haloalkyl aldehydes or dehydrative cyclizations are quite reasonable. These preparations have been described elsewhere.[2] Haloalkylbenzoxepins **2a–c** react with 4-arylpiperazines and 4-aryltetrahydropyridines to yield 1-(alkylamino)benzoxepins **3–5**. These agents are summarized in Table I.

**Pharmacology.** The oral hypotensive activity of benzoxepins of structural types **3–5** was evaluated in conscious rats. Certain structure–activity relationships may be deduced from the results of these studies (Table I). In general, compounds of structures **3** and **4** which bear a two-carbon alkyl chain at C-1 are more potent than their one-carbon analogues **5**. Also, at 4 h after oral administration, compounds of structure **3** are usually more active than comparable compounds of structure **4**. Thus, the 4-h activities of compounds **3a–e** exceed those of the corresponding compounds **4a–e**. Only **3f** and **4f** reverse this trend. The situation at 24 h is more complex. The relatively prolonged (i.e., 24 h) hypotensive activity of **4c** and **4d** relative to **3c** and **3d** suggests that ring methylation at C-4 may delay metabolic deactivation of this benzoxepin series. In this respect, however, other pairs of compounds **3** and **4** are ambiguous. Finally, the position of chloro substitution on the phenyl of the chlorophenylpiperazine analogues does markedly affect hypotensive activity. Thus, in the unmethylated series (**3**) para > meta > ortho (i.e., **3b** > **3e** > **3f**), while in the methylated series (**4**) ortho > para > meta (i.e., **4f** > **4b** > **4e**).

Compound **3a** was selected for further study because it is the most potent hypotensive in the series. In the anesthetized dog, intravenous administration of this compound decreased arterial blood pressure in a dose-related manner. Following compound **3a** at 0.5 mg/kg, the pressor responses to bilateral carotid occlusion and norepinephrine were inhibited by 30 and 36%, respectively. A dose of 5 mg/kg reduced the pressor responses to bilateral carotid occlusion and norepinephrine by 64 and 74%, respectively. Blood pressure responses to acetylcholine, histamine, isoproterenol, and angiotensin II were essentially unaltered by either dose of compound **3a**. These results suggested

Scheme I




that compound **3a** possessed $\alpha$-adrenergic blocking properties.

Further studies with compound **3a** in anesthetized dogs compared it to phentolamine, a classical $\alpha$-adrenergic blocking agent;[3] prazosin, a recently described $\alpha$-adrenergic blocking agent which elicits minimal tachycardia and hyperreninemia;[1] and minoxidil, a directly acting vasodilator.[4] Figure 1 illustrates the dose-related hypotensive responses of compound **3a**, together with its minimal effects on heart rate and plasma renin activity. This profile of activity was nearly identical with that displayed by prazosin (also Figure 1). It should be noted that the hypotensive potency of prazosin was approximately tenfold greater than that of compound **3a**. In contrast to the profiles of activity

(1) Stokes, G. S.; Oates, H. F. *Cardiovasc. Med.* **1978**, *3*, 41.
(2) (a) TenBrink, R. E.; McCall, J. M.; Johnson, H. G. *J. Med. Chem.* **1980**, *23*, 1058. (b) TenBrink, R. E.; McCall, J. M. *J. Heterocycl. Chem.*, submitted for publication.
(3) Goodman, L. S.; Gilman, A., Eds "The Pharmacological Basis of Therapeutics", 4th ed.; MacMillan: New York, 1970; p 559.
(4) DuCharme, D. W.; Freyburger, W. A.; Graham, B. E.; Carlson, R. G. *J. Pharmacol. Exp. Ther.* **1973**, *184*, 662.

0022-2623/81/1824-0064$01.00/0 

Table I. Hypotensive Activity of Selected Benzoxepins

| $NR_2$ | compd 3 | Δ BP (dose)[a] | compd 4 | Δ BP (dose) | compd 5 | Δ BP (dose) |
|---|---|---|---|---|---|---|
| 4-(*p*-fluorophenyl)piperazino | 3a | −49/−52 (50), −24/−9 (5) | 4a | −10/+3 (5) | 5a | −9/0 (50) |
| 4-(*p*-chlorophenyl)piperazino | 3b | −13/−33 (50), −8/−1 (5) | 4b | −10/−14 (50) | | |
| 4-(*o*-methoxyphenyl)piperazino | 3c | −22/−12 (50), −9/+2 (5) | 4c | −17/−30 (50) | 5c | −14/−10 (50) |
| 4-(*o*-tolyl)piperazino | 3d | −27/−19 (50), 0/+3 (15) | 4d | −22/−27 (50), 0/+3 (15) | | |
| 4-(*m*-chlorophenyl)piperazino | 3e | −11/0 (50) | 4e | −2/−1 (50) | | |
| 4-(*o*-chlorophenyl)piperazino | 3f | +1/0 (50) | 4f | −16/−10 (50) | | |
| 4-phenyl-1,2,3,6-tetrahydropyridino | 3g | −17/+2 (50) | | | | |
| 2-(3,4-dimethoxyphenyl)ethylamino | 3h | +1/−3 (50) | | | | |
| 4-(2-pyridinyl)piperazino | 3i | −20/−28 (50) | | | 5i | −7/0 (50) |
| 4-(*p*-chlorophenyl)-1,2,3,6-tetrahydropyridino | 3j | −18/−16 (50), −4/−6 (5) | | | | |
| 4-(2-keto-1-benzimidazolinyl)piperidino | 3k | −18/−18 (50), −12/−3 (15) | | | | |
| 4-phenylpiperazino | | | | | 5l | −4/−8 (50) |
| 4-(*p*-methoxyphenyl)piperazino | | | | | 5m | −1/+9 (50) |

[a] Δ BP (dose) refers to the average mmHg change in mean arterial blood pressure observed 4 and 24 h after oral administration (mg/kg). The average changes observed at 4 h are entered prior to the 24 h changes and are separated by a slash line.

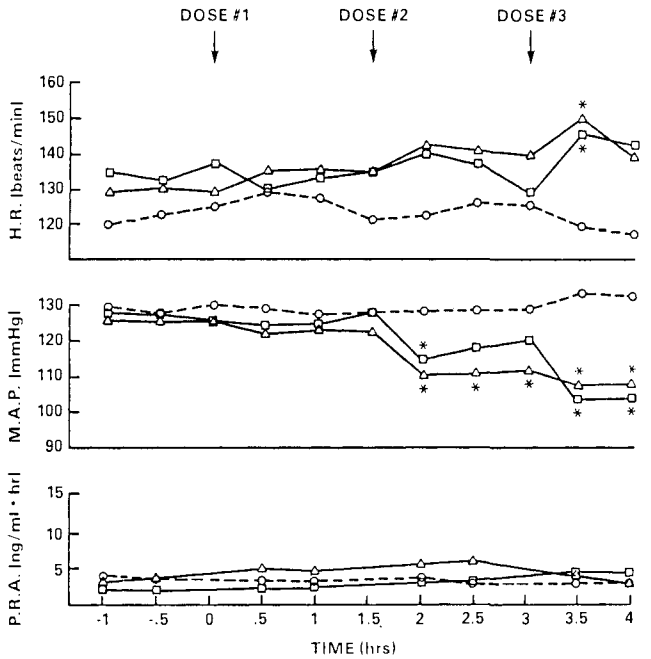



**Figure 1.** Effects of cumulative doses of vehicle (0.002, 0.02, and 0.2 mL/kg), ○; compound **3a** (0.03, 0.3, and 3.0 mg/kg), □; and prazosin (0.003, 0.03, and 0.3 mg/kg), △, on heart rate (HR), mean arterial blood pressure (MAP), and plasma renin activity (PRA) in the anesthetized dog. Each point represents the mean of 7, 5, and 5 animals in the vehicle, compound **3a**, and prazosin group, respectively. * = $p < 0.05$.

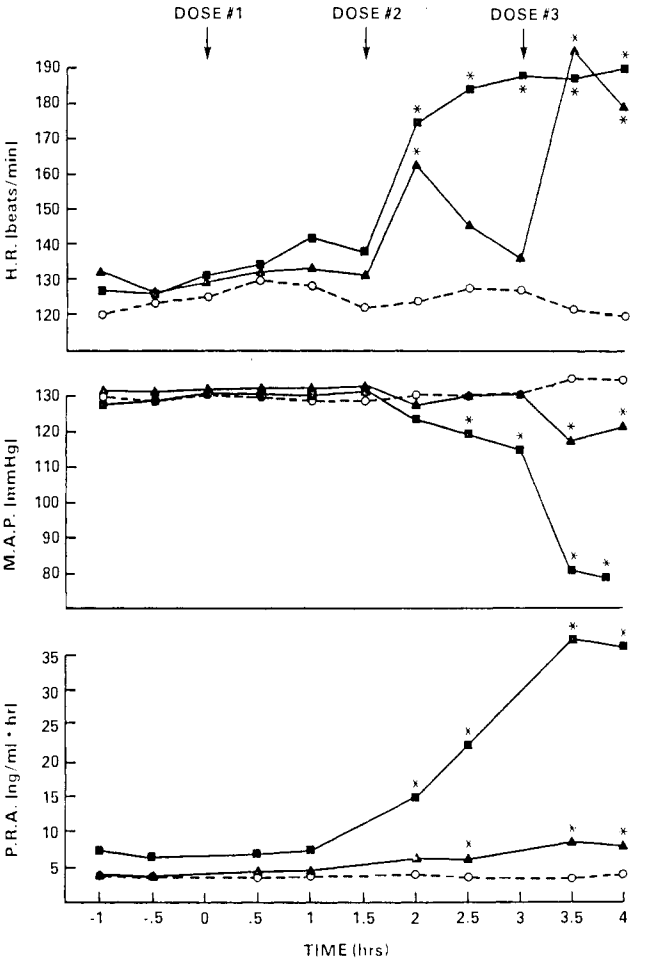



**Figure 2.** Effects of cumulative doses of vehicle (0.002, 0.02, and 0.2 mL/kg), ○; phentolamine (0.03, 0.3, and 3.0 mg/kg), ▲; and minoxidil (0.03, 0.3, and 3.0 mg/kg), ■, on heart rate (HR), mean arterial blood pressure (MAP), and plasma renin activity (PRA) in the anesthetized dog. Each point represents the mean of 7, 6, and 5 animals in the vehicle, phentolamine, and minoxidil group, respectively. * = $p < 0.05$.

shown in Figure 1, the activity profiles of phentolamine and minoxidil illustrated in Figure 2 indicate that tachycardia, as well as hyperreninemia, occurs concomitantly with the hypotension induced by each. These data suggest that compound **3a** and prazosin have a similar mechanism of action which appears to be quite different from that of both phentolamine and minoxidil.

The role of the central nervous system in the hypotensive action of compound **3a** was assessed by recording sympathetic nerve activity in the external carotid nerve of anesthetized baroreceptor denervated cats. Table II summarizes the effects of compound **3a** in comparison to its vehicle on blood pressure, heart rate, and sympathetic nerve activity in this preparation. Noteworthy is the almost parallel depression of blood pressure and sympathetic nerve activity elicited by compound **3a**. In two additional experiments, compound **3a** reduced sympathetic nerve activity recorded from the preganglionic splanchnic nerve of similarly prepared cats. These experiments disclosed a central component to the hypotensive mechanism of action of compound **3a**.

Table II. Effect of Compound 3a on Blood Pressure (MAP), Heart Rate (HR), and Sympathetic Nerve Activity (% SNA) in Baroreceptor Denervated Cats[a]

| | vehicle control, $n = 8$ | | | compd 3a (1.0 mg/kg, iv), $n = 6$ | | |
|---|---|---|---|---|---|---|
| time, min | MAP | HR | % SNA | MAP | HR | % SNA |
| 0 | 126 ± 7 | 233 ± 12 | 100 | 131 ± 6 | 229 ± 18 | 100 |
| 5 | 129 ± 7 | 232 ± 12 | 102 ± 2 | 75 ± 8[b] | 229 ± 15 | 72 ± 5[b] |
| 10 | 129 ± 8 | 233 ± 12 | 102 ± 4 | 85 ± 7[b] | 230 ± 16 | 76 ± 5[b] |
| 20 | 127 ± 8 | 234 ± 12 | 105 ± 3 | 95 ± 8[b] | 230 ± 17 | 86 ± 6[b] |
| 40 | 124 ± 7 | 237 ± 11 | 106 ± 3 | 107 ± 6[b] | 231 ± 18 | 88 ± 5[b] |
| 60 | 124 ± 7 | 240 ± 12 | 118 ± 4 | 109 ± 6[b] | 232 ± 18 | 96 ± 7[b] |

[a] All values are expressed as mean ± SE. [b] $p < 0.05$.

Table III. Melting Points and Elemental Analyses

| compd | mp, °C | recrystn solvent | formula | anal.[a] |
|---|---|---|---|---|
| 3a | 218-219 | $CH_2Cl_2$/EtOH | $C_{24}H_{31}FN_2O_3 \cdot HCl$ | C, H, N |
| 3b | 154.5-155.0 | $CH_2Cl_2$/$Et_2O$ | $C_{24}H_{31}ClN_2O_3$ | C, H, N |
| 3c | 146-149 | ether | $C_{25}H_{34}N_2O_4 \cdot HCl \cdot 0.5H_2O$ | C, H, N |
| 3d | 86.5-87.0 | $CH_2Cl_2$/$Et_2O$/ Skellysolve B | $C_{25}H_{34}N_2O_3$ | H, N; C[b] |
| 3e | 125-126 | $CH_2Cl_2$/toluene | $C_{24}H_{31}ClN_2O_3$ | C, H, N |
| 3f | 221-222 | EtOH | $C_{24}H_{31}ClN_2O_3 \cdot HCl$ | C, H, N, Cl |
| 3g | 144.0-144.5 | EtOH | $C_{25}H_{31}NO_3$ | C, H, N |
| 3h | oil | $Et_2O$ | $C_{24}H_{33}NO_5 \cdot HCl \cdot H_2O$ | C, H, N, Cl |
| 3i | 136.5-137.5 | $CH_2Cl_2$/Skelly-solve B | $C_{23}H_{31}N_3O_3$ | H, N; C[c] |
| 3j | 121.0-122.0 | $CH_2Cl_2$/Skelly-solve B | $C_{25}H_{30}ClNO_3$ | C, H, N |
| 3k | 109-112 | $CH_2Cl_2$ | $C_{26}H_{33}N_3O_4 \cdot HCl$ | C, H, N |
| 4a | 210-212 | EtOH | $C_{26}H_{35}FN_2O_3 \cdot HCl$ | C, H, N, Cl |
| 4b | 203-204 | EtOH | $C_{26}H_{35}ClN_2O_3 \cdot 2HCl$ | C, N, Cl; H[d] |
| 4c | 176-177 | EtOH/EtOAc | $C_{27}H_{38}N_2O_4 \cdot 2HCl \cdot H_2O$ | C, H, N, Cl |
| 4d | 171-173 | EtOH | $C_{27}H_{38}N_2O_2 \cdot 2HCl$ | C, H, N, Cl |
| 4e | 172-173 | EtOH | $C_{26}H_{35}ClN_2O_2 \cdot 2HCl$ | C, H, N, Cl |
| 4f | 187-189 | EtOH | $C_{26}H_{35}ClN_2O_3 \cdot HCl$ | C, H, N, Cl |
| 5a | 135-136 | $Et_2O$ | $C_{23}H_{29}FN_2O_3$ | C, H, N |
| 5c | oil | $Et_2O$ | $C_{24}H_{32}N_2O_4 \cdot HCl \cdot 0.5H_2O$ | C, H, N |
| 5i | 196-199 | $Et_2O$ | $C_{22}H_{29}N_3O_3 \cdot HCl \cdot 0.5H_2O$ | C, H, N |
| 5l | 106-108 | $CH_2Cl_2$/$Et_2O$/ pet. ether | $C_{23}H_{30}N_2O_3$ | C, H, N |
| 5m | oil | $Et_2O$ | $C_{24}H_{32}N_2O_4 \cdot HCl \cdot H_2O$ | C, H, N |

[a] Unless otherwise noted, elemental analyses are within ±0.4% of the calculated value. [b] C: calcd, 73.14; found 72.76. [c] C: calcd, 69.49; found 69.03. [d] H: calcd, 7.01; found 7.45.

The mechanism of the hypotensive action of compound **3a** appears to be due to peripheral $\alpha$-adrenergic receptor blockade in conjunction with a centrally mediated inhibition of sympathetic nerve activity. The absence of pronounced tachycardia and renin hypersecretion observed in the present studies with compound **3a** and prazosin may be the result of a selective affinity of both agents for postsynaptic $\alpha$-receptors as has been described in the case of prazosin.[1] Such a mechanism of action would leave the presynaptic $\alpha$-receptors unoccupied and presumably able to inhibit the release of additional norepinephrine from sympathetic neurons. Alternatively, the central component of compound **3a**'s action could be responsible for the minimal tachycardia and hyperreninemia. Such a mechanism has recently been postulated for the similar effects observed with prazosin.[5] In any event, the present studies have provided evidence suggesting a remarkable similarity in the mechanisms of action of compound **3a** and prazosin.

## Experimental Section

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Elemental analyses and melting points are recorded in Table III. NMR spectra of $CDCl_3$ solutions were recorded on a Varian HFT-80 and are consistent. Typical procedures for the synthesis of compounds 3–5 are given in the following paragraphs.

**General Procedure for Compound 3. 1-(4-Fluorophenyl)-4-[(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]piperazine (3a).** A mixture of 1.60 g (5.0 mmol) of 7,8-dimethoxy-1-(chloroethyl)-1,3,4,5-tetrahydro-2-benzoxepin[2] and 2.5 g (13.8 mmol) of 1-(*p*-fluorophenyl)piperazine was heated at 90 °C for 3 h. Benzene (3 mL) was added and the mixture was refluxed for 4 days. Ether was added and the insolubles were filtered. The organic phase was washed with aqueous sodium bicarbonate and then brine. The organic phase was concentrated. The residue was chromatographed on silica gel (2% methanol/methylene chloride) to yield 1.25 g (51%) of crystalline product, mp 115 °C.

**General Procedure for Compound 4. 1-(*o*-Tolyl)-4-[(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]piperazine (4d).** A mixture of 1.50 g (4.8 mmol) of 7,8-dimethoxy-4,4-dimethyl-1-(chloroethyl)-1,3,4,5-tetrahydrobenzoxepin[2] and 1.70 g (0.7 mmol) of 1-(*o*-tolyl)piperzine in 15 mL of ethylene glycol was heated at 80–90 °C for 19 h. The mixture was partitioned between methylene chloride and 5% aqueous sodium hydroxide. The organic phase was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel (2% methanol/methylene chloride) to give 2.00 g (94%) of product. This oil was converted to the dihydrochloride salt, mp 171–173 °C from ether.

**General Procedure for Compound 5. 1-Phenyl-4-[(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)methyl]piperazine (5l).** A mixture of 1.50 g (5.0 mmol) of 7,8-dimethoxy-1-(bromomethyl)-1,3,4,5-tetrahydro-2-benzoxepin,[2] 1.02 g (6.0 mmol) of *N*-phenylpiperazine, and 1.05 mL (6.0 mmol) of diisopropylethylamine in 50 mL of DMF was stirred at 95 °C for 5.5 h. The reaction was partitioned first with aqueous sodium bicarbonate and then brine. The organic phase was concentrated and the residue was chromatographed on silica gel (3% methanol/methylene chloride) to give 0.83 g (43%) of product. This

(5) McCall, R. B.; Humphrey, S. J. *Neurosci. Abstr.*, in press.

was crystallized from methylene chloride, ether, and petroleum ether, mp 106–108 °C.

**Hypotensive Activity in Rat.** The blood pressure of restrained female Sprague–Dawley rats was measured directly from chronic indwelling aortic cannulas exteriorized from the nape of the neck.[6] The rats were restrained in a towel during the period of blood pressure measurement via Statham transducer (P23G) and Grass Model 5 polygraph. Measurements were made before, as well as 4 and 24 h after, the oral administration of each compound suspended in a carboxymethylcellulose vehicle at 10 mL/kg. Blood pressure values of two animals were averaged at each of the three measurement times. An average change of at least 5 mmHg was required posttreatment for statistical significance ($p < 0.05$) to be attained.

**Methods for Anesthetized Dogs.** The initial cardiovascular evaluation of compound **3a** was carried out in male mongrel dogs which were anesthetized with sodium pentobarbital (30 mg/kg). Polyethylene catheters were inserted into the right femoral artery and vein to monitor arterial blood pressure and to administer drugs, respectively. Bilateral carotid occlusion was accomplished via compression of the exposed carotid arteries with small plastic snares. Blood pressure and heart rate were recorded via a Statham transducer (P23Dc) and a Grass polygraph. Responses to the following tests were recorded: (a) 30-s bilateral carotid occlusion, and intravenous injections of (b) 4 μg/kg acetylcholine, (c) 4 μg/kg norepinephrine, (d) 8 μg/kg histamine, (e) 2 μg/kg isoproterenol, and (f) 0.5 μg/kg angiotensin II. One complete series of tests was carried out before, as well as 30 and 90 min after, the intravenous administration of compound **3a** dissolved in propylene glycol and water (1:1) at 0.5 mL/kg. This volume of vehicle had negligible effects on the recorded parameters and tests in anesthetized control dogs.

In another series of experiments, mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 μg/kg), and the right femoral artery and both femoral veins were cannulated. Blood pressure and heart rate were recorded from the femoral artery catheter via a Statham transducer (P23Dc) and a Grass polygraph. Blood samples were collected and drugs were administered via the femoral venous catheters. Sequential doses of compound **3a**, phentolamine, and minoxidil were given at 90 min intervals as 0.03, 0.3, and 3.0 mg/kg. Prazosin was administered in the same manner in doses of 0.003, 0.03, and 0.3 mg/kg. All drugs were dissolved in propylene glycol and water (1:1) at concentrations allowing volumes of 0.002, 0.02, and 0.2 mL/kg to be administered. Blood samples (1 mL) were analyzed for plasma renin activity by radioimmunoassay utilizing the New England Nuclear angiotensin I ($^{125}$I) radioimmunoassay kit, which is based on the method of Haber et al.[7]

**Methods for Baroreceptor Denervated Cats.** Cats of either sex were anesthetized with a mixture of sodium diallylbarbituric acid (60 mg/kg) and urethane (240 mg/kg) administered intraperitoneally. Each animal was positioned in a Kopf stereotaxic apparatus, and a trachea tube was surgically inserted. A femoral artery and vein were cannulated to monitor arterial blood pressure and to administer drugs, respectively. Blood pressure was recorded via a Statham transducer (P23Gc) and a Grass polygraph, while heart rate was recorded continuously with a Grass tachograph triggered by the electrocardiogram. Carotid sinus, aortic depressor, and vagus nerves were exposed and sectioned after reflection of a portion of the trachea and esophagus into the mouth. The sympathetic postganglionic external carotid nerve was isolated distal to its junction with the superior cervical ganglion. Nerve potentials were recorded monophasically under oil with a bipolar platinum electrode after capacity-coupled preamplification (low and high half-amplitude responses at 1 and 500 Hz). Nerve activity was displayed on the polygraph and quantitated using a Grass 7P10B cumulative integrator. Compound **3a** was dissolved in 0.1 M citric acid at a concentration of 1 mg/mL.

**Statistical Analysis.** Statistical analysis for most experiments was performed using the Student's $t$ test for unpaired comparisons. The values obtained at each time period in the drug-treated groups were compared to the corresponding values in the vehicle group. The 0.05 level of probability was used to indicate statistical significance.

(6) Weeks, J. R.; Jones, J. A. *Proc. Soc. Exp. Biol. Med.* **1960**, *104*, 646.

(7) Haber, E.; Koerner, T.; Page, L.; Kliman, B.; Purnode, A. *J. Clin. Endocrinol.*, **1969**, *29*, 1349.

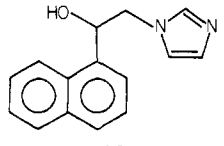
# 1-(Naphthylalkyl)-1*H*-imidazole Derivatives, a New Class of Anticonvulsant Agents[1]

Keith A. M. Walker,* Marshall B. Wallach, and Donald R. Hirschfeld

*Syntex Research, Palo Alto, California 94304.* *Received June 3, 1980*

Potent anticonvulsant activity has been demonstrated for a large number of 1-(naphthylalkyl)-1*H*-imidazoles containing a variety of functional groups in the alkylene bridge. The presence of a small oxygen function in the bridge, in general, confers a high therapeutic index between anticonvulsant and depressant activity. Clinical expectations are discussed for 1-(2-naphthoylmethyl)imidazole hydrochloride (**5**), which is undergoing development for testing in humans.

The new naphthalene compound **42**, prepared in connection with our interest in imidazole-containing antifungal agents, was submitted to pharmacological screening in the mouse based on its structural resemblance to phenethylamines. Following the finding of anticonvulsant activity,




**42**

and in view of the clearly expressed need[2] for more selective and less toxic anticonvulsant drugs, we initiated a synthetic program based on this lead. A series of analogues of **42** was prepared and evaluated for anticonvulsant activity in the maximal electroshock assay, with the goal of identifying a compound with an enhanced therapeutic index relative to currently available drugs.

**Chemistry.** All but four of the title compounds are *N*-(naphthoylalkyl)imidazoles or are synthetically accessible therefrom. The ketones **5**–**18** were prepared by al-

(1) Contribution no. 557 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.

(2) R. L. Krall, J. K. Penry, B. G. White, H. J. Kupferberg, and E. A. Swinyard, *Epilepsia*, **19**, 409–428 (1978). For a discussion of the side effects of anticonvulsant drugs, see M. J. Eadie, *Drugs*, 17, 213 (1979).

0022-2623/81/1824-0067$01.00/0 