sterile, pyrogen-free, 0.225% saline infusion. One day was allowed for recovery from surgery before the start of drug treatments. Arterial pressure was recorded continuously through Statham P-23Gb transducers on a Honeywell 906C Visicorder. Mean arterial pressure and heart rate data were printed at 0.5 h intervals through a data acquisition system (Data Graphics Corp., San Antonio, TX) by means of ASR-33 teletype units. Mean arterial pressure was recorded 0.5, 1, 2, 4, 8, 12, and 18 h after treatment.

Acknowledgment. We greatly appreciate the technical assistance of the following individuals: Mrs. E. P. Baskin, Mr. D. Weitz, Mr. S. L. Gaul, Mr. Y. C. Lee, Mr. K. Streeter, Mr. J. P. Moreau, Ms. J. S. Murphy, Dr. D. W. Cochran, Dr. B. H. Arison, and Ms. T. H. Brunner.

Registry No. (*S*)-**5**, 69500-51-2; (*RS*)-**5**, 69470-18-4; (*R*)-**5**, 69500-52-3; **7** [R = HC≡C(CH$_3$)$_2$C], 84945-38-0; **7** (R = HC≡CCH$_2$), 84945-39-1; **7** [R = (CH$_3$)$_2$CHCH$_2$CH$_2$], 84945-40-4; **7** (R = cyclohexyl), 84945-41-5; **7** (R = cyclooctyl), 84945-42-6; **7** (R = 1-adamantyl), 84945-43-7; **7** (R = 1,4-dimethylcyclohexyl), 84945-44-8; **7** (R = 4,4-dimethylcyclohexyl), 84945-45-9; **7** (R = 2,3-dihydro-1,4-benzodioxin-2-ylmethyl), 84945-46-0; **7** (R = 1-indanyl), 84945-47-1; **7** [R = PhCH$_2$CH$_2$(CH$_3$)$_2$C], 75561-37-4; **10**, 84945-48-2; **10** free base, 84945-49-3; **11**, 84945-50-6; **11** free base, 84945-51-7; **12**, 84945-52-8; **12** free base, 84945-53-9; **13**, 84945-55-1; **14**, 84945-57-3; **15**, 84945-58-4; **15** free base, 84945-59-5; **16**, 84945-60-8; **16** free base, 84945-61-9; **17**, 84945-62-0; **17** free base, 85026-17-1; **18**, 84945-63-1; **18** free base, 84945-64-2; **19**, 84945-65-3; **19** free base, 84945-66-4; **20**, 84945-67-5; **21**, 74944-03-9; **22**, 84945-68-6; **22** free base, 84945-69-7; **23**, 84945-70-0; **23** free base, 84945-71-1; **24**, 84945-72-2; **24** free base, 84945-73-3; **25**, 84945-74-4; **25** free base, 84945-75-5; **26**, 85026-19-3; **27**, 84945-76-6; **28**, 84945-77-7; **29**, 84945-78-8; **30**, 75598-87-7; **30** free base, 84945-79-9; **31**, 84945-80-2; **31** free base, 75561-41-0; **32**, 85026-21-7; **33**, 75561-54-5; **35**, 84945-81-3; **35** free base, 84945-82-4; **36**, 84945-83-5; **36** free base, 84945-84-6; **37**, 84945-86-8; **38**, 84945-87-9; **38** free base, 84945-88-0; **39**, 84945-90-4; **40**, 84945-92-6; **41**, 84945-94-8; **42**, 84945-96-0; **43**, 84945-98-2; 2-methyl-2-butanamine, 594-39-8; 4-(1,1-dimethylethyl)cyclohexanamine, 5400-88-4; 2-methoxybenzeneethanamine, 2045-79-6; 1,1-dimethyl-2-(4-hydroxyphenyl)ethylamine, 51706-55-9; 3,4-dimethoxy-2,2-dimethylbenzeneethanamine, 75561-47-6; 1,1-dimethyl-3-phenylpropylamine, 43052-72-8; (±)-2-methylbenzenepropanamine, 22148-77-2; 1-phenoxy-2-propanamine, 35205-54-0; 4-methoxy-2,2-dimethylbenzeneethanamine, 56490-94-9; α-methyl-1,3-benzodioxole-5-propanamine, 40742-32-3; 3,4-dimethoxy-2-methylbenzenepropanamine, 27487-78-1; 4-methoxy-α-methylbenzenepropanamine, 51062-15-8; 4-chloro-α-methylbenzenepropanamine, 74697-68-0; 3-(trifluoromethyl)-α-methylbenzenepropanamine, 73839-94-8; α-methylbenzeneethanamine, 60-15-1; 2-chloro-3-cyanopyridine, 6602-54-6; (*R*)-α-methylbenzenepropanamine, 937-52-0; (*S*)-α-methylbenzenepropanamine, 4187-57-9.

Synthesis and Antihypertensive Activity of 4′-Substituted Spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones[1]

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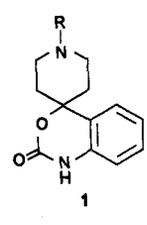
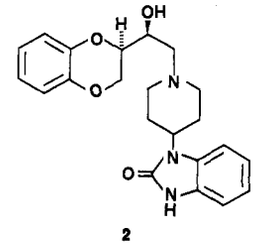
A series of 4′-substituted spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones was prepared and evaluated for antihypertensive activity in the spontaneously hypertensive rat (SHR). The basic ring system was prepared in one step by condensation of dilithiated (*tert*-butoxycarbonyl)aniline (**3**) with (*tert*-butoxycarbonyl)piperidinone. Deprotection afforded **6**, which was condensed with expoxides or alkyl halides to furnish the title compounds. The most active compound was *dl-erythro*-4′-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (**9**), and various modifications of this compound were made in order to elucidate the structure–activity relationships in the series. Preliminary indications are that **9** may act by both central and peripheral mechanisms.

We recently described the synthesis and antihypertensive activity of a series of 8-substituted 1-oxa-3,8-diazaspiro[4.5]decan-2-ones[2] and a series of 9-substituted 1-oxa-4,9-diazaspiro[5.5]undecan-3-ones.[3] We now describe related work on spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones **1**. Whereas the most active compounds of the two previous series exerted their antihypertensive effects predominantly through peripheral α_1-adrenoceptor blockade, the most interesting compound of the present series (**9**) appears to act by a more complex mechanism that may involve both peripheral and central sites of action. It should be recognized that **9** is structurally related to **2** (Janssen R 28935),[4] a centrally active antihypertensive agent that has been of considerable interest due to its complex and as yet not well understood mechanism(s) of action.[4,5]



1



2

[†] Institute of Organic Chemistry.
[‡] Institute of Pharmacology and Metabolism.

(1) Contribution No. 642 from the Institute of Organic Chemistry.
(2) Caroon, J. M.; Clark, R. D.; Kluge, A. F.; Nelson, J. T.; Strosberg, A. M.; Unger, S. H.; Michel, A. D.; Whiting, R. L. *J. Med. Chem.* **1981**, *24*, 1320.
(3) Clark, R. D.; Caroon, J. M.; Repke, D. B.; Strosberg, A. M.; Bitter, S. M.; Okada, M. D., *J. Med. Chem.*, in press.
(4) (a) Wellens, D.; De Wilde, A.; Van Bogaert, A.; Van Bogaert, P. P.; Wouters, L.; Reneman, R. S.; Janssen, P. A. J. *Arch. Int. Pharmacodyn.* **1975**, *215*, 91. (b) Van Zwieten, P. A.; Paver, M.; Van Spanning, H. W.; Fonck-Bentelaar, M. *Arch. Int. Pharmacodyn.* **1975**, *215*, 104. (c) Wellens, D.; Snoeckn, L.; De Reese, R.; Kruger, R.; Van de Water, A.; Wouters, L.; Reneman, R. S. *Arch. Int. Pharmacodyn.* **1975**, *215*, 119. (d) Wellens, D.; Van Nueten, J. M.; Janssen, P. A. J. *Arch. Int. Pharmacodyn.* **1975**, *213*, 334. (e) Finch, L. *Eur. J. Pharmacol.* **1975**, *33*, 409.
(5) (a) Kwa, H. Y.; Timmermans, P. B. W. M.; Van Zwieten, P. A. *Br. J. Pharmacol.* **1979**, *68*, 138P–139P. (b) Beckett, P. J.; Finch, L. *Br. J. Pharmacol.* **1981**, *74*, 190P. (c) Hicks, P. E.; Waldron, C. *Br. J. Pharmacol.* **1981**, *74*, 844P–845P.

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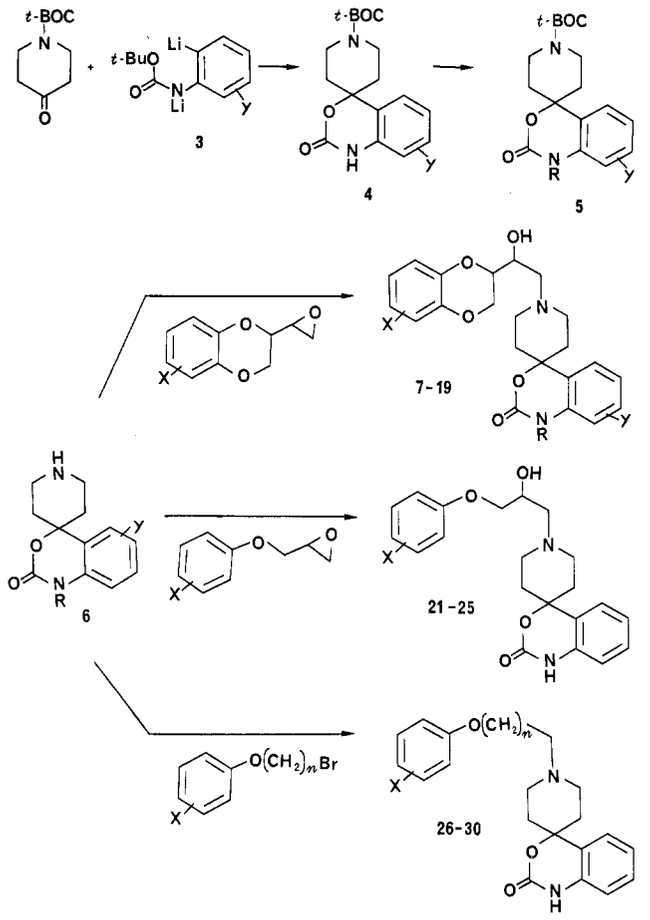
Scheme I



Chemistry. The compounds listed in Table I were prepared by the reaction sequences shown in Scheme I. Condensation of a dilithiated (*tert*-butoxycarbonyl)aniline[6] (**3**) with (*tert*-butoxycarbonyl)piperidinone gave directly the protected spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2-(1*H*)-one **4**. Alkylation of the sodium salt of **4** gave the N-alkylated derivatives **5**. Deprotection of **4** and **5** with trifluoroacetic acid gave piperidine **6**, which was reacted with the requisite epoxide or alkyl halide to afford **7–30**. The erythro–threo mixture **7** was prepared from the bromo alcohol as previously described.[2] The pure *threo*- and *erythro*-epoxides utilized for the synthesis of **8** and of **9-14**, respectively, were prepared as described in the literature.[7] The phenyl-substituted *erythro*-epoxide precursors for **15-18** were prepared from substituted salicylaldehydes or acetophenones by a reported general procedure.[8]

Alkylation of **6** (R=H) with the requisite alkyl halide gave **31**, **36**, and **37**. Reductive amination of 2-tetralone with **6** gave **32**. Compounds **33-35** were prepared by reaction of **6** with the 2-bromoacetophenone followed by reduction.

Results and Structure–Activity Relationships

The compounds in Table I were evaluated for their antihypertensive effects in male, Okamoto-Aoki strain, spontaneously 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.

(6) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.
(7) Gschwend, H. W.; Huebner, C. F. U.S. Patent 4 212 808.
(8) Gschwend, H. W.; Huebner, C. F. U.S. Patent 4 187 313.

The antihypertensive activity of the 1:1 erythro–threo mixture **7** was found to be due predominantly to the erythro isomer (**9**). This is consistent with the activity found with **2** where the active isomer was erythro. Both the potency and duration of action of **9** at the 12.5 and 25 mg/kg doses appear to be superior to that of **2**. At the 12.5 mg/kg dose, significant decreases in blood pressure were also observed at 8 (15%) and 24 h (17%) postdose.

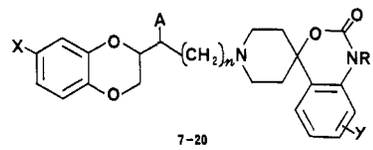
Modification of **9** by substitution in either the aromatic portion of the benzoxazine ring (**12–14**) or the benzodioxan ring (**15–18**) led to marked reduction (or elimination) of activity. Activity was retained in the *N*-methyl (**10**) and *N*-ethyl (**11**) derivatives, although neither compound demonstrated greater activity than the parent **9**. Interestingly, the dehydroxy analogue **20** showed significant activity at 50 mg/kg. However, this compound caused significant (20–34%) increases in heart rate and was not pursued further. Compound **9** did not cause significant tachycardia at any of the doses studied. Compounds **21–30** can be viewed as ring-opened forms of the benzodioxan moiety. Although significant activity was found for a number of these analogues, none demonstrated enhanced activity compared to the benzodioxan counterpart, and the general trend was toward a decrease in potency. Thus, modification of the maximally active **9** either by ring substitution or bond disconnections led to less active compounds.[9] The two-carbon spacing between the benzodioxan and the piperidine does appear to be important (**19** vs. **20**).

Substitution of N-4′ with phenylethyl, 2-tetrahydronaphthyl, or 2-hydroxyphenylethyl gave compounds (**31–33**) that were active, but less so than **9**. Placement of hydroxy or catechol equivalents into the aromatic ring of **31** gave inactive compounds (**34** and **35**). Substitution with 2-indolylethyl, which had given active compounds in the previous series,[2,3] gave the inactive **36**.[10]

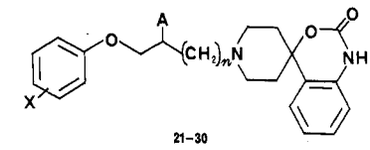
On the basis of its activity in the SHR, **9** has been chosen for further pharmacological evaluation. The mechanistic profile of **9** appears to be similar to that of **2**. The activity of **2** has been reported to be due to a central effect that does not involve stimulation of central α_2 adrenoceptors.[4] Thus, **2** differs mechanistically from the classical, centrally active, α_2-agonist clonidine. Blockade of central postsynaptic (α_1) adrenoceptors has been postulated as an explanation for the activity of **2**,[5a,b] although a peripheral effect may also be present.[5c] Central intraarterial injection of **9** into the vertebral artery in anesthetized cats produced a hypotensive response greater than that induced by the same dose of clonidine.[11] In the anesthetized dog, **9** demonstrated peripheral α_1-blocking activity, as evidenced by its reversal of the pressor effects of epinephrine, norepinephrine, and carotid artery occlusion.[12] Details of this

(9) Similar results have recently been reported for a small series of analogues of **2**: Timmermans, P. B. W. M.; Slothorst-Grisdijk, F. P.; Van Kemenade, J. E.; Schoop, A. M. C.; Batink, H. D.; Van Zwieten, P. A. *Arch. Int. Pharmacodyn.* **1982**, *255*, 321.
(10) It should be emphasized that the comparisons presented here are based on activity observed upon oral administration, which is dependent on a number of variable pharmacokinetic and chemical factors. An attempt to draw meaningful SAR on the basis of this data alone has therefore not been made.
(11) ID_{30} values of 0.8 and 1.7 μg/kg were obtained for **9** and clonidine, respectively. **9** (ID_{30} = 3 μg/kg) was also a more potent hypotensive agent than clonidine (ID_{30} = 15 μg/kg) when given iv in anesthetized cats.
(12) In the rat isolated, transversely bisected, vas deferens preparation (ref 2), 9 had a pA_2 (α_1) value of 8.45. For reference, the peripheral α_1-blocker prazosin had a pA_2 (α_1) of 8.7 in the same preparation.

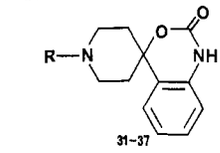
Table I. Antihypertensive Activity of Spiro[4*H*-3,1-benzoxazine-4,4'-piperidin]-2(1*H*)-ones



7-20



21-30



31-37

compd	X	A	*n*	R	Y	yield,[a] %	mp, °C	formula[b]	dose, mg/kg po	% fall SBP[c] 1 h	2 h	3 h	4 h
7	H	OH[d]	1	H	H	20	173-175	$C_{22}H_{25}ClN_2O_5 \cdot H_2O$	50	53	41	36	40
									25	39	33	26	30
									12.5	*	*	*	*
8	H	OH[e]	1	H	H	56	240-244	$C_{22}H_{25}ClN_2O_5$	12.5	*	*	*	*
9	H	OH[f]	1	H	H	67	275-277	$C_{22}H_{25}ClN_2O_5$	50	34	50	46	46
									25	52	42	27	26
									12.5	37	38	19	34
10	H	OH[f]	1	CH_3	H	55	140-142	$C_{23}H_{27}ClN_2O_5 \cdot 0.75H_2O$	25	32	40	39	27
11	H	OH[f]	1	CH_2CH_3	H	50	217-220	$C_{24}H_{29}ClN_2O_5$	25	40	38	19	29
									12.5	36	23	*	*
12	H	OH[f]	1	H	5-OCH_3	14	232-235	$C_{23}H_{27}ClN_2O_6$	12.5	*	11	*	*
13	H	OH[f]	1	H	6-Cl	62	165-168	$C_{22}H_{24}Cl_2N_2O_5 \cdot 0.5H_2O$	25	*	17	*	*
14	H	OH[f]	1	H	6-F	55	166-168	$C_{22}H_{24}FClN_2O_5 \cdot H_2O$	50	25	*	*	*
15	F	OH[f]	1	H	H	36	237-238	$C_{22}H_{24}FClN_2O_5 \cdot 1.25H_2O$	25	21	25	19	*
16	Cl	OH[f]	1	H	H	30	165-168	$C_{22}H_{24}Cl_2N_2O_5 \cdot H_2O$	25	*	15	*	21
17	Br	OH[f]	1	H	H	50	179-180	$C_{22}H_{24}BrClN_2O_5 \cdot H_2O$	25	*	*	*	*
18	CH_3	OH[f]	1	H	H	49	224-228	$C_{23}H_{27}ClN_2O_5 \cdot 0.5H_2O$	25	*	*	*	19
19	H	H	0	H	H	39	250-252	$C_{21}H_{23}ClN_2O_4 \cdot 0.5H_2O$	50	33	*	*	*
20	H	H	1	H	H	55	238-240	$C_{22}H_{25}ClN_2O_4 \cdot H_2O$	50	53	49	28	35
21	H	OH	1			83	263-265	$C_{21}H_{24}N_2O_4$[g]	50	24	23	15	25
22	2-OCH_3	OH	1			75	110-113	$C_{22}H_{27}ClN_2O_5 \cdot 0.5H_2O$[h]	50	38	33	33	*
23	2-CN	OH	1			78	237-238	$C_{22}H_{24}ClN_3O_4$	50	24	21	*	22
24	4-Cl	OH	1			59	246-248	$C_{21}H_{24}Cl_2N_2O_4 \cdot 0.25H_2O$	25	18	18	23	21
25	4-OCH_3	OH	1			55	230-231	$C_{22}H_{27}ClN_2O_5 \cdot 0.5H_2O$	50	*	16	*	*
26	H	H	0			87	247-250	$C_{20}H_{23}ClN_2O_3 \cdot 0.25H_2O$	50	26	25	8	16
27	2-OCH_3	H	0			18	151-152	$C_{21}H_{25}ClN_2O_4 \cdot H_2O$	50	15	18	10	*
28	H	H	1			28	250-252	$C_{21}H_{25}ClN_2O_3$	50	44	34	29	23
29	2-OCH_3	H	1			46	217-220	$C_{22}H_{27}ClN_2O_4 \cdot 0.5H_2O$	50	36	37	30	26
									25	*	*	*	*
30	2,6-OCH_3	H	0			28	243-245	$C_{22}H_{27}ClN_2O_5 \cdot 0.5H_2O$	50	23	22	*	*
31				$C_6H_5CH_2CH_2$		75	276-280	$C_{20}H_{23}ClN_2O_2 \cdot 0.25H_2O$	50	35	34	35	23
32				2-tetrahydronaphthyl		24	233-235	$C_{22}H_{24}N_2O_2 \cdot 0.25H_2O$	50	38	42	38	27
33				$C_6H_5CHOHCH_2$		43	275-278	$C_{20}H_{23}ClN_2O_3$	50	43	31	19	25
34				3-(CH_3SO_2NH)-$C_6H_4CHOHCH_2$		68	186-187	$C_{21}H_{26}ClN_3O_5S \cdot 0.5H_2O$	50	*	*	*	*
35				3-(NH_2CO)-4-$OHC_6H_3CHOHCH_2$		84	237-240	$C_{21}H_{24}ClN_3O_5$[i]	50	11	*	*	*
36				2-(3-indolyl)ethyl		51	206-208	$C_{22}H_{24}ClN_3O_2 \cdot H_2O$[j]	50	13	*	*	*
37				4-$FC_6H_4COCH_2CH_2CH_2$		34	225-228	$C_{22}H_{24}FClN_2O_3$	50	32	33	*	25
2				(R 28935)					50	32	26	20	27
									25	25	30	*	*
									12.5	16	22	*	*
clonidine									0.1	19	29	28	20

[a] Yield refers to reaction of the piperidine with the epoxide or alkyl halide. [b] Elemental analyses for C, H, and N were within 0.4% of theory, and, unless otherwise noted, they were obtained for the HCl salt. [c] 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 180-220 mmHg during the 4-h measurement period. Values in the table are statistically significant ($p \leq 0.05$) relative to control values; asterisks denote nonsignificance) ($p \geq 0.05$). [d] 1:1 erythro-threo mixture. [e] Threo isomer. [f] Erythro isomer. [g] Analysis of free base. N: calcd, 7.61; found, 7.06. [h] N: calcd, 6.31; found, 5.78. [i] Ethanol solvate. [j] N: calcd, 10.10; found, 9.55.

and further pharmacological evaluation of **9** will be presented in future publications.

Experimental Section

The melting points were taken on a Fischer-Johns hot stage and are not corrected. The IR spectra were measured with a Perkin-Elmer Model 237 grating infrared spectrometer. The ^1H NMR spectra were recorded on Varian A-60 and HA-100 and Bruker WM 300 instruments. ^{13}C NMR were obtained with a Bruker 90 instrument. Microanalyses were obtained from Syntex Analytical Research. Mass spectra were obtained in either an Atlaswerke CH-4 or CH-7 instrument.

***dl-erythro-* and *-threo*-2-Oxiranyl-1,4-benzodioxans.** These compounds were prepared according to the procedure of Gschwend and Huebner.[7] To a 10 °C solution of catechol (24 g, 218 mmol) and *cis*-2,3-bis(chloromethyl)oxirane (30.5 g, 216 mmol) in Me_2SO (200 mL) was added sodium hydroxide (15.6 g, 390 mmol), and the resulting mixture was stirred overnight at room temperature. Water was added, and the mixture was extracted twice with ether. The ether extract was washed with 1 M aqueous NaOH, water, and brine, dried over sodium sulfate, and evaporated. The crude product was purified by filtration through silica gel with 25% ether–hexane to afford 23 g (59%) of *dl-threo*-2-oxiranyl-1,4-benzodioxan as a colorless oil. The erythro isomer was prepared according to the same procedure from *trans*-2,3-bis(chloromethyl)oxirane, mp 49–50 °C (lit.[7] mp 51–52 °C). The threo epoxide had R_f 0.56 and the erythro isomer R_f 0.68 on TLC (silica gel, 50% ether–hexane).

***dl-erythro*-7-Fluoro-2-oxiranyl-1,4-benzodioxan.** This compound was prepared by a modification of a general patented procedure.[8] A mixture of 2-hydroxy-5-fluoroacetophenone (10 g, 65 mmol), *trans*-1,4-dichloro-2-butene (12 g, 97 mmol), and potassium carbonate (13.2 g, 97 mmol) in ethanol (200 mL) was heated at reflux for 2 h. The mixture was filtered, and the filtrate was diluted with water and extracted with ether. the ether extract was dried (Na_2SO_4) and evaporated to yield a residue, which was chromatographed on silica gel (30% ether–hexane) to yield 9.8 g (62%) of 2-[(4-chloro-*trans*-2-butenyl)oxy]-5-fluoroacetophenone. A solution of this material (21 g, 86 mmol) and *m*-chloroperoxybenzoic acid (85%, 36 g, 180 mmol) in chloroform (300 mL) was heated at reflux for 48 h. The cooled solution was filtered, and the filtrate was washed with aqueous sodium bicarbonate solution and evaporated to 26 g of crude 2-[(4-chloro-*trans*-2,3-epoxybutyl)oxy]-5-fluorophenyl acetate. To a solution of this material in methanol (100 mL) at 5 °C was added slowly 10% aqueous potassium hydroxide solution (90 mL). After stirring overnight at room temperature, the mixture was diluted with water and extracted with ether to afford an oil, which was chromatographed on silica gel (20% ether–hexane) to give 9.3 g of the *erythro*-epoxide as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.71–2.96 (m, 2 H), 3.03–3.23 (m, 1 H), 3.83–4.40 (m, 3 H), 6.38–6.91 (m, 3 H). The 7-chloro, 7-methyl, and 7-bromo-*erythro*-2-oxiranyl-1,4-benzodioxans were prepared in a similar manner from 2-hydroxy-5-chloroacetophenone, 2-hydroxy-5-methylacetophenone, and 5-bromosalicylaldehyde, respectively.

4′-(*tert*-Butoxycarbonyl)spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (4). A 2.0 M solution of *tert*-butyllithium in pentane (198 mL, 396 mmol) was added in a dropwise manner to a solution of *N*-(*tert*-butoxycarbonyl)aniline (34.7 g, 180 mmol) in THF (250 mL) at −70 °C. After 0.5 h at −70 °C, the solution was warmed to −20 °C and was maintained at that temperature for 2.5 h. The solution was cooled to −70 °C and *N*-(*tert*-butoxycarbonyl)-4-piperidinone (34.6 g, 173 mmol) in THF (100 mL) was added. The mixture was allowed to slowly warm to room temperature over 4 h, and potassium *tert*-butoxide (50 mg) was added. After an additional 16 h at room temperature, the mixture was diluted with ether and washed with 5% aqueous HCl. The ether was washed with water and brine, dried over sodium sulfate, and evaporated. Chromatography of the residue on silica gel (30–50% ethyl acetate–hexane) gave 25.7 g (47%) of **4**: mp 83–85 °C; IR (KBr) 3300, 1725, 1700, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 9 H), 2.10 (m, 4 H), 3.46 (m, 2 H) 4.10 (m, 2 H, 7.00–7.33 (m, 4 H); MS, *m/e* 318 (M^+) 245, 218, 174, 131. Anal. ($C_{17}H_{22}N_2O_4$) C, H, N.

Spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (6). A solution of **4** (20 g, 62 mmol) in CH_2Cl_2 (150 mL) and trifluoroacetic acid (50 mL) was stirred for 1 h at room temperature. Solvents were removed in vacuo, the residue was dissolved in brine, and the solution was made basic by addition of 35% aqueous NaOH. After cooling, the mixture was filtered to give 11.6 g (85%) of crude **6**, which was used without further purification.

***dl-erythro*-4′-[2-(1,4-Benzodioxan-2-yl)-2-hydroxyethyl]-spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (9).** A solution of **6** (2.2 g, 10.1 mmol) and *dl-erythro*-2-oxiranyl-1,4-benzodioxan[7] (1.78 g, 10 mmol) in methanol (30 mL) and toluene (60 mL) was heated at reflux for 3 h. The mixture was cooled and filtered to afford 4.0 g (67%) of the free base of **9**: mp 242–243 °C; ^1H NMR (Me_2SO-d_6) δ 1.92 (d, J = 12 Hz, 2 H), 2.04 (m, 2 H), 2.50 (m, 2 H), 2.68 (dd, J = 12 and 4.6 Hz, 1 H), 2.83 (m, 2 H), 3.88 (m, 1 H), 4.10 (m, 3 H), 4.40 (m, 1 H), 5.12 (d, 1 H, exchangeable), 6.78–6.90 (m, 5 H), 7.00 (m, 1 H), 7.25 (m, 2 H); ^{13}C NMR (Me_2SO-d_6) δ 34.7, 48.4, 48.8, 60.3, 64.6, 67.1, 74.6, 79.8, 114.2, 116.8, 117.1 121.1, 121.3, 122.8, 123.3, 125.5, 128.8, 135.3, 143.3, 150.3. Anal. ($C_{22}H_{24}N_2O_5$) C, H, N.

The HCl salt was prepared by dissolving the base in methanolic HCl and the precipitating with ether followed by recrystallizing from 2-propanol.

***dl-threo*-4′-[2-(1,4-Benzodioxan-2-yl)-2-hydroxyethyl]-spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (8).** A solution of **6** (1.0 g, 4.6 mmol) and *dl-threo*-2-oxiranyl-1,4-benzodioxan[7] (1.1 g, 6.0 mmol) in methanol (10 mL) and toluene (20 mL) was heated at reflux for 4 h. The mixture was cooled and filtered to afford 1.0 g (56%) of **8**: mp 238–239 °C; ^{13}C NMR ($CDCl_3$–CD_3OD) δ 35.6, 47.8, 49.7, 60.0, 65.6, 66.9, 74.6, 81.3, 114.9, 117.4, 117.7, 121.8, 123.5, 124.0, 125.4, 129.5, 134.9, 143.8, 143.9, 152.6.

The HCl salt was crystallized from 2-propanol–ether.

4′-(2-Phenoxyethyl)spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (26). A solution of **6** (1.0 g, 4.6 mmol) and 2-phenoxyethyl bromide (1.3 g, 6.5 mmol) in DMF (20 mL) and triethylamine (5 mL) was stirred at 60 °C for 12 h. The mixture was poured into water and filtered to give a solid, which was air-dried to give 1.6 g (87%) of **26**: mp 143–144 °C; IR (KBr) 3400, 1720, 1600, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.16 (m, 4 H), 2.80 (m, 2 H), 2.93 (t, J = 6 Hz, 2 H), 2.95 (m, 2 H), 4.15 (t, J = 6 Hz, 2 H), 6.90–7.34 (m, 9 H); MS, *m/e* 338 (M^+) 231, 187, 158, 144, 77. Anal. ($C_{20}H_{22}O_3$·$0.25H_2O$) C, H, N.

The HCl salt was crystallized from methanol.

***dl-erythro*-1-Methyl-4′-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2-(1*H*)-one (10).** Sodium hydride (50% in mineral oil, 0.38 g, 8 mmol) was added to a solution of **4** (1.9 g, 6 mmol) in DMF (25 mL), and the solution was stirred at room temperature for 0.5 h. Methyl iodide (2.8 g, 20 mmol) was added, and stirring was continued for 1 h. The mixture was added to water and extracted with ethyl acetate. The ethyl acetate was washed with water and brine, dried over sodium sulfate, and evaporated. The residue of crude **5** was dissolved in CH_2Cl_2 (20 mL) and trifluoroacetic acid (2.7 mL), and the solution was stirred for 2 h at room temperature. Solvents were evaporated, and the residue was partitioned between CH_2Cl_2 and ammonium hydroxide–brine. The aqueous layer was extracted again with CH_2Cl_2 and the combined extracts were evaporated. Trituration of the residue with hexane gave 1.0 g (78%) of **6** (R = CH_3): mp 130–132 °C; IR (KBr) 3350, 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95–2.14 (m, 4 H), 3.00 (br d, J = 12 Hz, 2 H), 3.28 (dd, J = 12 and 3 Hz, 2 H), 3.40 (s, 3 H), 6.95 (d, J = 8 Hz, 1 H), 7.12 (dd, J = 8 and 8 Hz, 1 H), 7.20 (dd, J = 8 and 1.5 Hz, 1 H),7.34 (ddd, J = 8, 8, and 1.5 Hz, 1 H); MS, *m/e* 232 (M^+) 188, 158, 144. Anal. ($C_{13}H_{16}N_2O_2$) C, H, N.

A solution of **6** (1.1 g, 4.7 mmol) and *dl-erythro*-2-oxiranyl-1,4-benzodioxan[7] (1.0 g, 6 mmol) in toluene (20 mL) and methanol (10 mL) was heated at reflux for 18 h. Solvents were evaporated, and the residue was chromatographed on silica gel (5% methanol–CH_2Cl_2) to give 1.0 g (55%) of the free base **10**: mp 142–143 °C; IR (KBr) 3400, 1700, 1600, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00–2.16 (m, 4 H), 2.60–3.10 (m, 6 H), 3.40 (s, 3 H), 3.86 (m, 1 H), 4.02 (m, 1 H), 4.18 (dd, J = 12 and 7 Hz, 1 H), 4.42 (dd, J = 12 and 3 Hz, 1 H), 6.85 (m, 4 H) 6.96 (dd, J = 8 and 0.5 Hz, 1 H), 7.12 (ddd, J = 8, 8, and 0.5 Hz, 1 H), 7.18 (dd, J = 8 and 1.5 Hz, 1 H), 7.36 (ddd, J = 8, 8, and 1.5 Hz, 1 H); MS, *m/e* 410 (M^+), 245, 172, 158. Anal. ($C_{23}H_{26}N_2O_5$) C, H, N. The HCl salt was crystallized from 2-propanol–ether.

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 2 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 with 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 by using a 1-tail Student's t test. Statistical significance was considered to be $p \leq 0.05$.

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Registry No. **4**, 84060-08-2; **6** (R = Y = H), 84060-09-3; **6** (R = CH_3; Y = H), 84060-10-6; (±)-**8**, 84787-02-0; (±)-**8**·HCl, 84787-28-0; (±)-**9**, 84787-01-9; (±)-**9**·HCl, 84787-29-1; (±)-**10**, 84787-03-1; (±)-**10**·HCl, 84787-30-4; (±)-**11**·HCl, 84787-14-4; (±)-**12**·HCl, 84787-15-5; (±)-**13**·HCl, 84787-16-6; (±)-**14**·HCl, 84787-17-7; (±)-**15**·HCl, 84787-18-8; (±)-**16**·HCl, 84787-19-9; (±)-**17**·HCl, 84787-20-2; (±)-**18**·HCl, 84787-21-3; (±)-**19**·HCl, 84787-22-4; (±)-**20**·HCl, 84787-04-2; (±)-**21**, 84787-05-3; (±)-**22**·HCl, 84787-06-4; (±)-**23**·HCl, 84787-07-5; (±)-**24**·HCl, 84787-08-6; (±)-**25**·HCl, 84787-09-7; **26**, 84060-43-5; **26**·HCl, 84060-31-1; **27**·HCl, 84787-10-0; **28**·HCl, 84787-11-1; **29**·HCl, 84787-12-2; **30**·HCl, 84787-13-3; **31**·HCl, 84060-33-3; (±)-**32**, 84787-23-5; (±)-**33**·HCl, 84787-24-6; (±)-**34**·HCl, 84787-25-7; (±)-**35**·HCl, 84787-26-8; **36**·HCl, 84787-27-9; **37**·HCl, 84070-64-4; catechol, 120-80-9; *cis*-2,3-bis(chloromethyl)oxirane, 50703-46-3; *dl-threo*-2-oxiranyl-1,4-benzodioxan, 65347-66-2; *dl-erythro*-2-oxiranyl-1,4-benzodioxan, 65347-62-8; 2-hydroxy-5-fluoroacetophenone, 394-32-1; *trans*-1,4-dichloro-2-butene, 110-57-6; 2-[(4-chloro-*trans*-2-butenyl)oxy]-5-fluoroacetophenone, 84786-98-1; (±)-2-[(4-chloro-*trans*-2,3-epoxybutyl)oxy]-5-fluorophenyl acetate, 84786-99-2; *dl-erythro*-7-fluoro-2-oxiranyl-1,4-benzodioxan, 84787-00-8; *N*-(*tert*-butoxycarbonyl)aniline, 3422-01-3; *N*-(*tert*-butoxycarbonyl)-4-piperidinone, 79099-07-3; 2-phenoxyethyl bromide, 589-10-6.

Nucleic Acid Related Compounds. 40. Synthesis and Biological Activities of 5-Alkynyluracil Nucleosides[1]

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Coupling of terminal alkynes with 5-iodo-1-(2,3,5-tri-*O*-*p*-toluyl-β-D-arabinofuranosyl)uracil and 5-iodo-3′,5′-di-*O*-*p*-toluyl-2′-deoxyuridine proceeded readily in triethylamine with catalytic quantities of bis(triphenylphosphine)-palladium(II) chloride and copper(I) iodide. The resulting products were deprotected to give 5-alkynyl-1-β-D-arabinofuranosyluracil and 5-alkynyl-2′-deoxyuridine nucleosides. The 5-ethynyl, followed by 5-propynyl, products had the highest antiviral potency, with the 2′-deoxy derivatives being more effective than the arabinosyl compounds. Activity was weak at hexynyl and disappeared at heptynyl. Inclusion of an ω-hydroxy function diminished the antiviral effect. None of the 5-alkynyluracil nucleosides tested had sufficient selectivity to qualify as a candidate antiviral drug. Several of the compounds exerted an inhibitory action on thymidylate synthetase, with 5-ethynyl-2′-deoxyuridine being the most cytotoxic against L1210 cells.

Potent antiviral and antitumor activities have been demonstrated with 5-substituted uracil nucleosides. A series of 5-(2-substituted-vinyl)-2′-deoxyuridine compounds has been shown to contain highly selective inhibitors of herpes virus replication, especially against HSV-1 (herpes simplex virus type 1).[2] The *E* configuration of the vinyl side chain at C-5 has been shown to be important for the 5-(2-bromovinyl) compounds.[3,4] Substituents at C-2 of the vinyl group, including Cl, Br, I, CF_3, and CH_3, provide good activity.[2] The HSV-1 induced thymidine kinase of the infected cell promotes selective phosphorylation of these (*E*)-5-(2-substituted-vinyl)-dUrd compounds relative to the native enzyme of the host cells.[4] The subsequently produced 5′-triphosphate of BVDU, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine, inhibits the HSV-1 DNA polymerase to a significantly greater extent than it does the native cellular DNA polymerases α and β.[5] This may amplify the antiherpes selectivity of BVDU.

In contrast with the 5-(2-substituted-vinyl)-dUrd series, 5-substituted-dUrd derivatives in which X = F, CF_3, NO_2, CHO, C≡CH, etc. show little selectivity against viral-in-

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