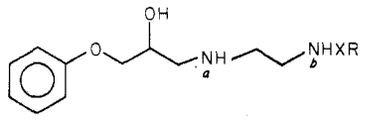

30, X = -CO-, -SO$_2$-; R = alkyl, aryl, substituted amino or oxygen

ethyleneamide was employed as the nitrogen substituent. Both compounds exhibited long durations of action. It should also be noted that the methyl ester **5** exhibited a shorter duration of action than its homologous ethyl ester **6**. This finding supports the previous suggestion that the enzymes responsible for degrading these β-blocker esters may be very sensitive to steric effects.[3] Finally, it is interesting that even modifications of the remote nitrogen substituents can significantly affect the rate of enzymatic hydrolysis of these esters.

In summary, with the exception of the phenylureido compound **13**, substitution with various ethylenediamine derivatives generally did not increase cardioselectivity within this series. That **13** was the most cardioselective compound is in accord with the recent report[11] that for the various amidic moieties, cardioselectivity is most evident in the ureido analogues. In the duration studies, only amides **4** and **5**, sulfamide **10**, and the pyridine compound **20** had durations of action comparable to the isopropyl standard **1**. In all other instances, the test compounds were found to have a significant increase in their duration of blocking activity.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Associates T-60A spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

The following experimental procedure leading to **13** is representative of the general procedures used to synthesize all of the compounds. Experimental data for **1–28** are provided in Table I.

Methyl 2-(2,3-Epoxypropoxy)benzoate (31). A mixture of 15.2 g (0.10 mol) of methyl 2-hydroxybenzoate, 27.6 g (0.20 mol) of potassium carbonate, and 31 mL (0.40 mol) of epichlorohydrin in 250 mL of acetone was heated to reflux for 24 h.[3] The reaction medium was then filtered and evaporated under reduced pressure. The resulting oil was dissolved in 100 mL of toluene and washed consecutively with 100 mL of water, 2 × 100 mL of 1.0 N sodium hydroxide, and 2 × 100 mL of water. The organic phase was then dried over magnesium sulfate and evaporated under reduced pressure to provide the crude product as an oil. Purification was effected by vacuum distillation to provide 5 g (25%) of an oil: bp 148 °C (75 μm); NMR ($CDCl_3$) δ 7.4 (m, 4, ArH), 4.2 (m, 2, OCH_2), 3.8 (s, 3, OCH_3), 3.3 (m, 1, OCH), 2.8 (m, 2, OCH_2). Anal. ($C_{11}H_{12}O_4$) C, H.

***N*-Acetylethylenediamine (32).** A mixture of 88 g (1.0 mol) of ethyl acetate and 180 g (3.0 mol) of ethylenediamine was heated in a Parr bomb at 100 °C for 36 h.[10] After cooling, the reaction medium was evaporated under reduced pressure to an oil, which was then taken up in 300 mL of ethyl acetate. Cooling this solution at 3 °C for 24 h caused undesired disubstituted byproduct to crystallize. This solid was removed by filtration, and the mother liquor was evaporated under reduced pressure to provide an oil. The oil was taken up in anhydrous ether, and the solution was cooled at 3 °C for 24 h to provide 72 g (81%) of white crystals: mp 51–52 °C (lit.[18] mp 50–51 °C); NMR spectrum identical with a commercial sample.[18]

2-[[(Phenylamino)carbonyl]amino]ethylamine Hydrochloride Hydrate (33). A 6.20 mL (0.057 mol) quantity of phenyl isocyanate was added dropwise to a stirred suspension of 5.82 g (0.057 mol) of **32** in 100 mL of methylene chloride at 10 °C. After the addition, a solid precipitated. Anhydrous ether (100 mL) was added, and the mixture was stirred for 30 min. The reaction medium was then filtered, and the solid was dissolved in 50 mL of 15% HCl. This solution was heated at 80 °C for 4 h and then evaporated under reduced pressure to a white solid, which was recrystallized from methanol–ether to provide 7.0 g (61%): mp 190–191 °C; NMR (CD_3OD) δ 7.3 (m, 5, ArH), 3.5 (t, J = 5 Hz, 2, CH_2), 3.1 (t, J = 5 Hz, 2, CH_2). Anal. ($C_9H_{14}N_3OCl \cdot 0.33H_2O$) C, H, N.

Methyl 2-[2-Hydroxy-3-[[2-[[(phenylamino)carbonyl]amino]ethyl]amino]propoxy]benzoate (13). A 4.8 g (0.024 mol) quantity of **33** was dissolved in 100 mL of methanol, and 2.5 g (0.024 mol) of triethylamine was added. While stirring, a solution of 5 g (0.024 mol) of **31** in 25 mL of methanol was added slowly. The solution was heated to reflux for 4 h. After the reaction, the methanol was removed under reduced pressure, and the resulting gel-like solid was dissolved in 100 mL of methylene chloride. The organic layer was washed twice with 100 mL of water and dried over anhydrous magnesium sulfate. Evaporation of the methylene chloride left an oil, which was dissolved in 50 mL of methanol/ether (1:1) from which the product crystallized slowly at 3 °C to provide 0.7 g (8%): mp 133–134 °C; NMR ($CDCl_3$) δ 7.3 (m, 9, ArH), 3.8 (s, 3, OCH_3). Anal. ($C_{20}H_{25}N_3O_5$) C, H, N.

Biological Studies. The biological experiments were performed in identical fashion with those described previously.[2,3]

Registry No. **1**, 33947-95-4; **2**, 51698-60-3; **2**·HCl, 33948-14-0; **3** oxalate, 83356-56-3; **4**, 85850-21-1; **5**, 85850-22-2; **6**, 85850-23-3; **7**, 85850-24-4; **8**, 85850-25-5; **9** 0.5-oxalate, 85850-27-7; **10**, 85850-49-3; **10**·HCl, 85850-28-8; **11**, 85864-51-3; **12**, 85850-29-9; **13**, 83019-57-2; **14**, 85850-30-2; **15** oxalate, 85850-32-4; **16** oxalate, 85850-34-6; **17** 2-oxalate, 85850-36-8; **18** 2-oxalate, 85850-38-0; **19** oxalate, 85850-40-4; **20** oxalate, 85850-42-6; **21**, 33947-97-6; **21**·HCl, 33947-96-5; **22**, 85850-50-6; **22**·2HCl, 85850-43-7; **23**, 85850-51-7; **23**·2HCl, 85850-44-8; **24**, 85850-52-8; **24**·2HCl, 85850-45-9; **25**, 85850-46-0; **26**, 85850-47-1; **27**, 53671-23-1; **28**, 29044-59-5; **28**·HCl, 16799-82-9; **31**, 22589-46-4; **32**, 1001-53-2; **33**·HCl, 85850-48-2; methyl 4-hydroxybenzoate, 99-76-3; 2-methylphenol, 95-48-7; methyl o-hydroxycinnamate, 20883-98-1; methyl 2-hydroxybenzoate, 119-36-8; ethyl acetate, 141-78-6; ethylenediamine, 107-15-3; phenyl isocyanate, 103-71-9.

Resolution and Absolute Configuration of an Ergoline-Related Dopamine Agonist, *trans*-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1*H*(or 2*H*)-pyrazolo[3,4-*g*]quinoline

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The title compound (±)-**5** (R = Pro) (LY141865) has been resolved into a (−) isomer and a (+) isomer as the D- and L-tartrate salts, respectively. Biological studies have shown that dopamine agonist activity is a property of only the (−) isomer. Crystallographic analysis has proven that the absolute configuration of the active (−) isomer is the same as that of the natural ergolines.

In a previous paper[1] we reported the synthesis of rigid bicyclic and tricyclic ergoline partial structures **1–3** and their pyrazole isosteres **4–6**. The pyrroles, especially the tricyclic members **2** and **3**, were shown to have very sig-

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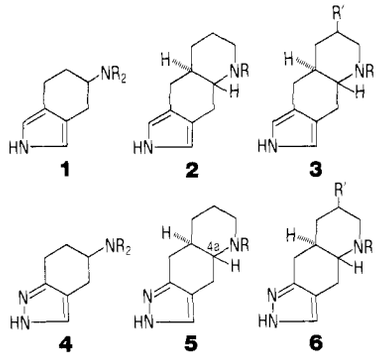
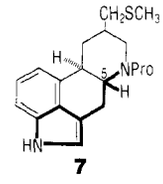


nificant dopaminergic activity in two standard tests. Of further interest was the observation that the pyrazoles **4–6** were at least as active as the pyrroles. Of particular note was the fact that pyrazoles **5** (R = Pro) and **6** (R = Pro, R′ = CH_2SCH_3) were of potency comparable with that of the highly active ergoline, pergolide (**7**).[2] This evidence



supported the idea that the rigid pyrrolethylamine (as shown shaded in **7**) was the dopaminergic moiety of the ergolines.

With this background it was of great interest (1) to resolve one of the above synthetic racemic compounds, (2) to evaluate the dopaminergic activity of the resulting optical antipodes, (3) to determine the absolute configuration of the resolved compounds, and (4) to relate the chirality of the synthetics to that of the natural ergolines. The ergolines, e.g., **7**, are of the *R* absolute configuration at C5, as shown,[3] and we had predicted[1] that the more active optical isomer of a resolved synthetic racemate should have the same absolute configuration (see **5**) as that in the ergolines. This prediction has now been confirmed.

The compound chosen for the resolution studies was the linear tricyclic pyrazole **5** (R = Pro) (the dihydrochloride salt was designated as LY141865). This compound was highly active,[1] it was more stable than the pyrroles **1–3**, and it was more easily synthesized than the more complex compound **6**. The resolution was readily accomplished by fractional recrystallization of the D-(−)- and L-(+)-(*R*)-tartaric acid salts. Pharmacological tests (see below) showed that essentially all of the dopaminergic activity was in the isomer crystallized as the D-(−)-tartrate salt ($[\alpha]^{20}$ −95.5°), while the opposite isomer, the L-(+)-tartrate ($[\alpha]^{20}$ +95.6°) was relatively inert biologically. The active (−) isomer was also converted to a monohydrochloride salt (LY171555).

We next attempted to determine the absolute stereochemistry by X-ray crystallography. Although the tartrate salts above formed nice crystals, a solution of the X-ray structure eluded us. We turned, therefore, to an alternate salt. We found that the biologically *in*active (+) isomer base formed a beautifully crystalline salt with D-(−)-(*tert*-butyloxycarbonyl)phenylglycine and that the X-ray

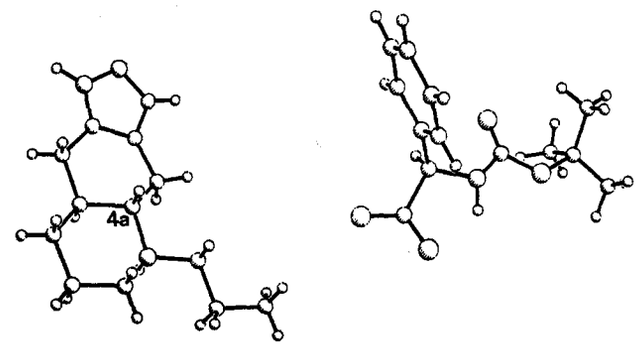


Figure 1. Drawing of (+)-(*S*)-**5** (R = Pro), D-(−)-(*tert*-butyloxycarbonyl)phenylglycine salt.

crystallographic structure of this salt, shown in Figure 1, was readily obtained. It may be noted in the drawing that the absolute configuration of carbon 4a is *S*, which corresponds to the C5-*S* configuration in the *in*active form of the ergolines. Therefore, the *active* isomer of **5** (R = Pro) must have the C4a-*R* configuration, corresponding to the C5-*R* configuration of the natural active ergolines. Of interest is the observation that the X-ray solution in Figure 1 confirms the trans ring junction as shown in our earlier X-ray study.[1] It is noteworthy also that in the crystal the pyrazole ring is protonated on the 1-nitrogen rather than on the 2-position as shown in the tautomer **5** (R = Pro). It is likely that *solutions* of **5** (R = Pro) contain a mixture of the 1 and 2 protonated tautomers. With this stereochemical question settled, we embarked on a detailed study of the biological properties of the racemate, **5** (R = Pro), in comparison with the active (−) and inactive (+) isomers.

Biological Properties. To extend studies previously reported[1,4–8] on the racemic compound, **5** (R = Pro), dihydrochloride and to make comparisons with the optically active (−) and (+) isomers above, we carried out the following work.

Toxicology. Mice dosed intraperitoneally tolerated 400 mg/kg of (±)-**5** (R = Pro) (no deaths), while doses of 800 mg/kg were lethal. In similar studies, apomorphine and pergolide killed at 200 mg/kg ip but not at 100 mg/kg ip. Both (±) and (−) isomers of **5** (R = Pro) gave negative results in the modified gradient Ames bacterial mutagen test[9] up to a concentration of 1000 mcg/mL. Emesis in single dogs was produced at oral doses of 300 mcg/kg or more of (±)-**5** (R = Pro). It is known that tolerance to the emetic action of dopamine agonists develops on repeated dosing.

Rat Locomotor Activity. Compound (±)-**5** (R = Pro) was compared with pergolide as to its effect on locomotor activity in the rat. Pergolide produced *decreases* in activity levels at doses from 0.01 to 0.1 mg/kg. At doses greater than 1 mg/kg, a concentration-dependent *stimulation* of rat activity was observed. A very similar biphasic dose effect was observed following intraperitoneal administration of (±)-**5** (R = Pro). Activity levels were *decreased* by 0.003–0.1 mg/kg of (±)-**5** (R = Pro), while doses of 0.3

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Table I. Effects of (±)-5 (R = Pro) and Its Resolved Isomers on Serum Prolactin Levels in Reserpinized Male Rats

compd	% reduction of serum prolactin levels at the following oral doses			
	0.017 μmol/kg	0.03 μmol/kg	0.17 μmol/kg	0.3 μmol/kg
(±)-5 (R = Pro)	19	20	65[a]	76[a]
(−)-5 (R = Pro)	26	38[a]	73[a]	88[a]
(+)-5 (R = Pro)			stimulation (not inhib)	

[a] Significantly different from control prolactin levels ($p < 0.05$).

Table II. Comparative Effects of the Enantiomers of 5 (R = Pro) in Rats

parameter	vehicle	(−)-5 (R = Pro)	(+)-5 (R = Pro)
serum corticosterone, μg/100 mL	5.4 ± 0.3	51.8 ± 1.9[a]	18.8 ± 3.2[a]
brain DOPAC, ng/g	0.61 ± 0.02	0.44 ± 0.01[a]	0.54 ± 0.01[a]
brain HVA, ng/g	0.49 ± 0.03	0.29 ± 0.01[a]	0.42 ± 0.01[a]

[a] Significant difference from control group ($p < 0.05$).

mg/kg and above significantly *increased* activity levels compared to vehicle-treated controls. A similar study comparing pergolide with apomorphine has been reported.[10] The activity increases seen above can be antagonized by dopamine blockers like haloperidol.

Prolactin Lowering Effects. Dopamine agonist drugs are known to lower serum prolactin levels.[11] A study of the prolactin effects of (±)-5 (R = Pro) and its enantiomers in reserpinzed male rats was conducted using standard methods.[11] The results are shown in Table I. It is evident from the data that both the (±) and (−) isomers are potent dopamine agonists, while the (+) isomer is inactive at the doses used.

Corticosterone, DOPAC, and HVA Effects. Dopaminergic drugs cause a dose-related *increase* in corticosterone levels in rats and a *decrease* in the levels of whole brain 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA).[12-14] Using methods previously described,[12-14] we compared the 5 (R = Pro) isomers. The compounds were injected intraperitoneally at a dose of 1 mg/kg, 1 h before the male Wistar rats were sacrificed. Mean values plus or minus standard errors for 10 rats per group are summarized in Table II. The elevation of serum corticosterone and the lowering of both DOPAC and HVA in whole brain are thought to result from stimulation of dopamine receptors. In all cases the (−) enantiomer was significantly more effective than the (+) enantiomer.

Dopamine Receptor Binding. Racemic compound 5 (R = Pro) and the resolved isomers were studied in order to determine the extent of dopamine receptor binding using standard preparations and methodology.[15] The results are shown in Table III, where values for the clinically effective agent pergolide are given for comparison. The binding of the racemate was weaker than that of pergolide in the radioreceptor assays. Nevertheless, (±)-5 (R = Pro) inhibited the binding of [^{3}H]apomorphine to rat striatal membranes more effectively than the binding of [^{3}H]dopamine or [^{3}H]spiperone to bovine striatal membranes. Once again, the effectiveness was limited to the (−) isomer. In similar studies the (±), (−), and (+) isomers showed little or no activity on serotonin receptors in vitro.

Table III. Effects of (±)-5 (R = Pro) and Its Isomers on ^{3}H-Labeled Ligand Binding to Dopamine Receptors

compd	IC_{50}, nM		
	[^{3}H]apomorphine[a]	[^{3}H]dopamine[b]	[^{3}H]spiperone[b]
pergolide	1.6	4.1	48
(±)-5 (R = Pro)	240	10 000 (35%)[c]	10 000 (42%)
(−)-5 (R = Pro)	71	10 000 (36%)	10 000 (45%)
(+)-5 (R = Pro)	3900	10 000 (27%)	10 000 (6%)

[a] Rat corpus striatum. [b] Calf corpus striatum. Percent inhibition at 10 000 nM in parentheses.

Turning Behavior in Lesioned Rats. The measurement of turning behavior in rats with unilateral 6-hydroxydopamine-induced lesions of the nigrostriatal tract constitutes a standard and reliable measure of the dopamine agonist properties of new drugs.[16] Compounds active in this assay are usually effective in Parkinsons disease. A comparison of (±)-5 (R = Pro) and its isomers in this test is summarized in Table IV. Once again the evidence points to (−)-5 (R = Pro) as the active species. Results with apomorphine are given for comparison.

Hypotensive Activity. It is now well established that dopaminergic drugs lower blood pressure in various animal species.[17] To assay this property of (±)-5 (R = Pro) we conducted various studies by the procedures of Hahn,[17] and these are summarized in Tables V–VII. It may be noted (1) that (±)-5 (R = Pro) is a potent hypotensive drug by the usual routes of administration in spontaneously hypertensive rats (SHR), (2) that the activity is a property of the (−) isomer in SHR, and (3) that similar blood pressure effects are seen in the dog and cat. A fuller account of this work is published elsewhere.[18]

Lordotic Behavior in Rats. The stimulation of lordosis in female rats by (±)-5 (R = Pro) and its isomers was measured by the method of Foreman and Moss.[19] The results are shown in Table VIII.

There was no statistical difference between the effects of vehicle and (+)-5 (R = Pro). However, (±)-5 (R = Pro) administration significantly enhanced lordotic behavior compared to either vehicle ($p < 0.001$) or (+)-5 (R = Pro) ($p < 0.001$), and injections of (−)-5 (R = Pro) produced

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Table IV. Effects of (±)-5 (R = Pro) and Its Resolved Isomers on Turning Behavior in Male Rats with Unilateral 6-Hydroxydopamine Lesions of the Nigrostriatal Tract

	turning behavior contralateral to lesioned side					
	100 μg/kg ip dose			500 μg/kg ip dose		
compd	% turning[a]	av no. of turns[b] 1st 15 min	1st h[c]	% turning	av no. of turns 1st 15 min	1st h[c]
(±)-5 (R = Pro)	50	37.3	83.2 (1.2)	100	45.1	167.8 (2.3)
(−)-5 (R = Pro)	67	46.0	128.2 (1.9)	100	57.8	201.8 (2.5)
(+)-5 (R = Pro)	0	0	0 (0)	0	0	0 (0)
apomorphine	50	20.2	34.2 (0.5)	100	72.4	192.4 (0.6)

[a] Six rats per group. Percent of these rats that turned at least one contralateral turn per minute for 15 min. [b] Average turns in the first 15-min period after turning behavior began. The usual latency from injection to initiation of turning with the compounds was 3-5 min. [c] Duration of turning behavior (hours) in parentheses.

Table V. Hypotensive Activity of (±)-5 (R = Pro) Following Various Routes of Administration in Pentobarbital-Anesthetized, Spontaneously Hypertensive Rats

	arterial BP, change,[a] %, at the following doses of 5			
route	1 μg/kg	10 μg/kg	100 μg/kg	1000 μg/kg
iv	−12.7 ± 2.2	−22.4 ± 0.7	−32.0 ± 2.1	−52.2 ± 6.9
ip		−6.1 ± 1.3	−40.5 ± 3.1	−45.7 ± 1.8
ig		−5.4 ± 1.8	−27.6 ± 3.5	−50.7 ± 2.8

[a] Maximum change immediately after intravenous administration or within 30 min following intraperitoneal (ip) or intragastric (ig) administration. Mean response plus or minus standard error of four rats.

Table VI. Relative Hypotensive Activities of (±)-5 (R = Pro), (−)-5 (R = Pro), and (+)-5 (R = Pro) in Anesthetized, Spontaneously Hypertensive Rats

compd	dose, μg/kg iv	arterial BP change,[a] %
(±)-5 (R = Pro)	1	−12.7 ± 2.2
	10	−22.4 ± 0.7
	100	−32.0 ± 2.1
	1000	−52.2 ± 6.9
(−)-5 (R = Pro)	0.1	−7.7 ± 1.6
	1	−14.3 ± 1.6
	10	−25.2 ± 2.1
	100	−38.6 ± 4.3
(+)-5 (R = Pro)	0.1	−8.5 ± 0.8
	1	−5.1 ± 0.8
	10	−5.0 ± 0.3
	100	−4.6 ± 0.3
	1000	−6.4 ± 1.1

[a] Mean response plus or minus standard error of four rats.

Table VII. Effect of Intravenous Injection of (±)-5 (R = Pro) on Arterial Blood Pressure in the Anesthetized, Spontaneously Hypertensive Rat (SHR) and Normotensive Dog and Cat

	arterial BP change,[a] %, at the following doses of 5			
species	1 μg/kg	10 μg/kg	100 μg/kg	1000 μg/kg
SHR	−13 ± 2	−22 ± 1	−32 ± 2	−52 ± 7
dog	−15 ± 3	−34 ± 4	−45 ± 2	−46 ± 3
cat	−9 ± 3	−23 ± 6	−45 ± 4	−48 ± 2

[a] Mean response plus or minus standard error of four preparations.

significantly greater elevations in lordotic behavior compared to all other groups ($p < 0.001$). With the same methodology, it was shown that (±)-5 (R = Pro) was about 10-fold more active than pergolide and about equal to apomorphine in stimulating sexual behavior.

Table VIII. Effect of (±)-5 (R = Pro) and Its Isomers on Lordotic Behavior in Rats[a,b]

drug[c]	preinjection L/M[d]	postinjection L/M	postinjection L/M vs. preinjection L/M
vehicle[e]	0.06 ± 0.02[c]	0.24 ± 0.06	0.18 ± 0.06
(±)-5 (R = Pro)	0.13 ± 0.02	0.63 ± 0.07	0.50 ± 0.06
(+)-5 (R = Pro)	0.12 ± 0.02	0.32 ± 0.06	0.19 ± 0.06
(−)-5 (R = Pro)	0.08 ± 0.02	0.90 ± 0.04	0.82 ± 0.05

[a] Values are expressed as $X \pm SE$. [b] $N = 20$ for all groups. [c] All drugs were given in 25 μg/kg dosages. [d] L/M = lordosis-to-mount ratio. [e] Vehicle = 1 mM ascorbic acid in 1 mM acetic acid.

Experimental Section

Elemental analyses are indicated only by symbols of the elements and are within 0.4% of the theoretical values. All new compounds were monitored by measurement of IR, UV, and NMR spectra. Mass spectra were determined also for most structures and were consistent with other spectral measurements. Melting points were determined on a Mel-Temp apparatus and are corrected. All reactions were followed by TLC carried out on Merck F254 silica gel plates.

***trans*-(−)-(4a*R*)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline D-(−)-Tartrate [(−)-5 (R = Pro)].** *trans*-(±)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline was dissolved in MeOH. To this was added 1.1 equiv of D-(−)-tartaric acid, and the solution was heated to boiling for 10 min. The solution was allowed to stand at room temperature. The crystals were recovered by vacuum filtration and recrystallized from methanol (0.1 g of salt/1 mL of MeOH) five times or until the melting point was 201–202 °C: $[\alpha]^{25}_D$ (H_2O) −95.5°; yield 10%. Anal. ($C_{13}H_{21}N_3 \cdot C_4H_6O_6$) C, H, N.

***trans*-(−)-(4a*R*)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline Hydrochloride.** (−)-5 (R = Pro) D-(−)-tartrate was dissolved in water, and the solution was made strongly basic with concentrated NH_4OH. The aqueous mixture was extracted with 3:1 $CHCl_3$/*i*-PrOH. The organic extracts were combined, washed with saturated, aqueous NaCl, and dried over Na_2SO_4. A colorless solid remained after evaporation of the solvent. This solid was dissolved in MeOH, and then exactly 1 equiv of aqueous hydrochloric acid was added. The solvents were evaporated, and the residue was crystallized from MeOH–Et_2O: mp 280 °C dec; $[\alpha]^{25}_D$ (H_2O) −120.6°. Anal. ($C_{13}H_{21}N_3 \cdot HCl$) C, H, Cl, N.

***trans*-(+)-(4a*S*)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline L-(+)-Tartrate [(+)-5 (R = Pro)].** This was obtained exactly as above by using 1.1 equiv of L-(+)-tartaric acid: mp 200.5–201.5 °C; $[\alpha]^{25}_D$ (H_2O) +95.6°. Anal. ($C_{13}H_{21}N_3 \cdot C_4H_6O_6$) C, H, N.

***trans*-(+)-(4a*S*)-4,4a,5,6,7,8,8a,9-Octahydro-5-propyl-1*H*-pyrazolo[3,4-*g*]quinoline D-(−)-(*tert*-Butyloxycarbonyl)-phenylglycine Salt.** (+)-5 (R = Pro) L-(+)-tartrate was dissolved

in water, and the solution was made strongly basic with concentrated NH_4OH. The aqueous mixture was extracted with 3:1 $CHCl_3$/*i*-PrOH. The organic extracts were combined, washed with saturated, aqueous NaCl, and dried over Na_2SO_4. A colorless solid remained after evaporation of the solvent. This solid was dissolved in absolute ethanol, and 1.1 equiv of D-(−)-(*tert*-butyoxycarbonyl)phenylglycine was added. The solution was heated to boiling for 10 min and then allowed to stand at room temperature. The crystals were collected by vacuum filtration and dried in the vacuum desiccator: mp 192–194 °C; $[\alpha]^{25}_D$ (H_2O) +3.79°. Anal. ($C_{13}H_{21}N_3 \cdot C_{13}H_{17}NO_4$) C, H, N, O.

The compound crystallized as colorless plates, in the space group $P2_1$, with two molecules in a unit cell having the dimensions $a = 9.557 \pm 0.002$, $b = 6.680 \pm 0.001$, $c = 20.795 \pm 0.003$ Å, and $\beta = 91.44 \pm 0.02°$. The density calculated for $C_{26}H_{38}N_4O_4$ (M_r 470.6) is 1.18 g cm^{-3}. The intensities of 1959 unique reflections were measured on a four-angle diffractometer with Cu $K\alpha$ radiation. The X-ray structure was solved by direct methods and refined by the least-squares method to a value of $R = 0.054$.

Biological Methods. Rat Locomotor Activity. Male Sprague–Dawley rats (Harlan Industries, Indianapolis, IN) were dosed intraperitoneally with saline or with increasing concentrations of pergolide or (±)-**5** (R = Pro). Immediately after injection, the rats were placed in electronic activity monitors (Stoelting Co., Chicago, IL) for a 1-h period. The rats were not allowed to acclimatize to the monitors so that they would have a relatively high level of spontaneous locomotor activity. External stimuli were minimized by isolating the monitors in a sound-attenuated laboratory. An activity count registered each time the radio-frequency field was interrupted. The monitors were not able to differentiate vertical and horizontal movements. Each animal was used only once, and six to nine rats were employed per group. Each time activity was monitored there was one vehicle control group with the other groups receiving the various drug doses to be tested.

Lordotic Behavior in Rats. Chronic ovariectomized Long-Evans hooded rats received subcutaneous injections of 100 μg of estrone in sesame oil 48 h prior to testing. Each of the female rats was exposed to a sexually active male rat for 15 mounts prior to the injection of the drug. The compounds were injected subcutaneously, and the animals were reexposed to the male rat 90 min following injection. The results are given in Table VIII.

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Registry No. (±)-**5** (R = Pr), 74196-92-2; (−)-**5** (R = Pr), 85760-74-3; (+)-**5** (R = Pr), 85760-75-4; (−)-**5** (R = Pr) D-(−)-tartrate, 85798-07-8; (−)-**5** (R = Pr) HCl, 85798-08-9; (+)-**5** (R = Pr) L-(+)-tartrate, 85798-09-0; (+)-**5** (R = pr) D-(−)-(*tert*-butyloxycarbonyl)phenylglycine, 85798-10-3; prolactin, 9002-62-4; dopamine, 51-61-6.

Supplementary Material Available: Table IX, atomic coordinates and *Uij* values; Table X, bond lengths; Table XI, bond angles; Table XII, anisotropic temperature factors; Table XIII, hydrogen coordinates; Figure 2, X-ray numbering diagram pertaining to the X-ray structure determination (6 pages). Ordering information is given in any current masthead page.

Synthesis and Biological Properties of Thiophene Ring Analogues of Mianserin

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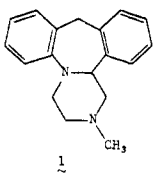
The synthesis of two thiophene-containing analogues of mianserin, i.e., 1,2,3,4,10,13b-hexahydro-2-methylpiperazino[1,2-*a*]thieno[2,3-*c*][1]benzazepine (**2**), and the corresponding [3,2-*c*] isomer (**12**) is described. The key step in the synthesis is the nucleophilic aromatic substitution reaction of the *N*-lithio derivative of 1-methyl-3-(2-thienyl)piperazine (**4**) with the oxazoline derivative of o-anisic acid (**7**) to give the *N*-phenylpiperazine **8**. This substance was converted via ethyl ester **10** to 1-[2-(hydroxymethyl)phenyl]-4-methyl-2-(2-thienyl)piperazine (**3**), which was cyclized with polyphosphate ester to a 5:1 mixture of **2** and **12**. The antidepressant potential of **2** maleate (CGS 11049A) and **12** fumarate (CGS 15413A) were compared with that of mianserin hydrochloride in a variety of biochemical and pharmacological test systems. The three substances exhibited generally similar profiles. However, the results suggest that **2** and **12** bind more strongly to central presynaptic α-receptors than does mianserin.

Mianserin (**1**), an antidepressant agent currently marketed in several countries throughout the world, has a level of efficacy comparable with that of amitryptyline and imipramine.[2] Significantly, this efficacy is associated with a lower incidence of anticholinergic side effects than that of equitherapeutic doses of the tricyclic drugs,[2a,c,3] while the liability of mianserin to cause cardiovascular side effects also appears to be less than that of the classical antidepressants.[2a,4] The neurobiochemical profile of mianserin differs significantly from that of the classical agents. Thus, mianserin causes pronounced blockade of central



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