(1 H, s), 7.72 (1 H, s, broad), 4.00 (4 H, A_2B_2), 2.63 (3 H, broad s).

Method F. 6-Phenyl-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine (2e). Step A. 3-Amino-6-phenyl-2-pyrazinecarboxylic Acid. A solution of methyl 3-amino-6-phenylpyrazine-2-carboxylate[22] (4.6 g, 0.02 mol) and 10 mL of 5 N NaOH in 200 mL of CH_3OH was stirred for 1 h at room temperature and then diluted with 1 L of water and adjusted to pH 2 with 6 N HCl. The 3-amino-6-phenyl-2-pyrazinecarboxylic acid precipitated, collected, and dried by suction to give 3.8 g (88%) of a yellow solid, mp 189–191 °C (dec). Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.09; H, 4.13; N, 19.55.

Step B. 2-Amino-3-bromo-5-phenylpyrazine. To a vigorously stirred suspension of the product from step A (3.5 g, 0.016 mol) and sodium acetate trihydrate (4.5 g, 0.033 mol) in 30 mL of glacial HOAc at room temperature was added dropwise a solution of bromine (2.8 g, 0.91 mL, 0.018 mol) in 10 mL of glacial HOAc. The mixture was stirred for 18 h at room temperature and poured into 200 mL of H_2O, and the tan solid, 2-amino-3-bromo-5-phenylpyrazine (3.7 g, 91%), was collected by suction and dried in vacuo, mp 146–147 °C. Anal. Calcd for $C_{10}H_8BrN_3$: C, 48.02; H, 3.22; N, 16.80. Found: C, 48.25; H, 3.13; N, 16.83.

Step C. 8-Bromo-6-phenylimidazo[1,2-*a*]pyrazine (3e) Hydrobromide. Condensation of the product from step B with bromoacetaldehyde by a procedure analogous to method C (step A) afforded the crystalline 8-bromo-6-phenylimidazo[1,2-*a*]pyrazine hydrobromide in 73% yield, mp 290–293 °C. Anal. Calcd for $C_{12}H_8BrN_3$·HBr: C, 40.59; H, 2.55; N, 11.84. Found: C, 40.99; H, 2.58; N, 11.46.

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Step D. 6-Phenyl-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine Hydrochloride (2e). Treatment of the product from step C with excess piperazine by a procedure analogous to method E (step B) gave 6-phenyl-8-(1-piperazinyl)imidazo[1,2-*a*]pyrazine hydrochloride (**2e**) as colorless crystals from EtOH in 60% yield, mp >300 °C. Anal. Calcd for $C_{16}H_{17}N_5$·HCl: C, 60.85; H, 5.74; N, 22.18. Found: C, 60.57; H, 5.70; N, 21.89.

Acknowledgment. We thank Dr. W. S. Saari for some helpful suggestions during the course of this work. We are grateful to Thelma H. Brunner for manuscript preparation and H. Dillman and staff for graphic art work.

Registry No. **1**, 64022-27-1; **2a**, 76537-28-5; **2a** (base), 76537-53-6; **2b**, 76551-54-7; **2b** (base), 84065-99-6; **2d**, 76537-24-1; **2d** (base), 77111-80-9; **2e**, 84066-00-2; **2e** (base), 84066-01-3; **2f**, 84066-02-4; **2f** (base), 84066-03-5; **2g**, 84066-04-6; **2g** (base), 76537-52-5; **2h**, 84066-05-7; **2i**, 84066-06-8; **2i** (base), 84066-07-9; **2j**, 76537-29-6; **2j** (base), 84073-46-1; **2k**, 76537-25-2; **2k** (base), 84066-08-0; **2l**, 84066-09-1; **2l** (base), 84066-10-4; **3a** (R^8 = Cl), 69214-33-1; **3a** (R^8 = Br), 69214-34-2; **3b** (R^8 = Cl), 76537-30-9; **3b** (R^8 = Br), 76537-31-0; **3c**, 76537-33-2; **3e**, 84066-12-6; **3f**, 84066-11-5; **3g**, 76537-32-1; **3h**, 63744-41-2; **3i**, 84066-13-7; **3k** (R^8 = Cl), 84066-14-8; **3k** (R^8 = Br), 76537-20-7; **3l**, 84066-15-9; **3m**, 84066-16-0; **3n**, 76537-23-0; **8**, 76537-36-5; **9a**, 84066-17-1; **9b**, 84066-18-2; **10**, 84066-19-3; 2-chloro-3-[(2-hydroxyethyl)amino]-pyrazine, 84066-20-6; **3d**, 76537-19-4; methyl 3-amino-6-phenylpyrazine-2-carboxylate, 1503-42-0; 3-amino-6-phenyl-2-pyrazinecarboxylic acid, 84066-21-7; 2-amino-3-bromo-5-phenylpyrazine, 67602-05-5; 2,3-dichloropyrazine, 4858-85-9; 3-bromo-5-chloro-2-aminopyrazine, 76537-18-3; 2-bromopropionaldehyde diethyl acetal, 3400-55-3; ethanolamine, 141-43-5; *N*-chlorosuccinimide, 128-09-6; 2-amino-5-chloropyrazine, 33332-29-5; piperazine, 110-85-0; bromoacetaldehyde, 17157-48-1; bromoacetaldehyde diethyl acetal, 2032-35-1.

Synthesis of (7*R*)-7*H*-Indolo[3,4-*gh*][1,4]benzoxazines, a New Class of *D*-Heteroergolines with Dopamine Agonist Activity

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Synthesis of several members of the 9-oxaergoline ring system is presented. Both the C/D cis and the C/D trans isomers of 4,6,6a,8,9,10a-hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine were prepared, and the C/D trans isomer was resolved into its optical isomers. The enantiomer having the highest affinity for the [^{3}H]apomorphine binding site, (−)-*trans*-6-ethyl-9-oxaergoline[9] [(−)-**6b**], was shown to have the same absolute configuration as the natural ergolines, namely, 6a*R*,10a*R*. In vivo and in vitro pharmacological evaluation shows these 9-oxaergolines to possess potent dopamine agonist properties.

Parkinsonism is a condition associated with reduced dopamine function and may be characterized by a decrease of transmission at dopamine D_2 receptors.[1] Levodopa, particularly in combination with a decarboxylase inhibitor (i.e., Sinemet), is the established drug of choice for the treatment of this condition. Recently, direct-acting dopamine agonists of the ergoline class, such as bromocriptine,[2] lisuride,[3-5] and pergolide,[6] have been reported to improve the condition of patients who have developed oscillation phenomena or have become partially refractory to levodopa. In addition, the anti-parkinson effect of these direct agonists may be synergistic with levodopa and Sinemet. This class of direct-acting agents has become increasingly attractive with the advent of peripherally selective dopamine antagonists capable of reducing side effects associated with receptor activation.

In this report we describe the pharmacological profile of a new class of heteroergolines, the 4,6,6a,8,9,10a-hexa-

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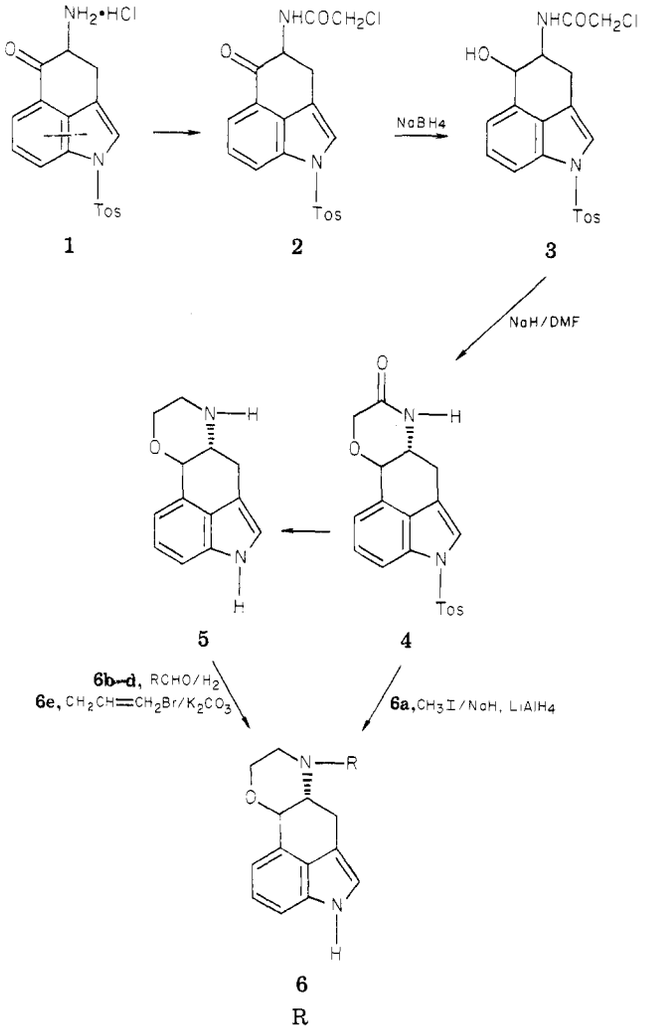
0022-2623/83/1826-0363$01.50/0

Scheme I



5	H	C/D trans
6a	CH_3	C/D trans
(±)-6b	C_2H_5	C/D trans
6c	C_3H_7	C/D trans
6d	C_4H_9	C/D trans
6e	$CH_2CH{=}CH_2$	C/D trans
(+)-6b	C_2H_5	C/D (+)
(−)-6b	C_2H_5	C/D (−)
9	C_2H_5	C/D cis

hydroindolo[3,4-*gh*][1,4]benzoxazines. These oxaergolines have been found to possess high affinity for the [^{3}H]apomorphine binding site and to exhibit potent dopaminergic activity in vivo.

Chemistry. The basic synthetic strategy used for the construction of the 9-oxaergoline[9] nucleus (**6b** and **9**) and the preparation of the enantiomers [(+)-**6b** and (−)-**6b**] (Scheme I) having the trans-fused C/D ring junction has been recently described.[7]

The individual enantiomers of the trans isomer (±)-**6b** were synthesized via resolution through the *l*-*O*-methylmandelic acid ester of the intermediate alcohol (see ref 7). Additionally, (±)-**6b** could be conveniently resolved as the di-p-toluoyl-*d*-tartaric acid salt; this procedure is described under Experimental Section. Initially, the assignment of absolute configuration for the enantiomers (+)-**6b** and

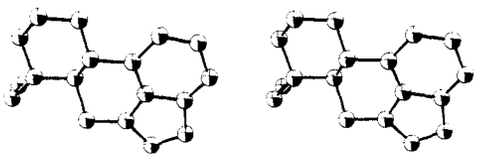


Figure 1. A computer-generated ORTEP drawing of (−)-**6b** from the crystal structure solution.

(−)-**6b** as *S*,*S* and *R*,*R*, respectively, was based on the rules of Moser and Dale.[10] This assignment has been confirmed by the single-crystal X-ray analysis of (−)-**6b**.

The crystal structure of (−)-**6b** was determined as the salt of di-*p*-toluoyl-*d*-tartaric acid by an X-ray diffraction experiment on a specimen grown in methanol. All crystals examined had some degree of twinning as evidenced by preliminary rotation photographs. We were able to determine the unit cell parameters by selectively focusing upon only one homogeneous portion of a twinned fragment and were thereby able to collect a complete set of data. Data were collected on a completely automated Enraf Nonius diffractometer at room temperature with graphite monochromated Cu $K\alpha$ radiation. The unit cell parameters were found to be a = 7.935 (2) Å, b = 13.920 (6) Å, c = 15.216 (7) Å, β = 102.59 (3)°, V = 1640 (1) Å^3, and p (calcd) = 1.244 g/cm^3 in the acentric space group $P2_1$ (Z = 2).

A preliminary trial structure containing 31 atoms was obtained from MULTAN[11] and expanded to 44 atoms through the recycling facility of MULTAN. A difference electron density synthesis provided the location of the two remaining non-hydrogen atoms. The structure was refined by full matrix least squares to a residual index of 0.08236 with anisotropic temperature factors. No hydrogen atoms were included in the least-squares refinement. Using the known *R*,*R* absolute configuration of the di-*p*-toluoyl-*d*-tartaric acid as reference, we found that the absolute configuration of (−)-**6b** at its two chiral centers was *R*,*R* with the hydrogen atoms lying trans axial to one another. A computer-generated stereo ORTEP[12] drawing of (−)-**6b** (less the tartaric acid derivative portion of the crystal structure) is shown in Figure 1. Lists of crystallographic coordinates, bond lengths, and bond angles are available in Supplementary Material.

In order to more fully explore the pharmacological effect of the N-substituent at position 6, a more general synthesis was required, and this is outlined in Scheme I. The key intermediate in this approach was the unsubstituted indolobenzoxazine **5**. This compound was obtained from oxazinone **4** by treatment with $LiAlH_4$, which reduced the amide and removed the protecting group in one step. NaH in DMF effected cyclization of the chloroacetamido alcohol **3** to the oxazinone **4**. The trans stereochemistry of **3** was obtained by $NaBH_4$ reduction of ketone **2**. This result had been previously observed by Bowman et al.[8] Ketone **2** was prepared by the acetylation of the known amino ketone **1**[8] with chloroacetyl chloride. Reductive alkylation of **5**, using the appropriate aldehyde, afforded **6b–d**. Alkylation of oxazinone **4** with methyl iodide, followed by $LiAlH_4$ reduction of the intermediate, afforded **6a**. Direct alkylation of **5** with allyl bromide gave **6e**.

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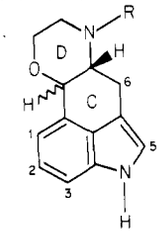
Table I



compd	C/D ring junction	R	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)
5	trans	H	55 ± 4	59.6 ± 13.3	0.76 (0.57, 1.02)
6a	trans	CH_3	27 ± 1	28.9 ± 4.7	0.18 (0.11, 0.28)
6b	trans	C_2H_5	15 ± 1	4.65 ± 1.18[b]	0.09 (0.05, 0.13)[b]
6c	trans	C_3H_7	31 ± 4	2.2 ± 0.60	0.028 (0.013, 0.04)
6d	trans	C_4H_9	46 ± 5	33 ± 5.8	1.1[a]
6e	trans	$CH_2CH=CH_2$	206 ± 20	23 ± 0.85	0.15 (0.08, 0.60)
(+)-6b	trans (+)	C_2H_5	34 ± 8	219 ± 30[b]	7.5[a,b]
(−)-6b	trans (−)	C_2H_5	7 ± 1	2 ± 0.46[b]	0.027 (0.003, 0.040)[b]
9	cis	C_2H_5	1354 ± 330	1240 (n = 1) >1000	>5.0
pergolide			41	3.1 ± 1.04	0.10 (0.05, 0.30)
bromocriptine			514	27.9 ± 14.3	2.80 (1.6, 5.2)

[a] Dose-response curve too steep to determine 95% CL. [b] See also ref 18.

Discussion

The ergot alkaloids possess a wide range of biological properties, one of which is dopaminergic activity. Recently, three semisynthetic ergoline derivatives, bromocriptine, lisuride, and pergolide, have demonstrated therapeutic usefulness in the treatment of Parkinson's disease. This utility is dependent upon the ability to activate postsynaptic dopamine receptors. An in vitro model of affinity for this receptor is the displacement of [^{3}H]apomorphine from binding sites on rat striatal membranes. As indicated in Table I, the affinity of the oxaergolines is primarily dependent upon conformation of the C/D ring junction: as shown by a comparison of the isomer (±)-**6b** (IC_{50} = 4.6 nM) and **9** (IC_{50} = 1240 nM), a trans fusion is required; a further comparison of the trans enantiomers (+)-**6b** (IC_{50} = 219) and (−)-**6b** (IC_{50} = 2) reveals an *R,R* conformational requirement. In agreement with structure–activity relationships reported[13] for other dopaminergic agents, affinity for the receptor is also secondarily dependent upon the N-substituent at position 7, with activity peaking with the *N*-propyl derivative **6c** (IC_{50} = 2.2 nM).

An accepted in vivo measure of dopaminergic activity is the induction of turning behavior in 6-hydroxydopamine (6-OHDA) lesioned rats.[14] Contralateral turning caused by apomorphine has been explained as a stimulation of the dopamine receptors that are hypersensitive due to degeneration of the nigrostriatal pathways.

Table I records the ED_{50} values obtained for the oxaergolines and standards in the 6-OHDA lesioned rat. The order of potency observed is in agreement with the relative affinity for the [^{3}H]apomorphine binding site. Again, the *R,R* trans-fused *N*-ethyl derivative (−)-**6b** is superior in potency to the *S,S* isomer (+)-**6b** and the cis-fused racemate **9**, verifying the conformational requirements observed in vitro.

In addition to affinity for the [^{3}H]apomorphine binding site, many dopaminergics also exhibit a tendency to interact with the α-adrenergic receptor. In order to assess the oxaergolines for α-receptor affinity, all examples were evaluated for their ability to displace [^{3}H]clonidine from calf cortical membranes. Such displacement can be viewed as a measure of the affinity for the α_2-adrenergic receptor.

Several key points emerge from an analysis of the data as presented in Table I. Unlike the dopamine receptor, the α-adrenergic receptor recognizes both enantiomers of the trans ring fused oxaergolines (+)-**6b** and (−)-**6b**, IC_{50} of 34 and 7 nM, respectively. This ratio of 5 compares with a ratio of 100 observed for the [^{3}H]apomorphine binding site. In addition, the propyl maximum observed at the dopamine receptor is not seen at the α_2 receptor; rather, activity is maximum with ethyl, i.e., **6b**. The *N*-methyl derivative **6a** has higher measured affinity for the clonidine site than the apomorphine site. Both pergolide and *N*-propyloxaergoline **6c** exhibited a 13- to 14-fold measured preference for the dopamine receptor. The effects of these subtle receptor affinity differences on pharmacological profile have yet to be delineated.

In summary, a new class of heteroergot derivatives, the oxaergolines, has been discovered that exhibit affinity for both the [^{3}H]clonidine and [^{3}H]apomorphine binding sites. The in vitro affinity translates in vivo to potent dopaminergic activity. These compounds offer promise as agents for the treatment of Parkinson's disease, and the trans *R,R* isomer (−)-**6b** is currently undergoing in-depth evaluation.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were taken on a Nicolet 360 MHz or a Varian T-60A spectrometer with Me_4Si as an internal standard. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Solutions were dried over Na_2SO_4 and concentrated with a Buchi rotary evaporator under water aspirator pressure.

4-(2-Chloroacetamido)-3,4-dihydro-1-(*p*-tolylsulfonyl)benz[*cd*]indol-5(1*H*)-one (2). To a stirred mixture of ethyl acetate (200 mL) and saturated aqueous $NaHCO_3$ (90 mL) was added solid 4-amino-3,4-dihydro-1-(*p*-tolylsulfonyl)benz[*cd*]indol-5(1*H*)-one hydrochloride[8] (11.28 g, 0.03 mol). After the solid dissolved, chloroacetyl chloride (5.08 g, 0.04 mol) was added in portions. The solid that separated was filtered and dried to yield 9.0 g (77%) of **2**: mp 180–183 °C. Anal. ($C_{20}H_{17}ClN_2O_4S$) C, H, N.

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***trans*-4-(2-Chloroacetamido)-1,3,4,5-tetrahydro-1-(*p*-tolylsulfonyl)benz[*cd*]indol-5-ol (3).** $NaBH_4$ (0.5 g) was added in portions to a stirred solution of **2** (4.0 g, 0.01 mol) in THF (70 mL) and EtOH (50 mL) at room temperature. Stirring was continued for 1 h, then the reaction mixture was poured into H_2O (250 mL) and acidified with dilute HCl and the precipitated product recovered by filtration and dried. The yield of trans-alcohol **3** was 3.8 g (95%): mp 218–220 °C. Anal. ($C_{20}H_{19}ClN_2O_4S$) C, H, N. The NMR spectrum indicated only the trans isomer was obtained from this reduction: ^1H NMR (Me_2SO-d_6) δ 5.4 (1 H, d, J = 9 Hz).

***trans*-4-(*p*-Tolylsulfonyl)-4,6,6a,7,9,10a-hexahydroindolo[3,4-*gh*][1,4]benzoxazin-8-one (4).** To a stirred suspension of NaH (2.4 g, 50% mineral oil suspension) in DMF (15 mL) was added a solution of **3** (15.0 g, 0.036 mol) in DMF (75 mL) over 30 min. After stirring for an additional 30 min, the reaction mixture was poured into H_2O (350 mL) and neutralized with dilute HCl, and the resulting solid was recovered by filtration. The yield of **4** was 7.2 g (52%): mp >250 °C (CH_3CN). Anal. ($C_{20}H_{18}N_2O_4S$) C, H, N.

***trans*-4,6,6a,8,9,10a-Hexahydro-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (5).** A solution of **4** (3.0 g, 0.0078 mol) in THF (150 mL) was added dropwise to a stirred slurry of $LiAlH_4$ (3.0 g) in THF (200 mL), and the reaction mixture was then heated at reflux for 17 h. To the cooled reaction mixture were added 2-propanol (to destroy excess $LiAlH_4$) and H_2O (6 mL). This mixture was filtered (Supercel), the filter cake was washed with ether (3 × 100 mL), and the organic solvents were dried (Na_2SO_4), and then evaporated at reduced pressure. The resulting oil was purified by column chromatography [SiO_2, $CHCl_3$ (saturated with NH_4OH)] to yield 0.7 g (42%) of **5**: mp 175–177 °C (MeOH). Anal. ($C_{13}H_{14}N_2O$) C, H, N.

***trans*-4,6,6a,8,9,10a-Hexahydro-7-methyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (6a).** Solid oxazinone **4** (7.0 g, 0.018 mol) was added in portions to a stirred suspension of NaH (1.1 g, 50% mineral oil suspension) in DMF (14 mL). After 0.5 h, methyl iodide (5.0 g, 0.035 mol) was added dropwise to the reaction mixture. After an additional 1 h, the reaction mixture was poured into H_2O (200 mL) and the solid that separated was recovered by filtration and dried. This solid was dissolved in THF, and the intermediate oxazinone was reduced with $LiAlH_4$ by the same procedure described for the reduction of **4**. Column chromatography of the crude product (SiO_2, $CHCl_3/NH_4OH$) afforded **6a** in 5.5% yield: mp 208–211 °C. Anal. ($C_{14}H_{16}N_2O$) C, H, N.

***trans*-4,6,6a,8,9,10a-Hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (6b).** A suspension of **5** (0.65 g, 0.003 mol), acetaldehyde (0.26 g, 0.006 mol), and 10% Pd/C (0.7 g) catalyst in absolute EtOH (50 mL) was hydrogenated on a Hirschberg apparatus for 4 h. The reaction mixture was then filtered, and the solvent was evaporated under reduced pressure. The resulting oil crystallized from CH_3OH to yield 0.43 g (58%) of **6b**, mp 217–219 °C dec. Anal. ($C_{15}H_{18}N_2O$) C, H, N.

Compounds **6c** and **6d** were prepared by the same reductive alkylation procedure described above for **6b** by substituting the proper aldehyde. The yield of **6c** was 65%, mp 208–209 °C. Anal. ($C_{16}H_{20}N_2O$) C, H, N. The yield of **6d** was 40%, mp 136–140 °C (hexane). Anal. ($C_{17}H_{22}N_2O$) C, H, N.

***trans*-4,6,6a,8,9,10a-Hexahydro-7-allyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (6e).** A mixture consisting of **5** (0.5 g, 0.0023 mol), K_2CO_3 (0.35 g), and allyl bromide (0.3 g, 0.0025 mol) in 2-butanone (55 mL) was refluxed for 4.5 h. The cooled reaction mixture was filtered, and the solvent removed under reduced pressure to yield 0.22 g (37%) of **6e**: mp 147–150 °C (CH_3OH). Anal. ($C_{16}H_{18}N_2O$) C, H, N.

Resolution of 4,6,6a,8,9,10a-Hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine (6b). To a solution of 45.0 g (0.186 mol) of **6b** dissolved in 2.75 L of boiling absolute ethanol was added a solution of 72.22 g (0.186 mol) of di-*p*-toluoyl-*l*-tartaric acid in 250 mL of hot absolute ethanol. The resulting clear solution was stirred and then allowed to cool at room temperature overnight. This procedure was carried out on a second 45.0-g batch of **6b**, and the two batches were combined. The crystalline precipitate that had formed was removed by filtration, and this salt was washed well with absolute ethanol, collected, and dried in a 65 °C vacuum oven to afford 110.6 g of crude (+)-4,6,6a,8,9,10a-hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine di-*p*-toluoyl-*l*-tartaric acid salt.

The above filtrate and washings were combined and concentrated to dryness on a rotary evaporator at 50 °C. The residue was partitioned between chloroform and an aqueous solution of sodium carbonate. The chloroform layer was washed with water, dried ($MgSO_4$), and filtered. Evaporation of the chloroform on a rotary evaporator gave 45.2 g of crude (−)-4,6,6a,8,9,10a-hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]benzoxazine: $[\alpha]_{589}$ −49.5° (*c* 0.66, DMF). This 45.2 g (0.1865 mol) of material was dissolved in 2.8 L of boiling absolute ethanol, and, while stirring, a solution of 72.25 g (0.187 mol) of di-*p*-toluoyl-*d*-tartaric acid in 200 mL of hot absolute ethanol was added. The clear solution was allowed to cool at room temperature overnight. The crystalline precipitate that formed was collected by filtration and washed well with cold absolute ethanol. The salt was dried in a vacuum oven at 65 °C to afford 98.4 g of material $[\alpha]^{25}_{589}$ −125° (*c* 1.269, pyridine). This salt was partitioned between chloroform and an aqueous solution of sodium carbonate. The chloroform layer was washed with water, dried over magnesium sulfate, and filtered. Evaporation of the chloroform on a rotary evaporator gave 40.0 g of material: $[\alpha]^{25}_{589}$ −67.0° (*c* 0.8, DMF). This material was dissolved in 5 L of boiling absolute ethanol and filtered, and the filtrate was concentrated by boiling to 3.5 L. The material that crystallized on standing at room temperature overnight was removed by filtration, washed with ethanol, collected, and dried at 65 °C to afford 31.6 g of product, $[\alpha]^{25}_{589}$ −69.8° (*c* 0.302, DMF). This product was recrystallized from 3.5 L of methanol to give 26.5 g of (−)-4,6,6a,8,9,10a-hexahydro-7-ethyl-7*H*-indolo[3,4-*gh*][1,4]-benzoxazine [(−)-**6b**]: mp 252–253.5 °C; $[\alpha]^{24}_{589}$ −68.8° (*c* 0.30, DMF); TLC homogeneous (Fluka alumina/$CHCl_3$).

Pharmacology. α-Receptor Binding Assay. [^{3}H]Clonidine was used as the radioligand to determine the interaction of the compounds with the α-adrenergic receptor in calf cerebral cortex in vitro. [^{3}H]Clonidine was obtained from New England Nuclear, Boston, MA, at a specific activity of 22.2–23.8 Ci/mmol and stored in ethanol/water (7:3) at 0 °C. The radiochemical purity of this ligand was periodically checked by thin-layer chromatography on E. Merck silica gel 60F-254 plates (1-butanol/acetic acid/water, 4:1:5 top layer). Laboratory glassware was used.

Assays were conducted with homogenates of previously frozen (−75 °C) calf cerebral cortex. A Brinkmann Polytron PT-10 (setting 6, 10 s) was used to homogenize sections of calf cerebral cortex in 20 vol (w/v) of ice-cold 50 mM pH 7.7 Tris-HCl buffer. The resulting homogenate was centrifuged twice at 48000*g* (Sorvall SS-34 rotor, 20000 rpm, RC-5 centrifuge) for 10 min at 4 °C, with rehomogenization of the intermediate pellet in 20 vol of fresh buffer. The final pellet was resuspended in 50 vol of ice-cold buffer.

Standard radioligand displacement assays utilized a [^{3}H]clonidine final concentration of 0.2 nM. Triplicate assay tubes contained [^{3}H]clonidine, 100 μL of various concentrations of the compound being tested, 1000 μL of tissue homogenate, and 50 mM pH 7.7 Tris-HCl buffer to a final volume of 2000 μL. The reaction was initiated by the addition of tissue, and incubation continued for 30 min at 25 °C, at which time it was terminated by rapid filtration through Whatman GF/B glass-fiber filters under vacuum. Each filter was immediately rinsed with 3 × 5 mL aliquots of ice-cold buffer. The filters were removed into 10 mL PCS (Amersham) and counted on either a Packard Model 2425 or 460C scintillation spectrometer at an efficiency of 35%. Specific binding was defined as the difference between samples with and without 100 nM unlabeled clonidine.

The specific binding data were converted to percent inhibition of [^{3}H]clonidine binding relative to control samples containing no inhibition. The percent inhibition vs. compound concentration, [C], data were fitted by nonlinear least squares to the following equation: $\%I = 100[C]/(IC_{50} + [C])$

Dopamine Receptor Binding Assay. [^{3}H]Apomorphine was used as radioligand to determine interaction with the DA receptors in rat striatal membranes in vitro. Using the method of Seeman et al.,[15] we incubated [^{3}H]apomorphine [specific activity = 34.5 Ci/mmol, New England Nuclear (NEN), Boston, MA] at a final

(15) Seeman, P.; Lee, T.; Chan-Wong, M.; Tedesco, T.; Wong, K. *Proc. Natl. Acad. Sci.* **1976**, *73*, 4354.

concentration of 0.2 nM using 10 μM (+)-butaclamol to determine nonspecific binding. IC_{50} values were determined by linear regression analysis with three to five concentrations of each compound assayed in triplicate. Results are expressed as the mean IC_{50} for three to five separate observations.

Contralateral Turning in 6-Hydroxydopamine-Lesioned Rats. In the anesthetized female Sprague–Dawley rat, weighing 140–170 g, 6-hydroxydopamine (8 μg/4 μL of 0.9% saline) was infused into the substantia nigra over a 4-min period with a Sage syringe pump. The 30-gauge injection needle was stereotaxically positioned rostral to the right substantia nigra with coordinates derived from König and Klippel.[16] One and two weeks after surgery, each rat was given apomorphine (1 mg/kg ip), and it was observed for contralateral turning, a sign of CNS dopamine receptor activation. Each rat that did turn was added to a colony that was used not more than once a week. With a random and blind design, three to eight doses of each compound were given ip to six rats housed three per cage. The presence or absence of contraversive turning was ascertained at 0.5 h after dosing. ED_{50} values and the 95% confidence limits were determined using log probit analysis.[17]

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Registry No. (±)-1, 84057-01-2; (±)-**2**, 84056-98-4; (±)-**3**, 77291-60-2; (±)-**4**, 77306-59-3; (±)-**5**, 77291-61-3; (±)-**6a**, 77306-60-6; (±)-**6b**, 77291-64-6; (−)-**6b**, 81244-91-9; (+)-**6b** di-*p*-toluoyl-*l*-tartaric acid salt, 84064-66-4; (−)-**6b** di-*p*-toluoyl-*d*-tartaric acid salt, 84057-00-1; (±)-**6c**, 77291-65-7; (±)-**6d**, 77291-66-8; (±)-**6e**, 84056-99-5; (±)-**9**, 81274-84-2; chloroacetyl chloride, 79-04-9; dopamine, 51-61-6; $CH_3CH{=}CH_2Br$, 106-95-6; CH_3CHO, 75-07-0; CH_3CH_2CHO, 123-38-6; $CH_3(CH_2)_2CHO$, 123-72-8; $CH_3(CH_2)_3CHO$, 110-62-3.

Supplementary Material Available: Tables I, II, and III containing fractional unit cell coordinates, bond lengths, and bond angles and a figure showing the crystallographic numbering system for (−)-**6b** and di-*p*-toluoyl-*d*-tartaric acid (5 pages). Ordering information is given on any current masthead page.

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2-Benzazepines. 4.[1,2] [1,2,3]Triazolo[4,5-*d*][2]benzazepines and Dibenzo[*c*,*f*][1,2,3]triazolo[3,4-*a*]azepines: Synthesis and Evaluation as Central Nervous System Agents

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The facile synthesis of [1,2,3]triazolo[4,5-*d*][2]benzazepines and dibenzo[*c*,*f*][1,2,3]triazolo[3,4-*a*]azepines by the addition of sodium azide to acetylenic benzophenones is described. Examination of the pharmacological data indicates that selected triazolobenzazepines are as potent as diazepam in the anti-pentylenetetrazole test and are weaker in the inclined screen and rotarod tests, suggesting that these compounds have antianxiety properties similar to diazepam with fewer deficits in motor coordination. In addition, a possible diazepam antagonist was found in the triazolobenzazepine series. The dibenzotriazoloazepines were found to be inactive in four standard CNS screening procedures.

The 1,4-benzodiazepine ring system has been extensively explored in CNS drug research, especially in the search for new antianxiety agents.[3] The 2-benzazepine ring system, a carbon isostere of a 1,4-benzodiazepine, has received much less attention in this area[4] but has been investigated for other therapeutic uses.[5] As part of our continuing program to develop novel heterocyclic systems of therapeutic benefit in the CNS area, we have investigated the synthesis and the biological activity of 4,5-heteroring-fused 2-benzazepines. In this report we describe the facile synthesis and some of the pharmacological activities of triazolobenzazepines and the related dibenzotriazoloazepines.

Chemistry. The readily available acetylenic benzophenones **1**, whose preparation has been previously described,[6] provided a convenient starting point for the synthesis of these ring systems, as shown in Scheme I. Treatment of **1a–e** with sodium azide in warm dimethyl sulfoxide containing acetic acid resulted in the formation of the triazoles **2a–e**.[7] Removal of the phthaloyl group from **2a–e** with 40% aqueous methylamine in ethanol generated the opened derivatives **3a–e**, which spontaneously ring closed to the desired triazolobenzazepines **4a–e**,[7] respectively.

When the benzophenone was substituted in the ortho position with a halogen atom, the sodium azide addition to the acetylene required the use of at least 1 equiv of acetic acid or a similar proton source. In the absence of acetic acid the initially formed triazole anion displaced the

(1) Dedicated to the memory of Dr. Willy Leimgruber, deceased July 8, 1981.

(2) For previous paper, see Gilman, N. W. *Synth. Commun.* **1982**, *12*, 373.

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(7) The position of the triazolo hydrogen was arbitrarily assigned to the 2-position For the conversion of **2b** into **5**, the anion must be on the 3-position of the triazole ring.

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