Synthesis and Antihypertensive Activity of a Series of 8-Substituted 1-Oxa-3,8-diazaspiro[4.5]decan-2-ones[1]

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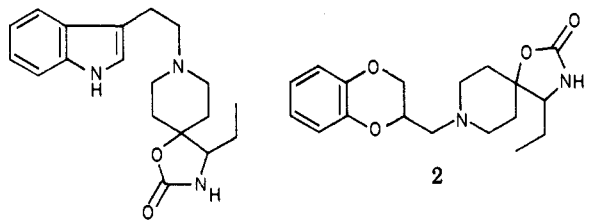
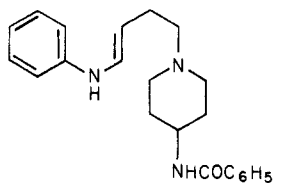
Forty-three new 1-oxa-3,8-diazaspiro[4.5]decan-2-ones optionally substituted with 2-(3-indolyl)ethyl, 3-(2-methoxyphenoxy)-2-hydroxypropyl, or 2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl at the 8 position were prepared for screening as antihypertensive agents in the spontaneous hypertensive rat. For the 8-[2-(3-indolyl)ethyl] compounds the most active were those substituted in the 4 position, where activity was at maximum with the 4-ethyl compound (1). The 8-[3-(2-methoxyphenoxy)-2-hydroxypropyl] compounds were less active than their 1,4-benzodioxane counterparts, which were tested as mixtures of erythro and threo diastereoisomers. Both the 4-ethyl-8-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-substituted **38** and (*S*)-3-methyl-8-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-substituted **42** were designed as mixed α- and β-adrenergic receptor blockers. Both compounds lowered blood pressure, but they gave no evidence of working as β-adrenergic blockers. Examination of 8-[2-(3-indolyl)ethyl]-1-oxa-3,8-diazaspiro[4.5]-decan-2-one (**8**) and 3-methyl-8-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one (**29**) in the dog showed them to be α-adrenergic blockers. Compound **29** was primarily an α_2-adrenoceptor antagonist, while **8** was more skewed toward α_1-adrenoceptor antagonism. Tilt-response studies for evaluating the potential for producing orthostatic hypotension showed that both **8** and **29** had little potential for avoiding orthostatic hypotension at therapeutically effective doses.

Previous reports on the α-adrenergic receptor blocking properties of 1-oxa-3,8-diazaspiro[4.5]decan-2-ones attracted us to the possibility of developing an antihypertensive agent through further modification of this series.[2-6] We selected compounds **1**[4] and **2**[6] for further modification.



1

2



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The choice of **1**[7] was based on its remote structural similarity to indoramin (**3**), an α-adrenergic blocker which also produces a slight bradycardia.[8] Compound **2** was selected to test the possibility of changing its 8-[(1,4-benzodioxan-2-yl)methyl] substituent into a functioning β-adrenergic receptor blocking unit while also attempting to retain α-adrenergic blocking properties. Such a "symbiotic" hybrid[9]—provided that both biological activities were operative at roughly the same dose—might lower blood pressure through α-adrenergic blockade while simultaneously controlling any reflex heart rate increase through β-adrenergic blockade.[10]

One might seriously question whether the analogues resulting from the proposed variations could be expected to function as β-adrenergic blockers, since they would contain a tertiary amino group in the putative β-adrenergic blocking pharmacophore. In addressing this point it is certainly worthwhile to note that while all of the clinically useful β-adrenergic blockers contain a secondary amino group in the (aryloxy)propanolamine unit, the literature also has many examples of potent β-adrenergic blocking compounds that contain a tertiary amino group in their (aryloxy)propanolamine unit.[11,12] The essential point is that β-adrenergic blocking activity is not always abolished by producing the tertiary amine modification in the (aryloxy)propanolamine unit. Moreover, one also finds that a similar situation holds for tertiary amine variations of the arylethanolamine class of adrenergic receptor blockers, as was recently demonstrated with a series of mixed α- and β-adrenergic receptor blockers related to medroxalol.[13] Therefore, we felt confident that modification of **2** through insertion of a hydroxymethyl group would produce compounds that would have a realistic chance of functioning both as α- and β-adrenergic blockers, even though the "β-adrenergic blocking" pharmacophore would necessarily contain a tertiary amino group.

(1) Contribution no. 576 from the Institute of Organic Chemistry.
(2) Maillard, J.; Delaunay, P.; Langlois, M.; Vo Van, T. *Bull. Soc. Chim. Fr.* **1970**, 1389.
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(5) Maillard, J.; Langlois, M.; Vo Van, T.; Delaunay, P.; Morin, R.; Benharkate, M.; Manuel, C.; Motosso, F. *Eur. J. Med. Chem.* **1973**, *8*, 393.
(6) Maillard, J.; Langlois, M.; Vo Van, T.; Morin, R.; Benharkate, M.; Ple, P. *Eur. J. Med. Chem.* **1974**, *9*, 128.
(7) Compound **1** was previously tested only for analgesic activity.[4]
(8) Archibald, J. L.; Alps, B. J.; Cavalla, J. F.; Jackson, J. L. *J. Med. Chem.* **1971**, *14*, 1054.
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(10) For information on labetalol, a prominent example of a combined α and β blocker, see: Brittain, R. T.; Levy, G. T. *Br. J. Clin. Pharmocol.* **1976**, *3*(Suppl 3), 681. Dollery, C. T. *Ibid.* **1976**, *3*(Suppl. 3), 823.
(11) Crowther, A. F.; Smith, L. H. *J. Med. Chem.* **1968**, *11*, 1009.
(12) Howe, R.; Rao, B. S.; Chodnekar, M. S. *J. Med. Chem.* **1970**, *13*, 169.
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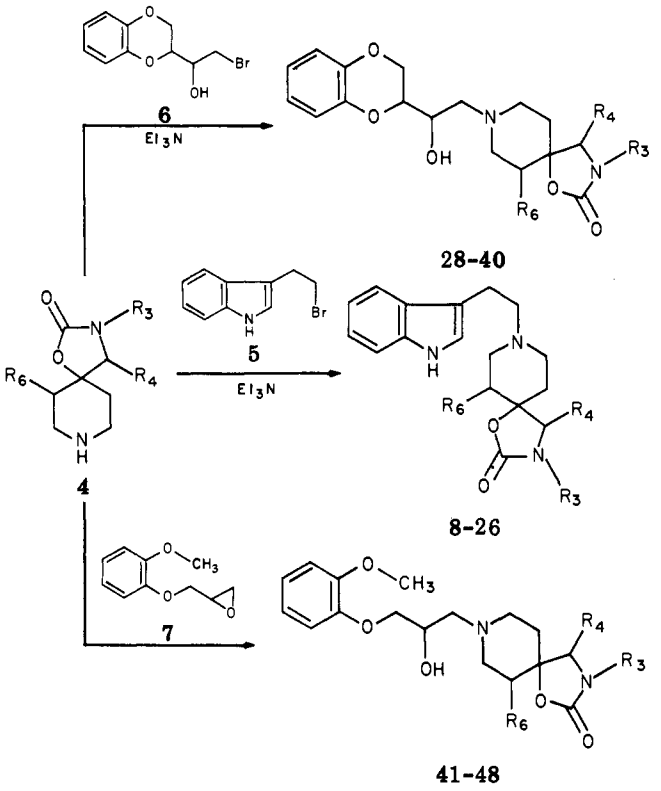
Scheme I



Chemistry. The preparation of 8-substituted 1-oxa-3,8-diazaspiro[4.5]decan-2-ones (Table I) as shown in Scheme I involved the condensation of the generalized spirocycle **4** with bromide **5** or **6** or with epoxide **7**. The intermediates **4** were obtained by hydrogenolytic removal of either an 8-benzyl or an 8-(carbobenzyloxy) blocking group from precursors that were prepared according to Scheme II.

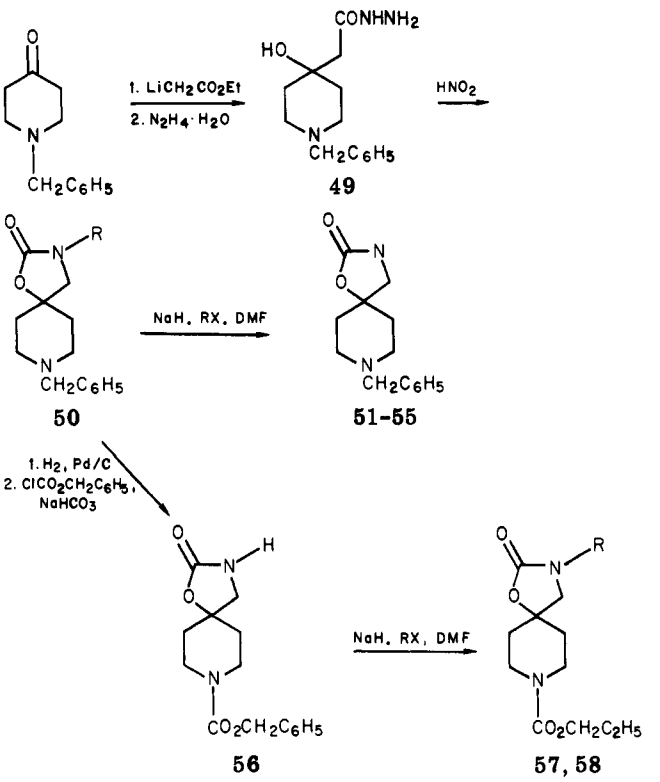
The 8-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-substituted compounds **28–40** were produced as mixtures of erythro and threo diastereoisomers. The diastereoisomeric pairs showed only minor separation by TLC, and therefore it was not possible to assay the relative compositions of these isomer mixtures. No conditions (chromatography or recrystallization) were found for effecting separation into individual diastereoisomers. Accordingly, these compounds were evaluated as mixtures for their antihypertensive activity.

Method A of Scheme II was used to prepare the 3-substituted compounds **51–55**, **57**, and **58** (Table II). Acylhydrazide **49**, which was prepared by addition of ethyl lithioacetate to *N*-benzyl-4-piperidinone, followed by condensation with hydrazine, was converted to **50**[14] by way of a Curtius rearrangement. Alkylation of the sodium salt of **50** with a variety of alkyl halides gave **51–55**. Attempted alkylation of the sodium salt of **50** with methyl iodide or benzyl bromide failed, presumably because of quaternization; therefore, **50** was converted to the carbobenzyloxy compound **56**, which was smoothly alkylated to give **57** and **58**.

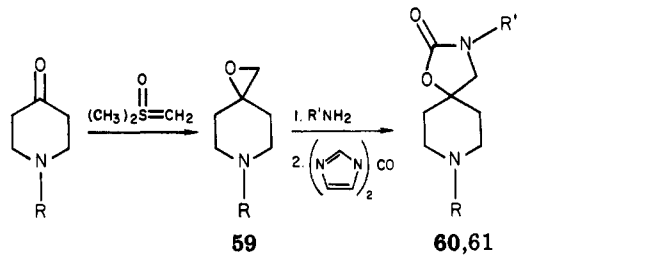
Method B of Scheme II was an epoxide-based route. Epoxide **59**[15] was readily opened by amines to give aminocarbinols, which were then combined with *N,N'*-carbonyldiimidazole to give **60** and **61**. The 6-substituted compounds **62** and **63** were prepared in a similar fashion. The structural assignments for **62** and **63** are based on the known thermodynamic course of the dimethylsulfoxonium

Scheme II. Preparation of Precursors to 4

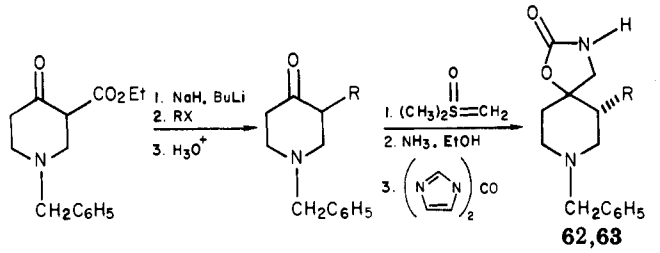
Method A



Method B

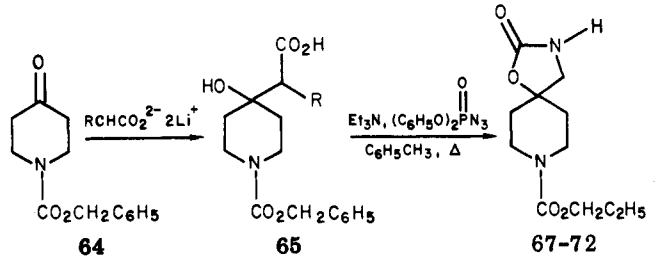


R = $CH_2C_6H_5$, $CO_2CH_2C_6H_5$



R = Et, *n*-Pr

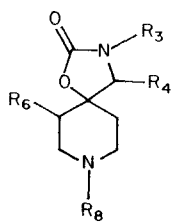
Method C



(14) (a) Netherlands Application 6 504 602; *Chem. Abstr.* **1969**, *64*, 12679*d*. (b) Regnier, G.; Canerari, R.; LeDouarec, J. C.; Laubie, M.; Duhault, J. *Eur. J. Med. Chem.* **1969**, *4*, 185.

(15) (a) Fishman, M.; Cruikshank, P. *J. Heterocycl. Chem.* **1968**, *5*, 467. (b) Popp, F. D.; Watts, R. F. *Ibid.* **1978**, *15*, 675.

Table I. 1-Oxa-3,8-diazaspiro[4.5]decan-2-ones and Antihypertensive Activity in Spontaneously Hypertensive Rats

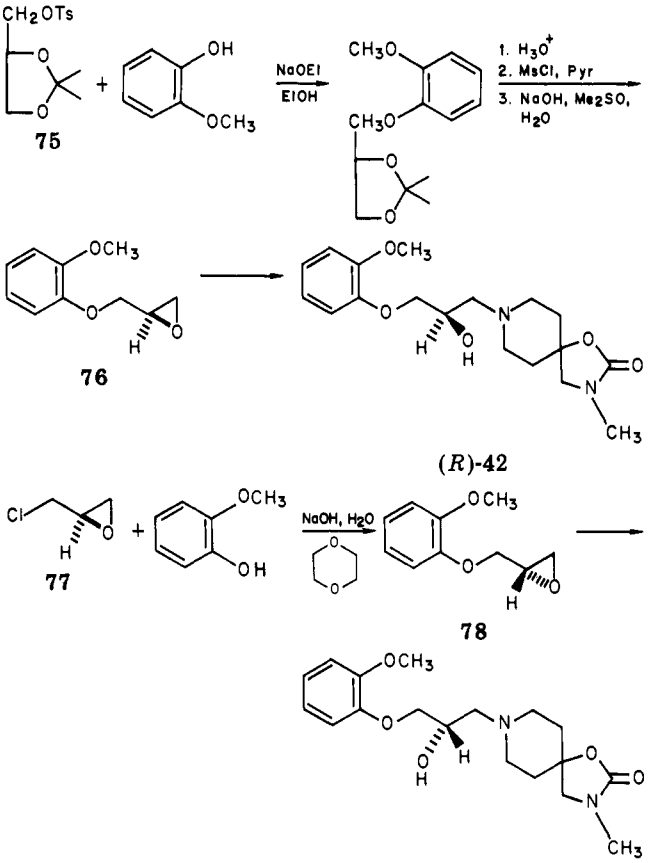


no.	R_3	R_4	R_6	R_8[a,b]	yield,[c] %	mp, °C	mp, °C, of the HCl salt	formula[d]	dose, mg/kg po	% fall in systolic blood pressure[e] 1 h	2 h	3 h	4 h	log D^f
8	H	H	H	IE	45	183–185	249–253	$C_{17}H_{22}ClN_3O_2$[g]	75	14	10	8	11	1.45
									50	16	10	7	8	
9	CH_3	H	H	IE	45	187–189	238–242	$C_{18}H_{24}ClN_3O_2$	75	23	18	8	9	1.73
									50	*	*	*	*	
10	CH_2CH_3	H	H	IE	32	indef	238–241	$C_{19}H_{26}ClN_3O_2$	50	*	*	*	*	1.92
11	$CH_2CH_2CH_3$	H	H	IE	58	141–143	227–230	$C_{20}H_{28}ClN_3O_2$[h]	50	14	*	*	*	2.36
12	$CH(CH_3)_2$	H	H	IE	57	137–138	248–252	$C_{20}H_{28}ClN_3O_2$	75	22	9	*	*	2.40
13	$CH_2CH_2CH_2CH_3$	H	H	IE	63	129–131	190–192	$C_{21}H_{30}ClN_3O_2 \cdot 0.5H_2O$[i]	50	*	*	*	*	
14	$CH_2C_6H_5$	H	H	IE	23	indef	225–230	$C_{24}H_{28}ClN_3O_2$	50	*	*	*	*	2.91
15	$CH_2CH_2C_6H_5$	H	H	IE	45	143–145	232–238	$C_{25}H_{30}ClN_3O_2$	50	*	*	*	*	2.95
16	$CH_2CH_2OCH_3$	H	H	IE	52	oil	168–170	$C_{20}H_{28}ClN_3O_3$[j]	50	21	*	*	*	
17	H	CH_3	H	IE	41	199–203	242–247	$C_{18}H_{24}ClN_3O_2$	50	18	*	*	*	1.43
1	H	CH_2CH_3	H	IE					50	23	27	17	22	1.95
									50	39	27	26	17	
18	H	$CH_2CH_2CH_3$	H	IE	18	218–220	252–260	$C_{20}H_{28}ClN_3O_2$	50	36	16	12	*	2.31
19	H	$CH(CH_3)_2$	H	IE	24	255–258	260–267	$C_{20}H_{28}ClN_3O_2$	50	26	17	*	*	
20	H	$CH_2CH_2CH_2CH_3$	H	IE	78	227–228	235–237	$C_{21}H_{29}N_3O_2$[g]	50	24	15	14	*	
21	H	$CH_2CH(CH_3)_2$	H	IE	45	215–218	265–270	$C_{21}H_{30}ClN_3O_2 \cdot H_2O$[k,l]	50	27	22	12	*	
22	H	C_6H_5	H	IE	27	181–187	187–190	$C_{23}H_{26}ClN_3O_2 \cdot 0.5H_2O$[i]	50	*	*	*	*	2.61
23	H	$CH_2C_6H_5$	H	IE	48	238–240	255–260	$C_{24}H_{27}N_3O_2$[g]	75	13	*	*	*	2.68
24	H	H	CH_2CH_3	IE	48	79–81	238–241	$C_{19}H_{26}ClN_3O_2$	50	16	19	*	*	2.01
25	H	H	$CH_2CH_2CH_3$	IE	32	76–68	237–238	$C_{20}H_{27}N_3O_2$[g]	50	21	*	*	*	2.42
26	CH_3	CH_2CH_3	H	IE	42	190–193	227–230	$C_{20}H_{28}ClN_3O_2$	50	*	*	*	*	2.14
27 (1·MeI)						175–179		$C_{20}H_{28}IN_3O_2$[m]	50	20	*	*	*	
28	H	H	H	BHE	29	indef	235–247	$C_{17}H_{23}ClN_2O_5$	100	24	14	11	16	0.98
									50	28	21	12	*	
29	CH_3	H	H	BHE	63	indef	240–250	$C_{18}H_{23}ClN_2O_5 \cdot H_2O$[k]	50	28	21	16	14	1.43
									25	27	*	15	*	
30	CH_2CH_3	H	H	BHE	21	indef	indef	$C_{19}H_{27}ClN_2O_5$	50	32	18	15	11	
									25	18	9	*	*	
31	$CH_2CH_2CH_3$	H	H	BHE	32	indef	240–244	$C_{20}H_{29}ClN_2O_5$	50	*	*	*	*	
32	$CH(CH_3)_2$	H	H	BHE	37	indef	245–253	$C_{20}H_{29}ClN_2O_5$	50	26	20	16	16	2.05
									25	14	*	*	*	
33	$CH_2CH_2CH_2CH_3$	H	H	BHE	37	indef	239–244	$C_{21}H_{31}ClN_2O_5$	50	*	*	*	*	
34	C_6H_5	H	H	BHE	39	115–137	217–228	$C_{23}H_{27}ClN_2O_5$	50	16	*	*	*	
35	$CH_2C_6H_5$	H	HG	BHE	38	109–114	232–255	$C_{24}H_{29}ClN_2O_5$	50	*	*	*	*	
36	$CH_2CH_2C_6H_5$	H	H	BHE	46	indef	215–230	$C_{25}H_{31}ClN_2O_5$	50	14	*	*	*	2.79
37	H	CH_3	H	BHE			242–250	$C_{18}H_{25}ClN_2O_5$	100	15	15	14	*	1.21
									50	*	*	*	*	
38	H	C_2H_5	H	BHE	17	174–176	indef	$C_{19}H_{26}N_2O_5$[g]	50	47	43	32	40	

39	H	C_6H_5	H	BHE	17	167–175	158–170	$C_{23}H_{27}ClN_2O_5$	50	*	*	*	*	2.41
40	H	$CH_2C_6H_5$	H	BHE	59	180–195	178–190	$C_{24}H_{29}ClN_2O_5 \cdot 0.5H_2O^i$	50	*	*	*	*	2.41
2									50	51	54	42	42	
									12.5	22	14	−13	−11	
41	H		H	MPHP	68	124–125	indef	$C_{17}H_{24}N_2O_5$	50	*	*	*	*	0.69
42	CH_3		H	MPHP	36	indef	153–155	$C_{18}H_{27}ClN_2O_5$	50	15	*	19	7	0.96
									25	9	*	*	*	
(*R*)-42	CH_3		H	MPHP	44	131–132	167–169	$C_{18}H_{26}N_2O_5$[g]	50	10	5	*	*	
(*S*)-42	CH_3		H	MPHP	71	128–130	indef	$C_{18}H_{26}N_2O_5$[g]	50	25	16	13	10	
43	CH_2CH_3		H	MPHP	65	122–123	162–164	$C_{19}H_{29}ClN_2O_5$	50	11	*	*	*	
44	$CH_2CH_2CH_3$		H	MPHP	91	95–96	170–171	$C_{20}H_{31}ClN_2O_5$	50	*	*	*	*	
45	$CH(CH_3)_2$		H	MPHP	72	108–110	135–140	$C_{20}H_{31}ClN_2O_5$	50	*	*	*	*	
46	$CH_2CH_2CH_2CH_3$		H	MPHP	97	73–76	185–190	$C_{21}H_{33}ClN_2O_5$	50	*	*	*	*	2.19
47	$CH_2C_6H_5$		H	MPHP	52	oil	178–180	$C_{24}H_{31}ClN_2O_5$	50	*	*	*	*	
48	$CH_2CH_2C_6H_5$		H	MPHP	33	oil	152–155	$C_{25}H_{33}ClN_2O_5$	50	*	*	*	*	
3 (indoramin)									50	33	20	11	13	2.13[n]
phentolamine									50	37	30	19	16	0.82[o]

[a] IE = 2-(3-indolyl)ethyl; BHE = 2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl; MPHP = 3-(2-methoxyphenoxy)-2-hydroxypropyl. [b] All compounds having R_8 = BHE were mixtures of erythro and threo diastereoisomers. [c] Yield refers to the condensation step in Scheme I. [d] Elemental analyses were within 0.4% of theory and, unless otherwise noted, they were obtained for the hydrochloride salt. [e] There were four rats per dosage group. Percentage falls in systolic blood pressure were recorded at the indicated times after dosing on the 2nd day of dosing. Systolic pressures in the controls started at about 200 mmHg and varied over the range of 180 to 220 mmHg during the 4-h measurement period. Values in the table are statistically significant ($p \leq 0.05$) relative to control values; asterisks indicate nonsignificant ($p \geq 0.05$). [f] 1-Octanol distribution coefficient determined by HPLC method at pH 7.4 (phosphate buffer). See Unger, S. H.; Cook, J. R.; Hollenberg, G. S. *J. Pharm. Sci.* **1978**, *67*, 1364. [g] The elemental analysis was obtained with the free base. [h] Calcd for $C_{20}H_{28}ClN_3O_5$: C, 63.56; H, 7.47; N, 11.12; Cl, 9.38. Found: C, 63.26; H, 7.63; N, 11.04; Cl, 8.93. [i] The hydrochloride salt elemental analysis corresponded to a hemihydrate. [j] Calcd for $C_{20}H_{28}ClN_3O_3$: C, 60.98; H, 7.17; N, 10.67. Found: C, 60.42; H, 6.91; N, 10.46. [k] The hydrochloride salt elemental analysis corresponded to a monohydrate. [l] Calcd for $C_{21}H_{30}ClN_3O_2 \cdot H_2O$: C, 61.52; H, 7.87; N, 10.25; Cl, 8.65. Found: C, 61.87; H, 8.03; N, 9.84; Cl, 8.80. [m] Analysis was for C, H, and N. [n] Shake flask determination, pH 7.4 (phosphate, sodium chloride). See Unger, S. H.; Chiang, G. H. *J. Med. Chem.* **1981**, *24*, 262. [o] 1-Octanol distribution coefficient determined by HPLC method at pH 7.4 (phosphate, sodium chloride, 0.004 M dimethyloctylamine). See reference in footnote *n*.

Scheme III. Preparation of (*R*)- and (*S*)-42



methylide epoxidation,[16] wherein the incoming methylene would be expected to end up trans to the original α-carbonyl substituent.

Method C of Scheme II was used to prepare the 4-substituted derivatives **67–72**. By this method **64** was converted to acid **65** by addition of an α-lithiocarboxylate. The conversion of **65** to the spirocycles **67–72** was accomplished by treatment with diphenylphosphoryl azide.[17] This two-step method was more convenient than the previously reported procedures for making 4-substituted 1-oxa-3,8-diazaspiro[4.5]decan-2-ones.[18]

Procedures used in making (*R*)- and (*S*)-**42** are outlined in Scheme III. The epoxide enantiomers **76** and **78** were both derived from the same chiral source, D-mannitol: the key intermediate **75** was readily obtained from D-mannitol in four steps,[19] and **75** was converted to **77** in five steps.[20] The melting points and optical rotations of **76** (mp 52–54 °C; $[\alpha]_D$ −11.7°) and **78** (mp 43–47 °C; $[\alpha]_D$ +13.6°) did not match exactly. From NMR measurements using the chiral shift reagent tris[3-(heptafluorobutyryl)-*d*-camphorato]europium(III), it was reported that (*R*)-epichlorohydrin (**77**), the precursor of **78**, had a chiral purity of 97 ± 2%.[20]

Both **76** and **78** were evaluated for their chiral purity using tris[3-(trifluoroacetyl)-*d*-camphorato]europium(III)

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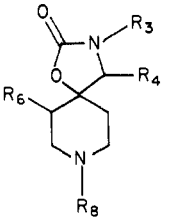
Table II. Intermediate 8-Benzyl- and 8-(Carbobenzyloxy)-1-oxy-3,8-diazaspiro[4.5]decan-2-ones



no.	R_3	R_4	R_6	R_8[a]	prep method	mp, °C	formula	anal.[b]
51	CH_2CH_3	H	H	Bzl	A	105-106	$C_{16}H_{22}N_2O_2$	C, H, N
52	$CH_2CH_2CH_3$	H	H	Bzl	A	98-99	$C_{17}H_{24}N_2O_2$	C, H, N
53	$CH(CH_3)_2$	H	H	Bzl	A	118-120	$C_{17}H_{24}N_2O_2$	C, H, N
54	$CH_2CH_2CH_2CH_3$	H	H	Bzl	A	80.5-81	$C_{18}H_{26}N_2O_2$	C, H, N
55	$CH_2CH_2C_6H_5$	H	H	Bzl	A	156-157	$C_{22}H_{26}N_2O_2$	C, H, N
57	CH_3	H	H	Cbz	A	oil	$C_{16}H_{20}N_2O_4$	C, H, N
58	$CH_2C_6H_5$	H	H	Cbz	A	oil	$C_{22}H_{24}N_2O_4$	C, H, N
60	C_6H_5	H	H	Cbz	B	100-102	$C_{21}H_{22}N_2O_4$	C, H, N
61	$CH_2CH_2OCH_3$	H	H	Bzl	B	79-80	$C_{17}H_{24}N_2O_3$	C, H, N
62	H	H	CH_2CH_3	Bzl	B	oil		c
63	H	H	$CH_2CH_2CH_3$	Bzl	B	oil		c
66	H	CH_3	H	Bzl	d	157-158	$C_{15}H_{20}N_2O_2$	C, H, N
67	H	CH_2CH_3	H	Cbz	C	oil	$C_{17}H_{22}N_2O_4$	C, H, N
68	H	$CH(CH_3)_2$	H	Cbz	C	oil	$C_{18}H_{24}N_2O_4$	C, H, N
69	H	$CH_2CH_2CH_2CH_3$	H	Cbz	C	151-152	$C_{19}H_{26}N_2O_4$	C, H, N
70	H	$CH_2CH(CH_3)_2$	H	Cbz	C	155-157	$C_{19}H_{26}N_2O_4$	C, H, N
71	H	$CH_2C_6H_5$	H	Cbz	C	119-121	$C_{22}H_{24}N_2O_4$	C, H, N
72	H	C_6H_5	H	Cbz	C	168-169	$C_{21}H_{22}N_2O_4$	C, H, N
73	H	$CH_2CH_2CH_3$	H	Bzl	e	135-137	$C_{17}H_{24}N_2O_2$	C, H, N
74	CH_3	CH_2CH_3	H	Cbz	f	oil	$C_{18}H_{24}N_2O_4$	C, H, N

[a] Bzl = $CH_2C_6H_5$; Cbz = $CO_2CH_2C_6H_5$. [b] Elemental analyses were within 0.4% of theory. [c] Compound not characterized at this stage, but carried onto final product in Table I. [d] Method was the same as for **50**, except ethyl propionate was the starting material. See Experimental Section. [e] The Hoffmann hypobromite-based method of ref 18 was used to prepare this compound. [f] Prepared by alkylation of **67** with sodium hydride/methyl iodide.

(Eu-Opt). The best separation on a *d,l* mixture of the two isomers occurred on the OCH_3 signal, where a difference of 10 Hz was observed between the two optical isomers at a molar ratio of 8:1 epoxide to Eu-Opt. Subsequently, the areas under the OCH_3 peaks for **76** and **78** were analyzed at 8:1 ratios of epoxide to Eu-Opt. The chiral purity of **78** was 98 ± 1% and the chiral purity of **76** was 93 ± 2%. The chiral purity determined for **78** is within the limits that were reported for its antecedent **77**.[20] The value for the chiral purity of **76** indicates that some racemization occurred at one or more of the intermediate stages in synthesis. One likely source of racemization is at the intermediate mesylation step leading to **76** in Scheme III. Any formation of a secondary mesylate at that stage would lead to an inversion of the chiral center upon hydroxide-promoted epoxide formation.

Structure–Activity Relationships. The compounds in Table I were evaluated for their antihypertensive effects in male, Okamoto-Aoki strain, spontaneous hypertensive rats (SHR). Data in Table I represent the percentage decrease in systolic blood pressure for the drug-treated group relative to the value for the untreated control.

Activity variations within the 8-[2-(3-indolyl)ethyl] compounds are clearly a function of substituent bulk and/or lipophilicity and also of the position of substitution. For the 3-substituted series **8–16** at the 50 mg/kg dose, the activity declines for substituents larger or more lipophilic than hydrogen. In the 4-substituted series (**1** and **17–23**) the activity is maximum with ethyl (**1**) and it declines gradually as the size and/or lipophilicity of the 4-substituent is increased. The activity progressions within sets of positional isomers (ethyl isomers: **1**, **10**, and **24**; *n*-propyl isomers: **11**, **18**, and **25**) show that for a given substituent, position 4 is more important than position 6, which in turn is more important than position 3. Moreover, since there is little variation in lipophilicity (log *D* values in Table I) within each isomer set, the wide variation in activity indicates a high dependence on steric accessibility to the receptor and a relatively lower dependence on drug transport.

Further indications of the specificity of receptor fit are seen in the activity changes that accompany modification of the maximally active **1**. Addition of a methyl group to position 3 gives the inactive compound **26**. Having achieved an "optimum" fit with **1**, the receptor is very sensitive to any additional bulk at position 3. Quaternization of **1** with methyl iodide abolishes activity (**27**), a result which implies the need for having a nonbonded electron pair at N-8 in order to achieve good interaction with the receptor. Of course, quaternization greatly alters drug transport, and that change might also explain the loss of activity.

In the 8-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl] series (**28–40**), the effect of substitution at the 3 position was slightly different from that found in the indole series. Compounds **29** (3-Me), **30** (3-Et), and **32** (3-*i*-Pr) were all significantly active in the SHR at the 50 mg/kg dose, whereas in the indole series the optimum 3-substituent was hydrogen.

One of our initial goals was to hybridize a β-adrenergic blocker with **2**. Insertion of a CHOH moiety into **2** gave **38**, a compound of equivalent potency. Unfortunately, while this modification produced a molecule containing a formal β-adrenergic blocker substructure ($ArOCH_2CHOHCH_2N$), it seems unlikely that it produced any relevant β-adrenergic blockade: at a 50 mg/kg dose of **38** in the SHR, the drop in blood pressure was accompanied by reflex increases in heart rate of from 15 to 30% ($p < 0.05$) over the 4-h test period. Because **38** was a mixture of four diastereoisomers, we did not examine it further for a direct

Table III. Changes in Mean Arterial Pressure in Pentobarbital-Anesthetized Dogs

	change in mean arterial pressure, mmHg					
compd[a]	iv dose:[b] 0.01 mg/kg	0.1 mg/kg	0.316 mg/kg	1 mg/kg	3.16 mg/kg	10 mg/kg
8		−2, −6		−11, −19		−8, −6
29	+4	+4	0	−25, −13	−18	
3		−5, −13		−28, −45		−38
phentolamine		−9		−11		−33

[a] Each compound was administered to two dogs; however, each dose was not given to both dogs. Administration of a saline control produced a *transient* 0-2 mmHg fall in pressure. [b] Each dose represents the full dose administered (not cumulative dose). The change in mean arterial pressure is the maximum change induced by the given dose at 10-15 min following administration of that dose. Responses do not represent cumulative change from pretreatment blood pressure. Confidence limits for each measurement are ± 3 mmHg.

Table IV. Percent Inhibition of the Pressor Responses to Epinephrine, Norepinephrine, and Phenylephrine in Pentobarbital-Anesthetized Dogs

	% inhibn of pressor response					
compd	iv dose: 0.1 mg/kg	0.316 mg/kg	1.0 mg/kg	3.16 mg/kg	5.0 mg/kg	10.0 mg/kg
	A. Epinephrine (1 μg/kg iv)					
8	26, >100[a]		83, >100[a]			97[b]
29			>100[b]			
indoramin	54, 74[a]		71, 92[a]			>100[b]
phentolamine	41[b]		>100[b]			>100[b]
	B. Norepinephrine (0.75 μg/kg iv)					
29		41[b]	60[b]	69[b]		
indoramin	21[b]		23[b]			
phentolamine			>100[b]		>100[b]	>100[b]
	C. Phenylephrine (7.5 μg/kg)					
8	17[b]		84[b]			100[b]
29	0[b]		44[b]			
indoramin	65[b]		83[b]			93[b]
phentolamine	42[b]		86[b]			100[b]

[a] Compound was administered to two dogs. [b] Compound was administered to one dog.

evaluation of its α and β-adrenergic properties. Instead, we chose to examine the *o*-methoxyphenoxypropanol **42**, a system in which the stereochemistry could be defined more precisely than was the case with **38**.

In a further attempt to achieve a symbiotic combination of an α- and a β-adrenergic blocker, we prepared and evaluated the *R* and *S* enantiomers of **42**. Antihypertensive activity resided primarily with the *S* enantiomer. Since the absolute configuration in (*S*)-**42** corresponded to that for the β-adrenergic blockers propranolol[21] and practolol,[22] it was tempting to assume that the structural requirements for both α- and β-adrenergic receptor blockade were simultaneously operational in (*S*)-**42**. Unfortunately, examination of iv-administered (*S*)-**42** (0.3-3.0 mg/kg) in the dog failed to show any blockade of either the heart rate or blood pressure response caused by administration of isoproterenol, thereby indicating no β-blocking activity for (*S*)-**42**. We therefore conclude that the antihypertensive superiority of (*S*)-**42** over the *R* isomer is due to a goodness of fit at the α-adrenergic receptor; moreover, the result suggests a similarity in structural acceptance criteria for antagonists at both α- and β-adrenergic receptors.

Pharmacological Mechanistic Studies. The two representative compounds, **8** and **29**, and the two standards, phentolamine and indoramine, were studied in pentobarbital-anesthetized dogs. All four compounds were hypotensive when administered iv (Table III), and the relative potencies were indoramin > phentolamine > **29** > **8**. All four compounds exhibited α-adrenergic blocking activity as indicated by their marked inhibition of pressor responses elicited by epinephrine, norepinephrine, and phenylephrine (Table IV). Neither **8** nor **29** blocked the pressor effects of angiotensin I, and neither compound blocked the depressor responses to bradykinin, histamine, or acetylcholine.

In order to evaluate their potential to cause orthostatic hypotension, all four compounds were tested for their ability to inhibit the compensatory response to vertical tilt (head up 90° from horizontal for 2 min) in α-chloralose-anesthetized dogs. Immediately upon tilting, the blood pressure of the anesthetized dog decreases markedly and then gradually increases ("compensates") toward the level observed in the supine position. Compounds that interfere with this reflex compensation—ganglionic blockers and adrenergic neuron blocking agents quite effectively block reflex compensation in this model—are likely to produce orthostatic hypotensive effects in man.[23] Both phentolamine (9.2 mg/kg iv) and indoramin (1 and 3 mg/kg iv) inhibited the compensatory rise in blood pressure. Compound **8** did not affect the compensatory response to tilt at dose levels up to 10 mg/kg iv; however, it also showed little affect on lowering blood pressure in the dog at that dose (Table III). Compound **29** at 10 mg/kg iv delayed the compensatory rise in blood pressure following tilt, and therefore it is likely that it would have a high potential for producing orthostatic hypotension in man.

Finally, **1**, **8**, and **29** were tested for α_1- and α_2-adrenergic blocking potential[24,25] using the isolated rat vas deferens.

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(23) (a) Pruss, T. R.; Johnson, R. *Arch. Int. Pharmacodyn.* **1967**, *169*, 295. (b) Antonaccio, M. J.; Robson, R. D.; Povalski, H. S. *Eur. J. Pharmacol.* **1973**, *22*, 23.

Table V. α_1- and α_2-Adrenoceptor Blockade. pA_2 Values[a]

compd	pA_2 (α_1) ± SE of mean	n	pA_2 (α_2) ± SE of mean	n	selectivity ratio (α_1/α_2)[b]
1	7.6 ± 0.21	2	6.0 ± 0.12	2	40.0
8	5.5 ± 0.17	2	<5.0	2	>3.0
29	4.5 ± 0.23	2	6.4 ± 0.12	2	0.013
prazosin	8.7 ± 0.06	11	5.6 ± 0.18	6	1258.9
phentolamine	7.9 ± 0.07	12	8.0 ± 0.07	12	0.794
yohimbine	6.2 ± 0.06	12	7.7 ± 0.08	12	0.032

[a] Determined in rat isolated, transversely bisected vas deferens preparation. [b] Antilog of the difference of the pA_2 values at α_1 and α_2 adrenoceptors.

Because it was known that prostatic and epididymal portions of the tissue vary considerably in both their sensitivity to agonists and their response to nerve stimulation,[26-28] we determined the affinity of antagonists for the α_1- and α_2-adrenoceptors by using the transversely bisected rat vas deferens. Antagonist activity at the α_2-adrenoceptor was assessed in the prostatic portions of the vasa by determination of the pA_2 value against the inhibitory effect of the α_2-adrenoceptor agonist xylazine on the contractile response of vasa to single pulse field stimulation. This response, although predominantly nonadrenergic in nature, has been shown to be subject to prejunctional α_2-adrenoceptor mediated inhibition.[26] Antagonism of the α_1-adrenoceptor was assessed by determination of the pA_2 value against the contractile effect of amidephrine, a selective α_1-adrenoceptor agonist in epididymal portions of vasa.[29] Data presented in Table V show that **8** is only modestly selective for postsynaptic α-adrenergic blockade, while **29** is strongly skewed toward presynaptic adrenergic blockade. While **29** could therefore be classed as a "presynaptic α-blocker", it was, nonetheless, effective in lowering blood pressure in the SHR. The blood pressure lowering effects of **29** could be ascribed to its α_1-adrenergic receptor blocking activity ($pA_2 = 4.5$) and/or to its working through some undetermined mechanism. Interestingly, since there was no simple correlation of activity at either receptor with lipophilicity of the three compounds, there is a strong likelihood of intrinsic structural differences between the two adrenergic receptor subtypes.

In summary, these mechanistic studies show that these 8-substituted 1-oxa-3,8-diazaspiro[4,5]decan-2-ones are moderately active antihypertensive agents in the rat. They have been shown through antagonism studies to lower blood pressure through α-adrenergic blockade. With the compounds that were studied in the tilt model there appeared to be little possibility for avoiding orthostatic hypotension at therapeutically effective doses.

Experimental Section

Melting points (uncorrected) were obtained on a Fisher-Johns apparatus, infrared spectra with a Perkin-Elmer 237 grating instrument, ^{13}C NMR with a Bruker 90, ^1H NMR using a Bruker WM 300, and mass spectra with either an Atlaswerke CH-4 or CH-7 instrument. Combustion analyses were obtained from Syntex Analytical Research and from Alfred Bernhardt, Muhlheim/Ruhr.

Antihypertensive Screen. After an initial training period, 24 male, Okamoto-Aoki strain, spontaneously hypertensive rats (Taconic Farms, Germantown, NY) were distributed into six groups of four animals with approximately equal mean systolic blood pressures. The six groups were studied concurrently in a 2-day procedure. Test compounds were randomly assigned to each group. Five groups received test substances, and one control group received vehicle only. On two consecutive mornings, a group of four rats was orally dosed with a test substance that had been dissolved or suspended in water at concentrations such that 0.1 mL of solution was administered per 10 g of body weight. Immediately after dosing on day 2, all 24 rats were put in restrainers and then into a heated chamber (30.0 ± 1.0 °C) for 4 h. Systolic blood pressures (tail cuff) were recorded using photoelectric transducers at 1, 2, 3, and 4 h after drug administration. The coccygeal arteries of the rats were simultaneously occluded by inflated tail cuffs that were automatically inflated to 300 mmHg and then deflated. Tail pulses were simultaneously recorded, along with a pressure curve on a recorder. Four consecutive (at 3-s intervals) traces were recorded for each rat at each hour after dosing. The systolic pressure was considered to be the pressure at the appearance of the first pulse. The mean systolic pressure of each rat at each observation time in both drug-treated and control groups was calculated. Systolic pressures in the controls varied over the range 180 to 220 mmHg during the 4-h measurement period. The mean values of the respective drug-treated and control groups were then compared using a 1-tail Student's t test. Statistical significance was considered to be $p \leq 0.05$.

General Cardiovascular Evaluation in the Dog. Dogs were anesthetized with sodium pentobarbital (35 mg/kg iv) and were instrumented to record blood pressure from a cannulated femoral artery. Heart rate was recorded by a cardiotachograph triggered by the R wave of a limb lead ECG. A femoral vein was cannulated for drug administration. Epinephrine (1 μg/kg), norepinephrine (0.75 μg/kg), phenylephrine (7.5 μg/kg), angiotensin I (0.3 μg/kg), acetylcholine (5 μg/kg), histamine (1–2 μg/kg), and bradykinin (3–5 μg/kg) were adminstered at approximately 10-min intervals before and after increasing dose levels for the four test compounds: phentolamine, indoramin, **8**, and **29**. Doses of test compounds were administered at 90-min intervals.

Tilt Studies. These were performed by the method of Pruss et al.[23a]

pA_2 Values. The α_1- and α_2-adrenoceptor blockade was assessed using the method outlined by Michel and Whiting.[30] Vasa deferentia were removed from male (200–300 g) Sprague–Dawley rats and placed in a petri dish containing oxygenated Krebs–bicarbonate solution (mM: NaCl, 119; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.0; $KH_2PO_4 \cdot 2H_2O$, 1.0–1.2; $CaCl_2 \cdot 6H_2O$, 2.5; $NaHCO_3$, 25.0; glucose, 11.1). Connective tissue was removed and the vasa were transversely bisected. Prostatic portions, 12 mm in length, and epididymal portions, 14 mm in length, were prepared. Stainless-steel threads (0.0004-cm diameter) were tied through the walls of the lumen at each end of the bisected portions, and the tissues were mounted under 0.5-g tension in 30 mL (prostatic portions) or 10-mL (epididymal portions) organ baths containing oxygenated Krebs–bicarbonate solution at 37 °C. Isometric contractions of the tissues were monitored on a Devices MX4 recorder and a Tektronix DM63 storage oscilloscope. The antagonist was added to the Krebs–bicarbonate solution bathing one tissue while the contralateral portion served as a control.

For α_2-adrenoceptor studies we used the prostatic portion of the vas deferens. Responses were elicited from contralateral prostatic portions of vasa deferentia by supramaximal single-pulse nerve stimulation (0.3-ms duration, 15 V, 15 mA) every 5 min using an S88 Grass stimulator and a pulse power amplifier. After a 45-min equilibration period, cumulative concentrations of agonist were increased when consecutive responses to field stimulation were identical (usually 20 min). Results were expressed as a percentage of the maximal inhibition of the response to single pulse nerve stimulation obtained in the control tissue.

For α_1-adrenoceptor studies, we used the epididymal portion of the vas deferens. After a 45-min equilibration period, con-

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centration–response curves to phenylephrine were obtained on both tissues. Each concentration of agonist was allowed to act for 45 s or until a maximal response was obtained before replacing the bathing fluid. A 6-min dose cycle was used, the Krebs–bicarbonate solution being replaced four times between additions. Responses were expressed as a percentage of the maximal response obtained in the control tissue.

The antagonistic potency of the test compounds at α-adrenoceptors was expressed in terms of the their pA_2 value. These values were obtained from the ratio of the doses of agonist causing 50% of the maximal response in the presence and absence of the test compound, according to the method of Arunlakshana and Schild.[31]

Scheme I. Method A. The 8-[2-(3-indolyl)ethyl]-substituted compounds in Table I were prepared by "method H" of Archibald et al.[8] The crude products obtained by this method were purified by filtration through 70–230 mesh silica gel (~20 g per gram of compound) using 10% MeOH–methylene chloride. Hydrochlorides were obtained by dissolving the compound in a minimum volume of 2-propanol and then adding a slight excess of concentrated HCl, followed by precipitation by addition of diethyl ether.

Method B. The 8-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-substituted compounds in Table I were prepared according to "method B" of Howe et al.[12] Purification and HCl salt formation were performed according to method A.

Method C. The 8-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-substituted compounds in Table I were prepared according to Archibald et al.[32] Purification and HCl salt formation were performed according to method A.

Scheme II (Method A). 8-Benzyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (50). To a 500-mL, three-neck flask equipped with a gas inlet tube, alcohol thermometer, rubber septum, and overhead mechanical stirrer were added 12.6 g (125 mmol) of diisopropylamine and 150 mL of THF. The solution (under argon) was cooled to −70 °C and 89 mL of 1.4 M *n*-butyllithium (124.6 mmol) in hexane was added over 5 min with a syringe. Ethyl acetate (11 g, 125 mmol) was added over 10 min at −70 °C. A solution of 18.9 g (100 mmol) of *N*-benzyl-4-piperidinone in 20 mL of THF was added dropwise over 10 min. The mixture was allowed to warm to ~20 °C and was poured onto 100 mL of diethyl ether. This solution was washed with two 150-mL portions of 3 N HCl. The combined HCl extract was washed with 100 mL of diethyl ether, basified with 20% NaOH, and extracted with two 100-mL portions of methylene chloride. The extract was dried over sodium sulfate and evaporated to give 26 g of ethyl (1-benzyl-4-hydroxy-4-piperidinyl) acetate, which was carried on without further purification.

A mixture of 6 g (21.7 mmol) of the above ester and 6 mL of 85% hydrazine hydrate was heated at 100 °C for 2 h. After 40 mL of water was added and the mixture was cooled in an ice bath, the acylhydrazide was collected by filtration: yield 3.3 g (58%); mp 157–158 °C. Anal. ($C_{14}H_{21}N_3O_2$) C, H, N.

A mixture of 9.93 g (37.8 mmol) of the above hydrazide in 60 mL of water was made acidic with HCl. The mixture was cooled to 10 °C in an ice bath, and a solution of 2.98 g (43.2 mmol) of sodium nitrite in 30 mL of water was added dropwise over 10 min. The stirred mixture was warmed to 60 °C and held at that temperature for 20 min. After the mixture was cooled and basified with 20% NaOH, the product **50** was collected by filtration: yield 6.3 g (68%); mp 182–183 °C (lit. mp 177–178 °C).[14]

Alkylation of 50: 3-Propyl-8-benzyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (52). To a stirred mixture of 2.4 g (50 mmol) of a 50% suspension of sodium hydride in mineral oil in 60 mL of DMF was added 10 g (40.7 mmol) of **50**. After 30 min, 7.6 g (61.6 mmol) of *n*-propyl bromide was added, and the mixture was heated at 80 °C for 3 h. The mixture was poured into 300 mL of 1 N HCl, and this mixture was extracted with three 100-mL portions of hexane. After the mixture was basified with 20% NaOH, the product was extracted into methylene chloride. The extract was dried over sodium sulfate and, after filtration and evaporation, gave a residue, which was recrystallized from hexane: yield 7.2 g (62%); mass spectrum, *m/e* 288 (M^+); IR (KBr) 1745, 1730 cm^{-1}.

8-(Carbobenzyloxy)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (56). A mixture of 15 g (60.9 mmol) **50**, 75 mL of EtOH, and 2 g of 10% Pd/C was shaken at 50 °C for 16 h in a Parr apparatus. After the mixture was cooled and filtered, the solvent was evaporated to give 9.7 g of crude 1-oxa-3,8-diazaspiro[4.5]decan-2-one. This material was taken up in 75 mL of water at 5 °C. To this solution were added 6.3 g of sodium bicarbonate and 10.9 g of benzyl chloroformate. After stirring in an ice bath overnight, the mixture was acidified with concentrated HCl and stirred at room temperature for 4 h. The product was extracted into methylene chloride and, after drying over sodium sulfate, the solvent was removed to give a residue, which upon trituration with diethyl ether gave 14.4 g (81%) of **56**: mp 126–128 °C; mass spectrum, *m/e* 290 (M^+).

Alkylation of 56: 3-Methyl-8-(carbobenzyloxy)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (57). To a stirred mixture of 1.85 g (43.9 mmol) of a 57% suspension of sodium hydride in mineral oil, 6 mL of methyl iodide, and 15 mL of DMF was added 9.1 g (31.4 mmol) of **56** in 30 mL of DMF. The mixture was stirred for 1 h at 60 °C and poured into 200 mL of water. The product was extracted into 200 mL of methylene chloride. The solvent was evaporated and the residue was washed with three 100-mL portions of hexane. The product was obtained as a thick oil after evaporation of residual solvent under vacuum: yield 8.95 g (94%); mass spectrum, *m/e* 304 (M^+).

Scheme II (Method B). 3-Phenyl-8-(carbobenzyloxy)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (60). A mixture of 3.8 g (15.4 mmol) of **59** and 5 g of aniline was heated in a stainless-steel bomb at 160 °C for 4 h. The crude product was transferred to a 500-mL flask, and the aniline was removed by steam distillation. The residue was isolated by methylene chloride extraction and chromatographed from 100 g of 70–230 mesh silica gel using 250 mL of 40% diethyl ether–hexane, followed by 350 mL of diethyl ether. Evaporation of the diethyl ether eluate gave 2.9 g of crude 1-(carbobenzyloxy)-4-hydroxy-4-(anilinomethyl)piperidine. This material (~8.5 mmol) was dissolved in 35 mL of THF, 1.94 g (12 mmol) of *N,N'*-carbonyldiimidazole was added, and the mixture was heated at reflux for 30 min. The solvent was removed by evaporation, and the residue was taken up in 200 mL of diethyl ether. The organic phase was washed with two 50-mL portions of 1 N HCl and dried (sodium sulfate). Removal of solvent by evaporation and recrystallization from diethyl ether–hexane afforded the crystalline product: yield 2.9 g (51% from **59**); mass spectrum, *m/e* 366 (M^+); IR (KBr) 1740, 1675 cm^{-1}.

(5*S,6*R**)-6-Ethyl-8-[2-(3-indolyl)ethyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one (24).** To a mechanically stirred mixture of 6.9 g (144 mmol) of a 50% mineral oil suspension of sodium hydride in 150 mL of THF at 0 °C was added dropwise over 20 min a solution of 35 g (133.6 mmol) of *N*-benzyl-3-carboethoxy-4-piperidinone in 120 mL of THF. After 30 min, 7.5 mL of 1.6 M *n*-butyllithium in hexane (156 mmol) was added via syringe over 15 min. Ethyl iodide (23.4 g, 150 mmol) was added, and the mixture was stirred for an additional 2.5 h at ~5 °C. The mixture was diluted with 250 mL of 10% HCl and extracted with diethyl ether. The aqueous phase was heated at ~90 °C for 3 h and then left at room temperature for 4 h. The crude product was obtained by basification with sodium bicarbonate, followed by extraction into diethyl ether. Evaporation of the ether extract, followed by chromatography on a column of 250 g of 70–230 mesh silica gel with 50% diethyl ether–hexane, gave 8.9 g of *N*-benzyl-3-ethyl-4-piperidinone (31%). This intermediate was converted to a spirooxirane in 98% crude yield by the procedure described for **59**.[14] A mixture of the spirooxirane (9.2 g) and 100 mL of 25% NH_3 in methanol was heated for 4 h at 100 °C in a stainless-steel bomb. Evaporation of the solvent gave 9.2 g of crude *N*-benzyl-3-ethyl-4-hydroxy-4-(aminomethyl)piperidine. A mixture of this aminocarbinol (~37 mmol), 8.1 g (50 mmol) of *N,N'*-carbonyldiimidazole, and 100 mL of THF was heated at reflux for 5 h. The THF was evaporated and the residue was taken up in 100 mL of methylene chloride. After the solution was washed with water, the solvent was evaporated, the residue was dissolved in 100 mL of THF, and 5 g of potassium *tert*-butoxide was added. After 16 h, the mixture was diluted with 200 mL of methylene

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chloride and 200 mL of 2 N HCl. The aqueous layer was washed with methylene chloride, basified with sodium hydroxide, and extracted with methylene chloride. Evaporation of the final extract gave 9.2 g (~91%) of 6-ethyl-8-benzyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one as a pasty solid. A mixture of this material, 150 mL of EtOH, and 750 mg of 10% Pd/C was hydrogenated for 8 h at 60 psi and 50 °C. After filtration and evaporation, there was obtained 2.7 g of solid 6-ethyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one. A mixture of this material (~14.7 mmol), 4.1 g (18.4 mmol) of 2-(3-indolyl)ethyl bromide, 12 mL of DMF, and 3 mL of triethylamine was heated for 20 h at 90 °C under argon. A crude product was obtained upon dilution with 100 mL of water. Chromatography using 125 g of silica gel eluting with 5% methanol–methylene chloride gave 2.3 g of **24**: IR (KBr) 3400, 1745, 1720 (sh) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 12.03 (CH_2), 19.15 (CH_2Ar), 22.98 (CH_2CH_3), 37.52 (C-10), 45.83 (C-6), 49.25 (CH_2N), 49.61 (C-4), 53.90 (C-9), 59.17 (C-7), 111.31 (C-5), 114.01, 118.82, 119.21, 121.62, 129.94, 127.57, 136.34, 159.85 (C-2). A hydrochloride was obtained using methanolic HCl–diethyl ether.

Scheme II (Method C). 4-Phenyl-8-(carbobenzyloxy)-1-oxa-3,8-diazaspiro[4.5]decan-2-one (72). To a 500-mL flask equipped with gas inlet tube, overhead mechanical stirrer, dropping funnel, and rubber septum were added 10.1 g (100 mmol) of diisopropylamine and 80 mL of THF. The mixture was cooled to −40 °C, and 67 mL 1.5 M *n*-butyllithium (100 mmol) was added over 5 min. The solution was warmed to 0 °C, and a solution of 6.8 g (50 mmol) of phenylacetic acid in 75 mL of THF was added. The mixture was stirred for 20 min at ~20 °C. The mixture was cooled to −78 °C, and a solution of 14 g (60 mmol) of *N*-(carbobenzyloxy)-4-piperidinone in 10 mL of THF was added dropwise over 15 min. This mixture was warmed to ~20 °C and was then poured into a mixture of 200 mL of diethyl ether and 100 mL of water. Three layers formed. The lowest layer contained phenylacetic acid and was discarded. The middle layer was diluted with 100 mL of water and washed with two 50-mL portions of diethyl ether. Acidification of the aqueous layer with concentrated HCl was followed by extraction with methylene chloride and evaporation of the organic extract to give 16 g of a thick gum. This material was dissolved in 150 mL of toluene, and 25 mL of toluene was distilled to remove water. To the toluene solution at ~20 °C were added 5 g of triethylamine and 11.9 g (43.3 mmol) of diphenylphosphoryl azide. This mixture was heated at reflux overnight. The solvent was removed by evaporation, and the residue was taken up in 250 mL of methylene chloride. This solution was extracted with two 75-mL portions of 1 N HCl and two 75-mL portions of 5% sodium bicarbonate. Evaporation of the solvent afforded the solid product: yield 11.05 g (60% based on phenylacetic acid); mass spectrum, *m/e* 366 (M^+).

Scheme III. (*R*)-2-(2,3-Epoxypropoxy)anisole (76). To a solution obtained from the reaction of 3.68 g of sodium (160 g-atoms) with 200 mL of EtOH were added 18.6 g (150 mmol) of guiacol and 39 g (136 mmol) of **75**.[19] The mixture was heated at reflux for 18 h, and the EtOH was removed by evaporation. The residue was mixed with 700 mL of diethyl ether and 150 mL of water. The ether layer was separated and washed with 150 mL of water, two 100-mL portions of 5% sodium hydroxide, and 100 mL of saturated sodium chloride solution. After drying (sodium sulfate) and evaporation there was obtained 28.3 g of an oil (~87%). This oil was stirred at 50 °C for 40 min with 200 mL of 0.01 N HCl. Evaporation under vacuum afforded 22.4 g of a solid. A stirred solution of this solid in 75 mL of pyridine was cooled to 0 °C, and 9.41 mL (13.83 g, 121 mmol) of mesyl chloride was added dropwise over 10 min. After 10 min, a solution of 18 g of sodium hydroxide in 94 mL of water and 78 mL of Me_2SO was added at −5 °C. After 15 min, this mixture was diluted with 170 mL of ice–water, and the product was extracted into three 120-mL portions of toluene. The combined extract was washed with four 120-mL portions of ice-cold 20% acetic acid, 120 mL of water, 120 mL of 5% sodium bicarbonate, and 120 mL of saturated sodium chloride solution. After the toluene was evaporated, the product was isolated by Kugelrohr distillation (120 °C, 0.1 mm): yield 9.95 g (41% based on **75**): mp 52–54 °C; $[\alpha]_D$ −11.7° (*c* 0.995, MeOH); mass spectrum *m/e* 180 (M^+). Anal. ($C_{10}H_{12}O_3$) C, H.

(*R*)-3-Methyl-8-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one [(*R*)-42]. A mixture of 1.37 g (7.6 mmol) of **76**, 1.29 g of 3-methyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one (obtained by hydrogenolysis of **57** in EtOH with 10% Pd/C), 5 mL of MeOH, and 20 mL of toluene was heated at reflux for 72 h. The cooled solution was diluted with 150 mL of diethyl ether, and a solid was isolated by filtration. This material was filtered through 25 g of 70–230 mesh silica gel with 150 mL of 10% MeOH–methylene chloride. Evaporation and trituration with diethyl ether afforded 1.17 g of (*R*)-**42**: mp 167–169 °C; $[\alpha]_D$ −1.7° (*c* 0.997, MeOH). Anal. ($C_{18}H_{26}N_2O_5$) C, H, N. A hydrochloride was obtained by the addition of a slight excess of concentrated HCl to a 2-propanol solution of (*R*)-**42** followed by precipitation with diethyl ether: $[\alpha]_D$ +16.8° (*c* 1, MeOH).

(*S*)-2-(2,3-Epoxypropoxy)anisole (78). A mixture of 8.3 g (89.7 mmol) of **77**,[20] 7.95 g (64.1 mmol) of guiacol, 25 mL of dioxane, and a solution of 3 g of sodium hydroxide in 7 mL of water was heated at reflux for 3 h. The mixture was diluted with 200 mL of water, and the product was extracted into 100 mL of diethyl ether. Evaporation and Kugelrohr distillation (120 °C, 0.1 mm) afforded 2.89 g (25%) of **78**: mp 43–47 °C; $[\alpha]_D$ +13.6° (*c* 0.997, MeOH). Anal. ($C_{10}H_{12}O_3$) C, H.

(*S*)-3-Methyl-8-[3-(2-methoxyphenoxy)-2-hydroxypropyl]-1-oxa-3,8-diazaspiro[4.5]decan-2-one [(*S*)-42]. A mixture of 2.8 g (15.6 mmol) of **78**, 3.5 g (20.6 mmol) of 3-methyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one, 7 mL of MeOH, and 50 mL of toluene was heated at reflux for 48 h. The solvent was removed by evaporation, and the residue was dissolved in 100 mL of 0.05 N HCl. This solution was extracted with 100 mL of diethyl ether and then basified with 20% sodium hydroxide solution. Extraction with methylene chloride, followed by evaporation and chromatography from 20 g of 70–230 mesh silica gel, gave 3.87 g of (*S*)-**42**: mp 128–130 °C; $[\alpha]_D$ +2.5° (*c* 0.99, MeOH). Anal. ($C_{18}H_{26}N_2O_5$) C, H, N. A hydrochloride was obtained by adding concentrated HCl to a 2-propanol solution of (*S*)-**42**, followed by precipitation with diethyl ether: $[\alpha]_D$ −15.5° (*c* 0.96, MeOH).

Chiral Purity of 76 and 78. Both **76** and **78** were examined in deuteriochloroform solution using tris[3-(trifluoroacetyl)-*d*-camphorato]europium(III) (Eu-Opt) (Alfa). The best separation was found for the OCH_3 signal. At a molar ratio of epoxide to Eu-Opt of 8:1, the OCH_3 signal of **76** was at δ 3.98 and that for **78** was at δ 3.95. The absorption for **78** was broader than that for **76**. The chiral purity was determined by integration. As a final check on the validity of the analysis, the two final solutions of **76** and **78** containing Eu-Opt were mixed and analyzed by NMR. The resulting spectrum contained two OCH_3 signals of approximately equal intensity.

Acknowledgment. We thank Lillia Kurz, Dr. Michael Maddox, Dr. Ian Massey, Ann Nitzan, Jim Cook, Grace Chiang, and Paul Cheung for technical assistance.