heat-inactivated calf serum (Flow Laboratories, Stanmore, Australia), kanamycin sulfate (6 μg/mL), and a serially diluted test sample in a 96-well microtest tissue culture plate (Falcon no. 3040) in a humidified atmosphere of 5% CO_2 in air at 37 °C for 48 h, and the viable cells were counted by the Trypan Blue dye exclusion method. Means of triplicate determinations were compared to respective controls by Student's t test.

Registry No. 1, 3190-71-4; **2a**, 25014-27-1; **2a** SRU, 25038-53-3; **25a**, 92694-88-7; **2b**, 25513-46-6; **2b** SRU, 24991-23-9; **2b**·Na, 26247-79-0; **25b**, 92694-90-1; **25b**·Na, 92694-91-2; **3**, 92694-86-5; DTT, 3483-12-3; PDS, 2127-03-9; cystamine, 51-85-4.

Synthesis of 4-Substituted 2*H*-Naphth[1,2-*b*]-1,4-oxazines, a New Class of Dopamine Agonists

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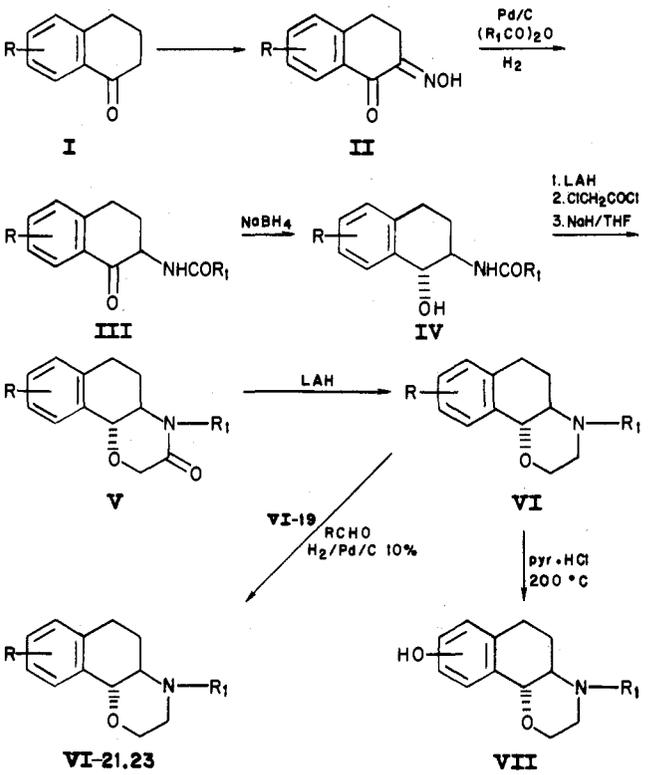
Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486. *Received May 14, 1984*

A series of tricyclic oxazines, namely, the 4-substituted 2*H*-naphth[1,2-*b*]-1,4-oxazines, have been synthesized and assayed for dopamine agonist activity. One of the members of this series, compound (+)**VII-15**, was found to be a remarkably potent agonist in vivo when tested in the standard 6-hydroxydopamine lesioned rat assay. The absolute configuration of the compound corresponds to that found in the active isomer of apomorphine. Its activity at the α_2 receptor (vs. [^{3}H]clonidine) is relatively low. It also failed to stimulate the synthesis of cAMP in the carp retina assay, thus giving the compound a highly selective profile in favor of the D_2 receptor.

A direct-acting dopamine agonist with selectivity for the D_2 receptor[1] would have significant therapeutic utility in the treatment of Parkinson's disease. The classical examples for such an agent are apomorphine and the ergolines. Through the work of Cannon[2] and McDermed[3] and others,[4] it is known that many molecules that can be viewed as partial structures of these complex alkaloids have potent dopaminergic activity. We have recently reported[5] the synthesis of a new class of *D*-heteroergolines, the 9-oxaergolines. Partial structures related to these oxaergolines, namely, the naphth[1,2-*b*]-1,4-oxazines, have been prepared and are reported here to be dopamine receptor agonists. The most potent member of this series (+)-**VII-15** was examined by X-ray analysis[6] and its absolute configuration was found to be 1a*R*,4a*R*. The computer-generated ORTEP drawing of this molecule is presented in Figure 1. This is consistent with the chirality of the active isomer of apomorphine. Additionally, we have found (+)**VII-15** to have selectivity for the dopamine receptor vs. the α_2 receptor and the compound failed to stimulate cAMP synthesis when tested in the carp retina assay.

Chemistry. The synthetic strategy used for construction of the oxazine ring system was described in the first paper of this series[7] and is shown in Scheme I. Various tetralones were successfully annulated by using this method. Ether cleavage of the methoxynaphth[1,2-*b*]-1,4-oxazines using pyridine hydrochloride (Scheme I, step 5)

Scheme I



or several other methods failed for the 8- and 10-methoxy derivatives, necessitating the use of the benzyl protecting group, which was removed by catalytic hydrogenation to the desired phenols (Scheme II). Medium-pressure chromatographic separation[8] of the enantiomeric *l*-*O*-methylmandelate esters[7] of **IV-11** (Scheme III) provided the optical isomers (+)**VII-15** and (−)**VII-16**. Reductive alkylation (Scheme I, step 6) of **VI-19** afforded the N-substituted derivatives **VI-21,23**. The cis isomer **VII-18** was derived from medium-pressure chromatographic separation[8] of the mixture of cis and trans isomeric alcohols formed in the sodium borohydride reduction of ketone

(1) Kebabian, J. W.; Calne, D. B. *Nature (London)* **1979**, *277*, 93.
(2) Cannon, J. G.; Kim, J. C.; Aleem, M. A. *J. Med. Chem.* **1972**, *15*, 348.
(3) McDermed, J. D.; McKenzie, G. M.; Phillips, A. P. *J. Med. Chem.* **1975**, *18*, 362.
(4) Neumeyer, J. L.; Dafeldecker, W. P.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1977**, *20*, 190. Neumeyer, J. L.; Neustadt, B. R.; Oh, K. H.; Weinhardt, K. K.; Boyce, C. B.; Rosenberg, F. J.; Tieger, D. G. *Ibid.* **1973**, *16*, 1223.
(5) Anderson, P. S.; Baldwin, J. J.; McClure, D. E.; Lundell, G. F.; Jones, J. H.; Randall, W. C.; Martin, G. E.; Williams, M.; Hirschfield, J. M.; Clineschmidt, B. V.; Lumma, P. K.; Remy, D. C. *J. Med. Chem.* **1983**, *26*, 363.
(6) A description of the X-ray experiment and lists of crystallographic coordinates, bond lengths, and bond angles are available as supplementary material.
(7) Anderson, P. S.; Baldwin, J. J.; McClure, D. E.; Lundell, G. F.; Jones, J. H. *J. Org. Chem.* **1982**, *47*, 2184.
(8) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

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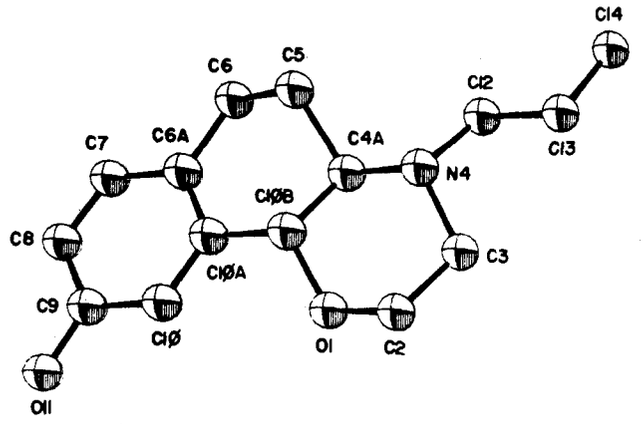
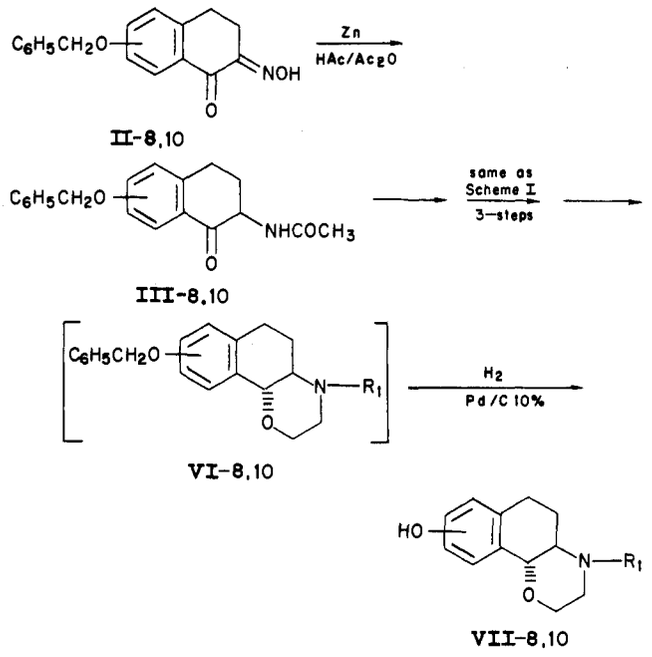
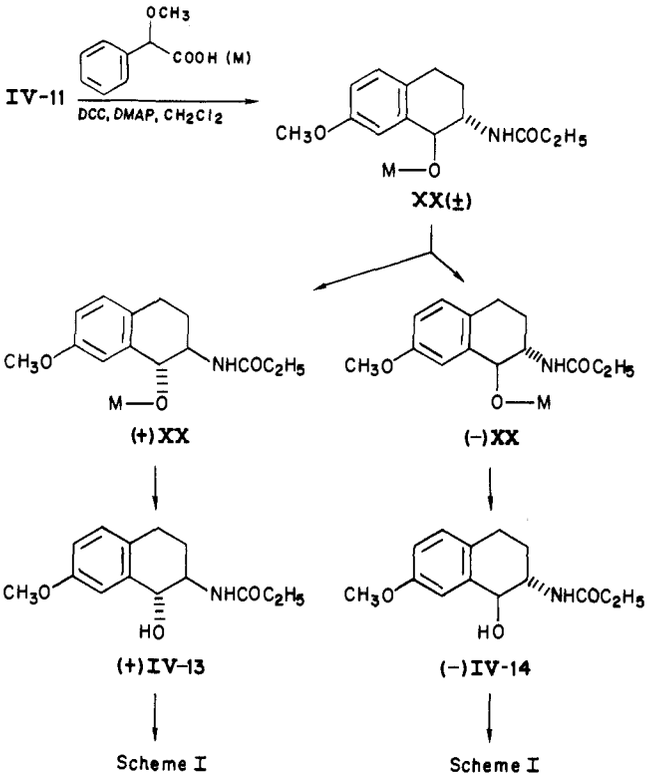


Figure 1. X-ray structure of (+)VII-15.

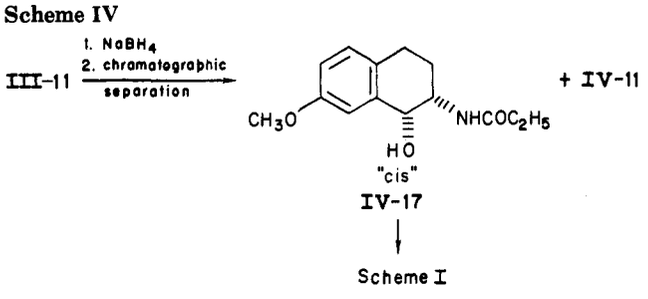
Scheme II



Scheme III



Scheme IV



III-11 (Scheme IV). This reduction generally gives predominately the trans geometry;[9] however, in this case about 16% of the cis isomer was formed. The pure cis alcohol was carried through the remaining steps of the synthesis to give the cis oxazine **VII-18**.

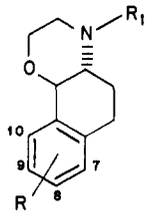
Discussion

The tricyclic oxazines described here were evaluated for dopaminergic and α_2-adrenergic activity (Table I). Dopaminergic activity was assessed in vitro by determining each compound's IC_{50} (nM) for displacement of [^{3}H]apomorphine from specific binding sites on rat striatal membranes.[10] Determination of an ED_{50} for induction of turning contralateral from the lesion[10] in 6-hydroxydopamine (6-OHDA) lesioned rats[11] was used as a corresponding measure of in vivo activity. The affinity of these compounds for the α_2-adrenergic receptor was determined in vitro by assaying inhibition of [^{3}H]clonidine binding to calf cortical membranes.[10] On inspection of the data for compounds **VI-1–VI-3** in Table I, it can be seen that the naphthoxazines possess intrinsic dopaminergic activity which is enhanced by an *N*-propyl substituent. It, therefore, was of interest to further optimize this activity by appropriate placement of an hydroxyl group(s) on the aromatic ring. Since the ultimate goal of this study was to obtain compounds with potent in vivo dopaminergic activity in the CNS, monohydroxylated compounds were pursued in preference to those with a catechol nucleus. The strategy was to prepare each of the isomeric monohydroxylated naphthoxazines, select the most active isomer for determination of the best N-substituent for optimal dopaminergic activity, and resolve this compound into its enantiomers.

Since the naphthoxazines described in this paper contain a fully extended phenethylamine moiety analogous to that found in the 2-aminotetralins and apomorphine, it seemed appropriate to expect similar structure–activity relationships here. Studies with 2-aminotetralins with an hydroxyl group in the 5-, 6-, or 7-positions have established the 5- and 7-isomers, where the substituent is meta to the ethylamine side chain, to be the more active dopamine-like compounds with the former having the greater potency.[15a,b]

(9) Bowman, R. E.; Evans, D. D.; Guyett, J.; Nagy, H.; Weale, J.; Weyell, D. J. *J. Chem. Soc., Perkin Trans.* **1973**, *1*, 438.
(10) The complete description of these test procedures is given in ref 5.
(11) Ungerstedt, U. *Acta. Physiol. Scand., Suppl.* **1971**, 367.
(12) Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 341.
(13) Camerman, N.; Camerman, A. *Mol. Pharmacol.* **1981**, *19*, 517.
(14) Neumeyer, J. L.; Granchelli, F. E.; Fuxe, K.; Ungerstedt, U.; Corrodi, H. *J. Med. Chem.* **1974**, *17*, 1090.

Table I

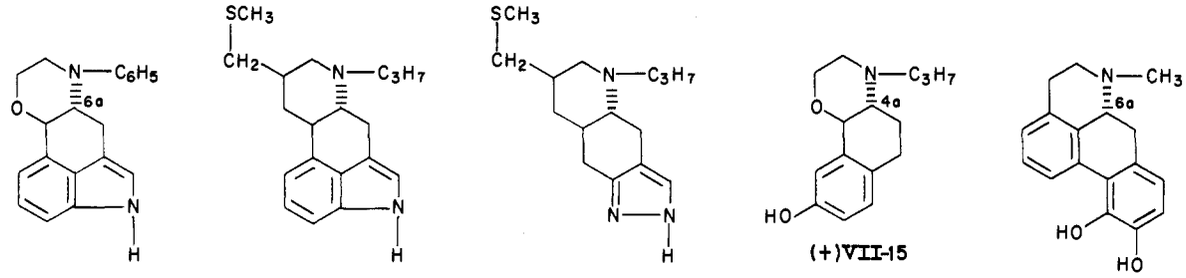


VI and VII

	R	R_1	method of synth	α-receptor binding: IC_{50}, nM (clonidine)	dopamine receptor binding: IC_{50}, nM (apomorphine)	contralateral turning in 6-OHDA-lesioned rats: ED_{50}, mg/kg, ip (95% CL)
VI-1	H	H	A	150	421	30.0
VI-2	H	C_2H_5	A	19	185	1.7[a]
VI-3	H	C_3H_7	A	51	182	0.34[a]
VI-4	7-OCH_3	C_2H_5	A	85	82	5.0[a]
VI-5	8-OCH_3	C_2H_5	A	1300	4730	3.4[a]
VI-6	9-OCH_3	C_2H_5	A	200	1242	0.16 (0.12–0.24)
VII-7	7-OH	C_2H_5	B	53	120	0.8[a]
VII-8	8-OH	C_2H_5	C	110	110 ± 23	2.3[a]
VII-9	9-OH	C_2H_5	B	29	3.3 ± 1	0.01 (0.006–0.018)
VII-10	10-OH	C_2H_5	C	8900 ± 2100	62 400 ± 25 000	15.0
VI-11	9-OCH_3	C_3H_7 (±)	A	300 ± 70	2370 ± 790	0.14 (0.08–0.3)
VII-12	9-OH	C_3H_7 (±)	B	116 ± 14	19.6 ± 6	0.006 (0.003–0.01)
VI-13	9-OCH_3	C_3H_7 (+)	D	1300 ± 500	1520 ± 570	0.032 (0.017–0.058)
VI-14	9-OCH_3	C_3H_7 (−)	D	410 ± 60	10 210 ± 4500	0.75
VII-15	9-OH	C_3H_7 (+)	B	85 ± 23	23 ± 12	0.005 (0.003–0.007)
VII-16	9-OH	C_3H_7 (−)	B	1800	25 300 ± 10 800	30.0
VI-17	9-OCH_3	C_3H_7 "cis"	F	5600 ± 1300	65 300 ± 9800	15.0
VII-18	9-OH	C_3H_7 "cis"	B	6500 ± 2800	19 600 ± 4300	15.0
VI-19	9-OCH_3	H	A	2100 ± 500	2930 ± 700	1.8[a]
VII-20	9-OH	H	B	39 ± 7	14 ± 5	0.6 (0.2–1.7)
VI-21	9-OCH_3	CH_3	E	310 ± 60	3800 ± 400	3.7[a]
VII-22	9-OH	CH_3	B	71 ± 20	14 ± 3	0.16[a]
VI-23	9-OCH_3	C_4H_9	E	270 ± 30	8300 ± 1000	15.0
VII-24	9-OH	C_4H_9	B	1000 ± 300	572 ± 145	0.8 (0.2–2.7)

[a] Dose–response curve too steep or shallow to predict 95% CL.

Table II



A B C (+)VII-15 D

	α-receptor: IC_{50}, nM (clonidine)	dopamine receptor binding: IC_{50}, nM (apomorphine)	contralateral turning in 6-OHDA-lesioned rats: ED_{50}, mg/kg (95% CL)
(+)**VII-15**	85 ± 23	23 ± 12	0.005 (0.003–0.007)
A	7 ± 1	2 ± 0.46	0.027 (0.003–0.040)
B (pergolide)	41	3.1 ± 1.04	0.10 (0.05–0.30)
C (LY-141865)			0.05[7a]
bromocriptine	514	27.9 ± 14.3	2.80 (1.6–5.2)
D (apomorphine)	63	1.1 ± 0.1	0.14 (0.01–0.022)

The more dopaminergic enantiomers in each case are believed to be of opposite absolute configuration. When the nitrogen atoms of these enantiomers are superimposed with that of apomorphine so that the spatial orientation of the adjoining carbon atoms is identical, the hydroxyl groups align with the 11-hydroxyl group of the alkaloid. Thus, viewing the naphthoxazines as analogues of the 2-aminotetralins with greater conformational rigidity predicted that the 7- and 9-hydroxy isomers (**VII-7** and **VII-9**) would be the more potent dopaminergics with the former isomer having the greater potency. This prediction was further supported by comparing the distance between the hydroxyl group and nitrogen atom in the mono-

(15) (a) McDermed, J. D.; Freeman, H. S.; Ferris, R. M. "Catecholamines: Basic and Clinical Frontiers"; Usdin, E., Kopin, I. J., Barchas, J., Eds.; Pergamon Press: Elmsford, NY, 1979; Vol. 1, p 568. (b) McDermed, J. D.; 8th International Congress Pharmacology, Satellite Symposium on Dopamine, Okayama, Japan, July 1981, Abstr., p 22.

Table III

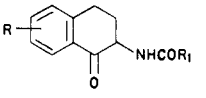
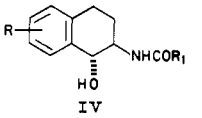
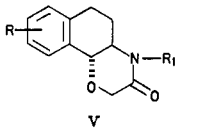
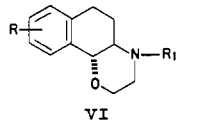
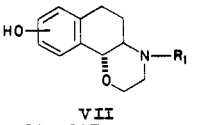
no.	R	R_1	mp, °C	yield, %	formula	anal.
						
			III			
1	H	CH_2Cl	121–123	57	$C_{12}H_{12}NO_2Cl$	C, H, N
2	H	CH_3	124–126	71	$C_{12}H_{13}NO_2$	C, H, N
3	H	C_2H_5	88–90	70	$C_{13}H_{15}NO_2$	C, H, N
4	5-OCH_3	CH_3	187–190	62	$C_{13}H_{15}NO_3$	C, H, N
5	6-OCH_3	CH_3	known[17]			
6	7-OCH_3	CH_3	132–134	56	$C_{13}H_{15}NO_3$	C, H, N
8	6-$OCH_2C_6H_5$	CH_3	145–147	88	$C_{19}H_{19}NO_3$	C, H, N
10	8-$OCH_2C_6H_5$	CH_3	145–147	19	$C_{19}H_{19}NO_3$	C, H, N
11	7-OCH_3	C_2H_5	120–122	50	$C_{14}H_{17}NO_3$	C, H, N
19	7-OCH_3	CH_2Cl	126–132	85	$C_{13}H_{14}NO_3Cl$	C, H, N
						
			IV			
1	H	CH_2Cl	136–138	71	$C_{12}H_{14}NO_2Cl$	C, H, N
2	H	CH_3	159–163	64	$C_{12}H_{15}NO_2$	C, H, N
3	H	C_2H_5	138–141	66	$C_{13}H_{17}NO_2$	C, H, N
4	5-OCH_3	CH_3	200–202	37	$C_{13}H_{17}NO_3$	C, H, N
5	6-OCH_3	CH_3	known[17]			
6	7-OCH_3	CH_3	149–151	61	$C_{13}H_{17}NO_3$	C, H, N
8	6-$OCH_2C_6H_5$	CH_3	140–144	75	$C_{19}H_{21}NO_3$	C, H, N
10	8-$OCH_2C_6H_5$	CH_3	154–157	22	$C_{19}H_{21}NO_3$	C, H, N
11	7-OCH_3	C_2H_5	136–139	55	$C_{14}H_{19}NO_3$	C, H, N
13 (+)	7-OCH_3	C_2H_5	162–163	87	$C_{14}H_{19}NO_3$	C, H, N
14 (–)	7-OCH_3	C_2H_5	162–164	70	$C_{14}H_{19}NO_3$	C, H, N
17 "cis"	7-OCH_3	C_2H_5	131–134	56	$C_{14}H_{19}NO_3$	C, H, N
19	7-OCH_3	CH_2Cl	164–165	60	$C_{13}H_{16}NO_3Cl$	C, H, N
						
			V			
1	H	H	232–235 dec	71	$C_{12}H_{13}NO_2$	C, H, N
2	H	C_2H_5	172–174	31	$C_{14}H_{17}NO_2$	C, H, N
3	H	C_3H_7	105–108	45	$C_{15}H_{19}NO_2$	C, H, N
4	7-OCH_3	C_2H_5	187–189	61	$C_{15}H_{19}NO_3$	C, H, N
5	8-OCH_3	C_2H_5	156–158	54	$C_{15}H_{19}NO_3$	C, H, N
6	9-OCH_3	C_2H_5	126–128	78	$C_{15}H_{19}NO_3$	C, H, N
8	8-$OCH_2C_6H_5$	C_2H_5	160–163	46	$C_{21}H_{23}NO_3$	C, H, N
10	10-$OCH_2C_6H_5$	C_2H_5	125–128	49	$C_{21}H_{23}NO_3$	C, H, N
11	9-OCH_3	C_3H_7	92–94	72	$C_{16}H_{21}NO_3$	C, H, N
13 (+)	9-OCH_3	C_3H_7	94–96	78	$C_{16}H_{21}NO_3$	C, H, N
14 (–)	9-OCH_3	C_3H_7	94–96	67	$C_{16}H_{21}NO_3$	C, H, N
17 "cis"	9-OCH_3	C_3H_7	120–121.5	52	$C_{16}H_{21}NO_3$	C, H, N
19	9-OCH_3	H	222–228	85	$C_{13}H_{15}NO_3$	C, H, N
						
			VI			
1	H	H	290 dec	95	$C_{12}H_{15}NO\cdot HCl$	C, H, N
2	H	C_2H_5	218–221 dec	46	$C_{14}H_{19}NO\cdot HCl$	C, H, N
3	H	C_3H_7	259–261	33	$C_{15}H_{21}NO\cdot HCl$	C, H, N
4	7-OCH_3	C_2H_5	279–284	73	$C_{15}H_{21}NO_2\cdot HCl$	C, H, N
5	8-OCH_3	C_2H_5	210–213 dec	25	$C_{15}H_{21}NO_2\cdot HCl$	C, H, N
6	9-OCH_3	C_2H_5	273–275	40	$C_{15}H_{21}NO_2\cdot HCl$	C, H, N
11	9-OCH_3	C_3H_7	237–241	38	$C_{16}H_{23}NO_2\cdot HCl$	C, H, N
13 (+)	9-OCH_3	C_3H_7	231–233	63	$C_{16}H_{23}NO_2\cdot HCl$	C, H, N
14 (–)	9-OCH_3	C_3H_7	231–233	28	$C_{16}H_{23}NO_2\cdot HCl$	C, H, N
17 "cis"	9-OCH_3	C_3H_7	234–236	82	$C_{16}H_{23}NO_2\cdot HCl$	C, H, N
19	9-OCH_3	H	250–253	65	$C_{13}H_{17}NO_2\cdot HCl$	C, H, N
21	9-OCH_3	CH_3	238–242	71	$C_{14}H_{19}NO_2\cdot HCl$	C, H, N
23	9-OCH_3	C_4H_9	221–225	41	$C_{17}H_{25}NO_2\cdot HCl$	C, H, N
						
			VII			
7	7-OH	C_2H_5	295–297	25	$C_{14}H_{19}NO_2\cdot HCl$	C, H, N

Table III (Continued)

no.	R	R_1	mp, °C	yield, %	formula	anal.
8	8-OH	C_2H_5	187–191	75	$C_{14}H_{19}NO_2$	C, H, N
9	9-OH	C_2H_5	223–225	42	$C_{14}H_{19}NO_2$	C, H, N
10	10-OH	C_2H_5	165–168	28	$C_{14}H_{19}NO_2 \cdot C_4H_4O_4$	C, H, N
12	9-OH	C_3H_7	164–166	69	$C_{15}H_{21}NO_2$	C, H, N
15 (+)	9-OH	C_3H_7	158–160	79	$C_{15}H_{21}NO_2$	C, H, N
16 (−)	9-OH	C_3H_7	158–161	65	$C_{15}H_{21}NO_2$	C, H, N
18 "cis"	9-OH	C_3H_7	265–267	52	$C_{15}H_{21}NO_2 \cdot HCl \cdot {}^1/_4H_2O$	C, H, N
20	9-OH	H	300–303	71	$C_{12}H_{15}NO_2 \cdot HCl$	C, H, N
22	9-OH	CH_3	200–202	26	$C_{13}H_{17}NO_2$	C, H, N
24	9-OH	C_4H_9	118–120	56	$C_{16}H_{23}NO_2$	C, H, N

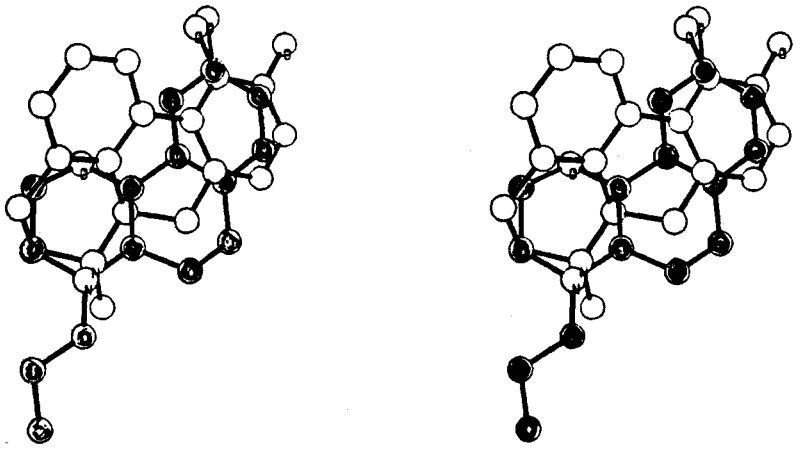


Figure 2. Computer-generated stereoscopic view of (+)**VII-15** (dark circles) superposed on (*R*)-(−)-apomorphine so that dopamine-like parts of the molecules are maximally fitted.

hydroxynaphthoxazines (7-OH isomer (**VII-7**)/6.5 Å, 8-OH (**VII-8**)/7.9 Å, 9-OH (**VII-9**)/7.4 Å). The nitrogen to hydroxyl group distance found in the 7-OH isomer (**VII-7**) is the same as that found in 5-hydroxy-2-aminotetralin and apomorphine (N to 11-OH distance). On the basis of this analysis, the biological results reported for naphthoxazines **VII-7**–**VII-9** in Table I were surprising in that **VII-7** was substantially less active than **VII-9** and approximately equal in potency to **VII-8**. It appeared that the analogy of naphthoxazines as 2-aminotetralins with a fused oxazine ring might be inappropriate. However, resolution of **VII-12**, the *N*-propyl analogue of **VII-9**, revealed that the more active enantiomer, (+)**VII-15**, had the *R* absolute configuration at the 4a chiral center as would be predicted from the 2-aminotetralin analogy. Further, the effect of N-substituents on in vivo dopamine-like activity (6-OHDA-lesioned rat) for 9-hydroxynaphthoxazines followed the pattern expected for 2-aminotetralins ($C_4H_9 < C_3H_7 > C_2H_5 > CH_3 > H$).[12] The in vitro SAR pattern was similar with the surprising exception the *N*-C_2H_5 analogue (**VII-9**) was more potent than *N*-C_3H_7 (**VII-12**). Finally, computer modeling of (+)**VII-15** and (*R*)-(−)-apomorphine (D) (Figure 2) so that the 9-hydroxyl group of (+)**VII-15** corresponds closely with the 11-hydroxyl substituent in D demonstrated an optimal matching of molecular volumes. This orientation was chosen on the basis of the structural analysis and arguments set forth by Camerman and Camerman[13] and the findings of Neumeyer et al.[14] concerning the importance of the 11-hydroxyl group of the aporphines in dopamine receptor binding. If the more active enantiomer of the corresponding 7-hydroxynaphthoxazine has the 4a*S* configuration, an important point that we have yet to confirm, an optimal overlap between the dopamine-like portions of this enantiomer and apomorphine can be achieved. However, the oxazine ring must be positioned so that the molecular volume overlap is not optimal. This may account for the potency differences observed between these naphthoxazines and the corresponding 2-aminotetralins. Should the more active enantiomer of the 8-hydroxynaphthoxazines have the 4a*R* configuration, support for this view would be obtained. We currently are pursuing both of these configurational determinations.

The effect of (+)**VII-15** on the dopamine-sensitive adenylate cyclase in carp retina was examined as a measure of D_2 receptor selectivity.[16] While 100 μM dopamine produced a 265% increase in cAMP formation, this concentration of (+)**VII-15** failed to stimulate cAMP synthesis. On the basis of this apparent selectivity for D_2 receptors, its remarkable in vivo dopaminergic potency (ED_{50} = 0.005 mg/kg, 6-OHDA rat assay), and dopamine vs. α_2-adrenergic receptor selectivity, compound (+)**VII-15** was selected for clinical evaluation.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^1H NMR spectra were taken on a Nicolet 360-MHz or a Varian T-60A spectrometer using Me_4Si as an internal standard. Optical rotations were determined with a Perkin-Elmer 141 polarimeter at 25 °C. Solutions were dried over Na_2SO_4 and concentrated with a Buchi rotary evaporator under water aspirator pressure. Each preparative method is illustrated by a representative example; pertinent data for other new compounds are summarized in Table III. Two TLC solvent systems were used, namely, $CHCl_3$–MeOH (9:1) or EtOAc–hexane (1:1).

2-(2-Chloroacetamido)-3,4-dihydronaphthalen-1(2*H*)-one (III-1). This compound was prepared by the method described in ref 5; the yield was 2.7 g (57%) of **III-1**: mp 121–123 °C. Anal. ($C_{12}H_{12}NO_2Cl$) C, H, N.

Scheme I, Step 1. 2-Acetamido-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (III-4). A mixture of potassium *tert*-

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butoxide (27.6 g, 0.25 mol), ether (360 mL), butanol (50 mL), and ethanol (50 mL) was stirred and heated at reflux for 1 h and then cooled in ice. A solution of isoamyl nitrite (34 mL) and 5-methoxy-1-tetralone (42 g, 0.2 mol) in ether (750 mL) was added over a period of 0.5 h. The mixture was stirred at room temperature for 4 h and then filtered to recover the potassium salt of the oxime. This solid was added in portions to cold, stirred 1 N HCl (750 mL). The resulting dark solid was filtered and dried. The oximes were not purified further. The solid oxime (32 g) was dissolved in a mixture of THF (90 mL), acetic anhydride (90 mL), and 10% Pd/C (1.2 g) as catalyst and hydrogenated on a Parr apparatus until hydrogen uptake ceased. The reaction mixture was filtered and the solvents removed in vacuo to yield 28.8 g (62%) of **III-4**: (EtOAc) mp 187–190 °C. Anal. ($C_{13}H_{15}NO_3$) C, H, N.

Step 2. *trans*-2-Acetamido-5-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (IV-4). Sodium borohydride (0.68 g, 0.018 mol) was added in portions to a stirred solution of **III-4** (3.75 g, 0.016 mol) in ethanol (75 mL). When the reaction was complete (TLC), excess borohydride was destroyed by the addition of HOAc. The reaction mixture was diluted with H_2O (150 mL) and extracted with ethyl acetate (3 × 100 mL). The acetate layer was separated, dried, and evaporated to afford a solid. The solid was purified by crystallization (EtOAc) to yield 1.39 g (37%) of **IV-4**: mp 200–202 °C. Anal. ($C_{13}H_{17}NO_3$) C, H, N.

Step 3. *trans*-1a,2,4,4a,5,6-Hexahydro-7-methoxy-4-ethylnaphth[1,2-*b*]-1,4-oxazin-3-one (V-4). A solution of **IV-4** (2.3 g, 0.01 mol) in THF (200 mL) and ethylene glycol–dimethyl ether (100 mL) was added to a stirred suspension of $LiAlH_4$ (1.0 g, excess) in THF (100 mL) at 0–5 °C over a period of 0.5 h. The reaction was allowed to come to room temperature and then heated at reflux for 1 h. After cooling (5–10 °C) excess hydride was destroyed with 2-propanol, several milliliters of a saturated aqueous solution of Na_2SO_4 were added, and the mixture was filtered. The filtrate was concentrated, the residue was dissolved in ethyl acetate (150 mL) and 75 mL of saturated Na_2CO_3 solution was added. Chloroacetyl chloride (1.2 mL) was added to the stirred mixture. After 1 h the organic layer was separated and dried and the solvent removed in vacuo. The resulting oil was dissolved in a solution of acetonitrile (5 mL) and THF (25 mL) and added dropwise to a suspension of NaH (1.0 g, 50% mineral oil) in THF (20 mL). After 1 h excess hydride was destroyed with ethanol, and the reaction mixture was diluted with H_2O (300 mL) and extracted with ethyl acetate (3 × 100 mL). The acetate layer was dried and concentrated to a solid that was recrystallized from cyclohexane to yield 1.58 g (61%) of **V-4**: mp 187–189 °C. Anal. ($C_{15}H_{19}NO_3$) C, H, N.

Step 4. *trans*-3,4,4a,5,6,10b-Hexahydro-7-methoxy-4-ethyl-2*H*-naphth[1,2-*b*]-1,4-oxazine Hydrochloride (VI-4). A solution of **V-4** (2.6 g, 0.01 mol) in THF (100 mL) was added to a stirred suspension of $LiAlH_4$ (0.8 g, excess) in THF (35 mL) cooled at 5–10 °C. The reaction mixture was allowed to come to room temperature and then heated at reflux for 1 h. After cooling (5–10 °C) excess hydride was destroyed by adding several milliliters of 2-propanol, saturated aqueous Na_2SO_4 (2.2 mL) was added, and then the reaction mixture was filtered (Supercel). The solvent was removed in vacuo, the resulting oil was dissolved in ether (75 mL), and a slight excess of ethanolic HCl (7.2 N) was added. The hydrochloric acid salt that separated was recrystallized from ethanol to yield 2.5 g (73%) of **VI-4**: mp 279–284 °C. Anal. ($C_{15}H_{21}NO_2$·HCl) C, H, N.

Step 5. *trans*-3,4,4a,5,6,10b-Hexahydro-4-ethyl-2*H*-naphth[1,2-*b*]-1,4-oxazin-7-ol Hydrochloride (VII-7). A mixture of pyridine hydrochloride (3.4 g, 0.03 mol) and **VI-4** (2.8 g, 0.01 mol) was heated in an oil bath at 200 °C for 1–2 h. When the reaction was complete (TLC) it was cooled, diluted with H_2O, made slightly basic with NH_4OH, and extracted with $CHCl_3$ (2 × 75 mL). The $CHCl_3$ layer was dried and evaporated in vacuo. The residue was dissolved in ethyl acetate and 4 N ethanolic HCl (excess) was added. The solid that separated was recrystallized from 2-propanol to yield 0.7 g (25%) of **VII-7**: mp 295–297 °C. Anal. ($C_{14}H_{19}NO_2$·HCl) C, H, N.

Step 6. *trans*-3,4,4a,5,6,10b-Hexahydro-9-methoxy-4-methyl-2*H*-naphth[1,2-*b*]-1,4-oxazine Hydrochloride (VI-21). A solution of **VI-19** (2.1 g, 0.01 mol) in ethanol containing 7 mL of 40% formalin and 200 mg of 10% Pd/C as catalyst was hydrogenated on a Parr apparatus for 4 h. The reaction mixture was removed from the Parr, filtered, and concentrated. The residue was taken up in ether and ethanolic hydrochloric acid added to yield 1.9 g (71%) of **VI-21**: mp 238–242 °C. Anal. ($C_{14}H_{19}NO_2$·HCl) C, H, N.

Scheme II, Step 1. 2-Acetamido-6-(benzyloxy)-3,4-dihydronaphthalen-1(2*H*)-one (III-8). The nitrosation reaction was carried out exactly as described in Scheme I, step 1. The crude oxime **II-8** (2.8 g, 0.01 mol) was dissolved in HOAc (15 mL), acetic anhydride (15 mL), and 2.5 g of Zn dust was added in portions. The reaction mixture was heated at 65 °C for 0.5 h, cooled, and filtered and the solvent removed in vacuo. The residue was purified by medium-pressure chromatography using methylene chloride–acetone (9:1) as the eluting solvent. The yield was 2.8 g (88%) of **III-8**: mp 145–147 °C. Anal. ($C_{19}H_{19}NO_3$) C, H, N.

Steps 2–4 were carried out exactly as described in Scheme I.

Step 5. *trans*-3,4,4a,5,6,10b-Hexahydro-4-ethyl-2*H*-naphth[1,2-*b*]-1,4-oxazin-8-ol (VII-8). A solution of **VI-8** (3.2 g, 0.01 mol) (**VI-8,10** were not obtained analytically pure) in ethanol–THF (1:1) (75 mL) containing 200 mg of 10% Pd/C catalyst was hydrogenated on a Parr apparatus until the hydrogen uptake ceased. The reaction mixture was filtered and the solvent removed in vacuo. The residue was crystallized from acetonitrile to yield 1.63 g (70%) of **VII-8**: mp 187–191 °C. Anal. ($C_{14}H_{19}NO_2$) C, H, N.

Scheme III, step 1: preparation of the *l*-*O*-methylmandelate esters of alcohol **IV-11** and separation of the enantiomers by medium-pressure chromatography. To 400 mL of methylene chloride was added alcohol **IV-11** (10 g, 0.04 mol), *l*-*O*-methylmandelic acid (12.0 g), dicyclohexylcarbodiimide (16 g), and 4-(dimethylamino)pyridine (1.0 g). This mixture was stirred for 0.5–1 h and then filtered. The filtrate was added directly to a medium-pressure chromatography column containing 2.5 kg of silica and the column was developed with the solvent system methylene chloride–ethyl acetate (4:1); 700-mL fractions were collected. Fractions 21–39 contained (+)**XX**; the yield was 9.23 g (116%); pure material had mp 103–105 °C; $[\alpha]_{Na}$ −34.06° (*c* 0.086, C_2H_5OH). Fractions 46–61 contained (−)**XX**; the yield was 9.0 g (113%); pure material had mp 50–52 °C; $[\alpha]_{Na}$ −77.81° (*c* 0.103, C_2H_5OH). The crude yields are high because the products contained some dicyclohexylurea. These products were purified by suspending in $CHCl_3$ (most dissolved), filtering, and then removing the solvent in vacuo. Two such cycles gave pure material.

Step 2. (+)-*trans*-2-Propionamido-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol [(+)IV-13]. A solution of (+)**XX** (23.85 g, 0.06 mol) in ethanol (200 mL) and H_2O (1 mL) containing KOH (5.2 g) was heated at 50 °C for 15–20 min. The reaction mixture was cooled, diluted with H_2O (300 mL), and extracted with $CHCl_3$ (3 × 150 mL). The $CHCl_3$ layer was dried and evaporated, ether was added to the residue, and a solid was obtained. The yield was 13 g (87%) of (+)**IV-13**: mp 162–163 °C; $[\alpha]_{Na}$ +71.02° (*c* 0.105, C_2H_5OH). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

Step 3. (−)-*trans*-1a,2,4,4a,5,6-Hexahydro-9-methoxy-4-propylnaphth[1,2-*b*]-1,4-oxazin-3-one [(−)V-13]. This compound was prepared by exactly the same procedure described in Scheme I, step 3. From 2.3 g (0.01 mol) of (+)**IV-13** there was obtained 2.15 g (78%) of (−)**V-13**: mp 94–96 °C; $[\alpha]_{Na}$ −36.94° (*c* 0.0896, C_2H_5OH). Anal. ($C_{16}H_{21}NO_3$) C, H, N.

Step 4. (+)-*trans*-3,4,4a,5,6,10b-Hexahydro-9-methoxy-4-propyl-2*H*-naphth[1,2-*b*]-1,4-oxazine Hydrochloride [(+)-VI-13]. This compound was prepared by exactly the same procedure described in Scheme I, step 4. From 12.5 g (0.045 mol) of (−)**V-13** there was obtained 8.5 g (63%) of (+)**VI-13**: mp 231–233 °C; $[\alpha]_{Na}$ +47.28° (*c* 0.103, C_2H_5OH). Anal. ($C_{16}H_{23}NO_2$·HCl) C, H, N.

Step 5. (+)-*trans*-3,4,4a,5,6,10b-Hexahydro-4-propyl-2*H*-naphth[1,2-*b*]-1,4-oxazin-9-ol [(+)VII-15]. This compound was prepared by exactly the same procedure described in Scheme I, step 5, however, omitting the conversion to the hydrochloric acid salt. From 5.0 g (0.017 mol) of (+)**VI-13** there was obtained 3.3 g (79%) of (+)**VII-15**: mp 158–160 °C; $[\alpha]_{Na}$ +59.54° (*c* 0.0964, C_2H_5OH). Anal. ($C_{15}H_{21}NO_2$) C, H, N.

The other enantiomer (−)**XX** was carried through the same series of procedures as described above for (+)**XX**; the pertinent

data for each compound can be found in Table III. Optical rotational data: (−)XX, $[\alpha]_{Na}$ −77.81° (c 0.103, C_2H_5OH); (−)IV-14, $[\alpha]_{Na}$ −73.44° (c 0.104, C_2H_5OH); (−)V-14, $[\alpha]_{Na}$ +36.63° (c 0.0982, C_2H_5OH); (−)VI-14, $[\alpha]_{Na}$ −47.44° (c 0.0978, C_2H_5OH); (−)VII-16, $[\alpha]_{Na}$ −62.63° (c 0.0942, C_2H_5OH).

Scheme IV, Step 1. *cis*-2-Propionamido-7-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (IV-17). The sodium borohydride reduction of ketone III-11 was carried out as described in Scheme I, step 2. By TLC there was noted to be a mixture of cis and trans alcohols obtained in this reduction. These isomers were separated cleanly by medium-pressure chromatography using CH_2Cl_2 saturated with NH_3 and containing 1% CH_3OH as the eluting solvent. The cis isomer was eluted first and evaporation of the proper fractions afforded 2.3 g (16%) of IV-17: mp 131–134 °C; ^1H NMR ($DCCl_3$) δ 4.57 (1 H, d, J = 3 Hz). Anal. ($C_{14}H_{19}NO_3$) C, H, N. For the trans isomer, ^1H NMR ($DCCl_3$) δ 4.35 (1 H, d, J = 9 Hz).

Steps 2–4 were carried out as described in Scheme I. The phenol *cis*-VII-18 was obtained by using the procedure of Scheme I, step 5.

Pharmacology. For the *α-receptor binding assay*, [^3H]clonidine was used as the radioligand to determine the interaction of the compounds with the α-adrenergic receptor in calf cerebral cortex in vitro. For the *dopamine receptor binding assay*, [^3H]apomorphine was used as radioligand to determine interaction with the DA receptors in rat striatal membranes in vitro. A detailed description of these test procedures is given in ref 5. A description of the assay for *contralateral turning in 6-hydroxydopamine-lesioned rats* is also provided in ref 5.

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Registry No. I-4, 33892-75-0; I-8, 32263-70-0; II-1, 39262-02-7; II-4, 92422-31-6; II-4-K, 92422-37-2; II-5, 2471-78-5; II-6, 2471-80-9; II-8, 92422-32-7; II-10, 92422-33-8; (±)-III-1, 92421-76-6; (±)-III-2, 88058-53-1; (±)-III-3, 92421-77-7; (±)-III-4, 92421-78-8; (±)-III-5, 92421-79-9; (±)-III-6, 92421-80-2; (±)-III-8, 92421-81-3; (±)-III-10, 92421-82-4; (±)-III-11, 88058-66-6; (±)-III-19, 92421-83-5; (±)-IV-1, 92471-25-5; (±)-IV-2, 88058-55-3; (±)-IV-3, 92421-84-6; (±)-IV-4, 92421-85-7; (±)-IV-5, 92421-86-8; (±)-IV-6, 92421-87-9; (±)-IV-8, 92421-88-0; (±)-IV-10, 92421-89-1; (±)-IV-11, 88058-67-7; (+)-IV-13, 88058-70-2; (−)-IV-14, 88058-73-5; (±)-IV-17, 92421-90-4; (±)-IV-19, 92421-91-5; (±)-V-1, 92471-26-6; (±)-V-2, 92421-92-6; (±)-V-3, 92421-93-7; (±)-V-4, 92421-94-8; (±)-V-5, 92421-95-9; (±)-V-6, 92421-96-0; (±)-V-8, 92421-97-1; (±)-V-10, 92421-98-2; (±)-V-11, 88058-68-8; (+)-V-13, 88058-74-6; (−)-V-14, 88058-71-3; (±)-V-17, 92421-99-3; (±)-V-19, 92422-00-9; (±)-VI-1, 92471-28-8; (±)-VI-1·HCl, 92471-27-7; (±)-VI-2, 92422-18-9; (±)-VI-2·HCl, 92422-01-0; (±)-VI-3, 92422-19-0; (±)-VI-3·HCl, 92422-02-1; (±)-VI-4, 92422-20-3; (±)-VI-4·HCl, 92422-03-2; (±)-VI-5, 92422-21-4; (±)-VI-5·HCl, 92422-04-3; (±)-VI-6, 92422-22-5; (±)-VI-6·HCl, 92422-05-4; (±)-VI-8, 92422-35-0; (±)-VI-10, 92422-36-1; (±)-VI-11, 92422-23-6; (±)-VI-11·HCl, 88058-52-0; (+)-VI-13, 88058-98-4; (+)-VI-13·HCl, 88058-72-4; (−)-VI-14, 88059-00-1; (−)-VI-14·HCl, 88058-75-7; (±)-VI-17, 92422-24-7; (±)-VI-17·HCl, 92422-06-5; (±)-VI-19, 92422-25-8; (±)-VI-19·HCl, 92422-07-6; (±)-VI-21, 92422-26-9; (±)-VI-21·HCl, 92422-08-7; (±)-VI-23, 92422-27-0; (±)-VI-23·HCl, 92422-09-8; (±)-VII-7, 92422-28-1; (±)-VIII-7·HCl, 92422-10-1; (±)-VII-8, 92422-11-2; (±)-VII-9, 89292-84-2; (±)-VII-10, 92422-12-3; (±)-VII-10·$C_4H_4O_4$, 92422-13-4; (±)-VII-12, 89292-85-3; (+)-VII-15, 88058-88-2; (−)-VII-16, 88058-89-3; (±)-VII-18, 92422-29-2; (±)-VII-18·HCl, 92422-14-5; (±)-VII-20, 92422-30-5; (±)-VII-20·HCl, 92422-15-6; (±)-VII-22, 92422-16-7; (±)-VII-24, 92422-17-8; (+)-XX, 88336-54-3; (−)-XX, 88058-69-9; $ClCH_2COCl$, 79-04-9; (±)-*trans*-2-(ethylamino)-5-methoxy-1-tetralol, 92422-34-9; *l*-*O*-methylmandelic acid, 3966-32-3; dopamine, 51-61-6.

Supplementary Material Available: Two tables containing bond lengths and angles for structure (+)VII-15 (4 pages). Ordering information is given on any current masthead page.

Mesoionic Pyridazine Ribonucleosides. A Novel Biologically Active Nucleoside Metabolite

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4-Cyano-3-oxido-1-β-D-ribofuranosylpyridazinium (**10a**) has been prepared from 4-cyano-3(2*H*)-pyridazinone (4) by using a low-temperature, kinetically controlled, silyl Hilbert–Johnson reaction followed by deblocking of the resulting triacetate derivative, **8a**, with $NaHCO_3$ in methanol. **10a** is apparently the first example of a mesoionic analogue of a pyrimidine nucleoside. It was discovered as a urine metabolite of 4-cyano-3(2*H*)-pyridazinone (4) in mice. **10a** possesses Gram-negative antibacterial activity in vivo against a systemic *Escherichia coli* infection in mice with an ED_{50} of 25–50 mg/kg. A series of 4-substituted 3-oxidopyridazinium ribonucleosides, **11a–h**, were synthesized as analogues of **10a**. 4-Chloro-3-oxido-1-β-D-ribofuranosylpyridazinium (**11a**) was found to be several times more active than **10a** against *E. coli* in vitro although it showed no in vivo activity.

Much attention has been given to the synthesis and biological evaluation of pyrimidine, pyridine, pyridazine, and related monoheterocyclic nucleosides.[1] There has also been extensive interest in mesoionic derivatives of these same bases.[2] The corresponding mesoionic nucleosides have been overlooked and would seem to be of interest especially as they relate to the biologically important pyrimidine nucleosides such as thymidine or cytidine. One might initially be concerned about the chemical stability of such molecules in view of the attachment of a positively charged nitrogen atom to the anomeric carbon with its high propensity to form a resonance-stabilized carbonium ion. However, the well-known chemical stability associated with related quaternary systems exemplified by nicotinamide adenine dinucleotide would suggest that the corresponding mesoionic structures may not pose a serious stability problem. Another concern in terms of biological potential is an expected increase in polar character associated with mesoionic nucleosides relative to isomeric nonmesoionic

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