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Stereoselective Syntheses of the *trans*-Decahydroquinoline-5-carboxylic Acid Epimers. Diastereomeric Zwitterionic Probes of γ-Aminobutyric Acid Related Biological Properties in Vitro and in Vivo

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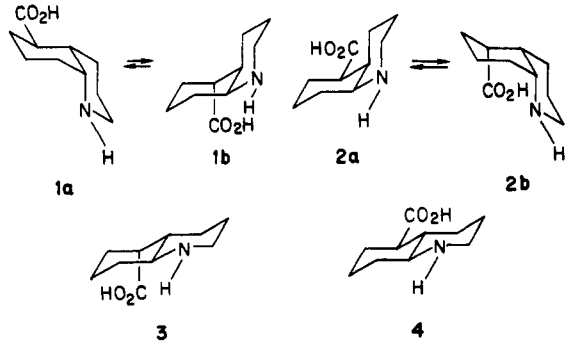
The syntheses of the 5β and 5α epimers of *trans*-(4aα,8aβ)-decahydroquinoline-5-carboxylic acids (**3** and **4**) from vinylogous bicyclic imide **10** are described. The reduction of *trans*-5-(1,3-dithian-2-ylidene)octahydro-2(1*H*)-quinolinone (**13**) to afford the 5α-(1,3-dithian-2-yl) compound **16** was a key step in the synthesis of *trans*-**4** while hydroboration–H_2O_2 treatment of phenylmethyl *trans*-octahydro-5-methylene-1(2*H*)-quinolinecarboxylate (**21**) to afford the 5β-hydroxymethyl compound **22** was a key step in the synthesis of **3**. These trans diastereomers **3** and **4** and the previously prepared cis analogues **1** and **2** were investigated for their ability to interact with $GABA_A$ and $GABA_B$ receptors and picrotoxin binding sites as well as with neuronal GABA transport systems in brain tissue. Like **1** and **2**, tonic-clonic seizures were induced when *trans*-**3** or -**4** were administered to mice intracerebroventricularly. Only *trans*-**4** weakly inhibited [^{3}H]GABA binding to $GABA_A$ and $GABA_B$ receptors in vitro. Large doses (10 mg/kg) of diazepam reversed the convulsant activity of both *trans*-**3** and *trans*-**4**. Although *trans*-**3** is the more potent convulsant, *trans*-**4** may have GABA antagonist activity in vivo. However, none of the decahydroquinoline diastereomers have a pronounced effect on GABA receptors that can currently be studied in vitro. Results obtained in vivo lead us to propose that these diastereoisomers may serve as unique conformational probes relating certain zwitterionic topographies to stimulatory activity in the central nervous system.

Diastereomeric decahydroquinoline-5-carboxylic acids (**1–4**) may be viewed as having centrally positioned GABA moieties each contained by two 1,3-propylene functions forming two six-membered rings of the bicyclic system. Given the flexible nature of the cis diastereomers **1** and **2** and the constrained conformations of the trans compounds **3** and **4**, these substances serve as unique central nervous system (CNS) conformational probes for stereostructure–activity analysis of a rich variety of zwitterionic topographies of amino and carboxylic acid functions. owing to the lipophilic properties and steric bulk of the propylene units positioned about the GABA pharmacophore, we previously proposed that **1–4** should not be expected to possess the intrinsic activities of GABA receptor agonists but may retain affinity for other GABA receptors/recognition sites thereby serving as stereoselective receptor antagonists or inhibitors of GABA uptake.[2,3]



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However, few of the known selective GABA-uptake inhibitors[4] can be formally considered as structural GABA analogues. Thus, (*R*)-(−)-nipecotic acid (**5**) and guvacine (**6**), which contain the β-alanine (or δ-aminovaleric acid) relationship of amino and carboxylic acid groups, are among the more potent inhibitors of neuronal and glial GABA uptake.[5] Cyclic GABA analogues of the type **7**[6] and **8**[7] (n = 1–4) did not significantly inhibit GABA uptake at concentrations up to 100 μM; however, the cyclopropyl

(1) A preliminary account of the chemistry of this series has been presented to the Division of Medicinal Chemistry, 188th National Meeting of the American Chemical Society, Philadelphia, PA. Patch, R. J.; Witiak, D. T., MEDI-108, 1984. This article was abstracted in part from a dissertation (1984) presented by R.J.P. to The Ohio State University.
(2) Witiak, D. T.; Tomita, K.; Patch, R. J.; Enna, S. J. *J. Med. Chem.* **1981**, *24*, 788–794.
(3) Fung, Y. K.; Bero, C.; Dircks, D.; Tomita, K.; Patch, R. J.; Witiak, D. T. *Res. Commun. Chem. Pathol. Pharmacol.* **1983**, *39*, 367–380.
(4) By "selective GABA-uptake inhibitors" we are referring to compounds that irrespective of their mechanism inhibit GABA uptake while exhibiting no significant affinity for GABA receptors. A recently published article of interest is Ali, F. E.; Bondinell, W. E.; Dandridge, P. A.; Frazee, J. S.; Garvey, E.; Girard, G. R.; Kaiser, C.; Ku, T. W.; Lafferty, J. J.; Moonsammy, G. I.; Oh, H.-J.; Rush, J. A.; Setler, P. E.; Stringer, O. D.; Venslavsky, J. W.; Volpe, B. W.; Yunger, L. M.; Zirkle, C. L. *J. Med. Chem.* **1985**, *28*, 653–660.
(5) Schousboe, A. In "Advances in Experimental Medicine and Biology, GABA—Biochemistry and CNS Functions"; Mandel, P., DeFeudis, F. V., Eds.; Plenum Press: New York, 1979; Vol. 123, pp 219–237.
(6) Kennewell, P. D.; Matharu, S. S.; Taylor, J. B.; Westwood, R.; Sammes, P. G. *J. Chem. Soc., Perkin Trans 1* **1982**, 2553–2562.
(7) Kennewell, P. D.; Matharu, S. S.; Taylor, J. B.; Westwood, R.; Sammes, P. G. *J. Chem. Soc., Perkin Trans 1* **1982**, 2563–2570.

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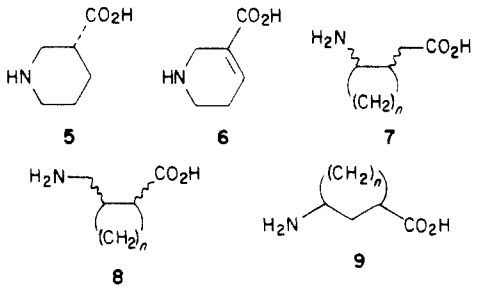
and cyclobutyl compounds of these series were stereoselective inhibitors of GABA binding to rat brain membranes.[6-9] Similar stereoselective activity was observed with structural analogues of the type **9** (n = 1–3).[10] Thus, the corresponding cyclobutyl compounds have little effect on GABA uptake but have good affinity for GABA receptors in brain membranes. On the other hand, the cyclohexyl compound, namely *cis*-3-aminocyclohexanecarboxylic acid (**9**, n = 3), selectively inhibited GABA uptake into rat brain slices (IC_{50} = 85 μM) and is 10 times as potent as the trans isomer in this regard.[10]



The preferred solution conformation of *cis*-**9** (n = 3) is thought to be that in which the zwitterionic centers are equatorial rather than axial.[11] However, since neither the cyclohexane nor the piperidine ring constitute a conformationally constrained system, solution conformations of **5** or **9** (n = 3) do not necessarily reflect their pharmacologically active orientations. The topography of the GABA pharmacophore found in diequatorial **9** (n = 3) is mimicked in decahydroquinolines *cis*-**2a** and *trans*-**4**, whereas the diaxial conformation of **9** (n = 3) is mimicked by *cis*-**2b**. Of particular interest is *trans*-**4**, since this structure constitutes a rigid analogue of diequatorial *cis*-**9** (n = 3). Of course, rigid isomer *trans*-**3** mimicks one possible conformation of *trans*-**9** (n = 3) also found in **1b**.

We report in this article the synthesis of trans diastereomers **3** and **4** and the results of a comparative biological evaluation of these substances in conjunction with additional studies of the previously synthesized cis isomers **1** and **2**.[2] The four isomers (**1–4**) were assessed in vitro for their ability to interact with rat brain $GABA_A$[12] and $GABA_B$[13] receptors, to affect isoproterenol-stimulated and baclofen-enhanced cyclic AMP formation,[14,15] to inhibit [^{3}H]GABA uptake into rat brain synaptosomes,[16] to affect [^{3}H]diazepam binding and GABA-activated diazepam binding,[17] and to inhibit *tert*-butyl[^{35}S]bicyclophosphorothioate (TBPS) binding.[18] GABA-activated [^{3}H]diazapam binding is a functional measure of $GABA_A$ receptor activity, whereas baclofen-enhanced cyclic AMP formation appears to be a functional measure of $GABA_B$ receptor activity. Additionally, the convulsant effect of trans diastereomers **3** and **4** were investigated following intracerebroventricular (ICV) administration in mice as has been done previously with *cis*-**1** and **2**.[3]

Synthetic Chemistry

The reported syntheses[2] of cis decahydroquinolines **1** and **2** employed both intra- and intermolecular Diels–Alder reactions as key steps in the reaction sequences. Given the preference for the formation of cis-decahydroquinoline ring systems in these reactions, use of intramolecular Diels–Alder methodology for trans targets **3** and **4** would have required extensive chemical manipulation, such as involvement of a masked carbonyl at position 4 allowing for eventual epimerization. Recognizing complications involved in the epimerization of such systems,[19] we elected to pursue other routes.[20] Dissolving-metal reductions of 5,6,7,8-tetrahydroquinolines using sodium in ethanol have been shown to afford trans decahydroquinolines (90%) along with approximately 10% of the corresponding cis isomers.[21,22] Whereas application of such methodology to the synthesis of decahydroquinoline-5-carboxylic acids might lead to *trans*-**4**, lack of stereochemical control at C-5 renders this approach of little use for the synthesis of **3**, wherein the epimerizable carboxyl function must assume the thermodynamically less favorable axial position.

A means by which both diastereomers could be stereoselectively prepared was therefore required. To this end we explored preparation of **3** and **4** from *trans*-deca-

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(13) Hill, D. R.; Bowery, N. G. *Nature (London)* **1981**, *290*, 149–152.
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(15) Solomon, Y.; Londos, C.; Rodbell, M. *Anal. Biochem.* **1974**, *58*, 541–548.
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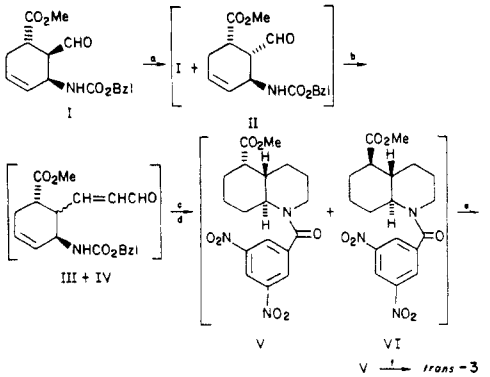
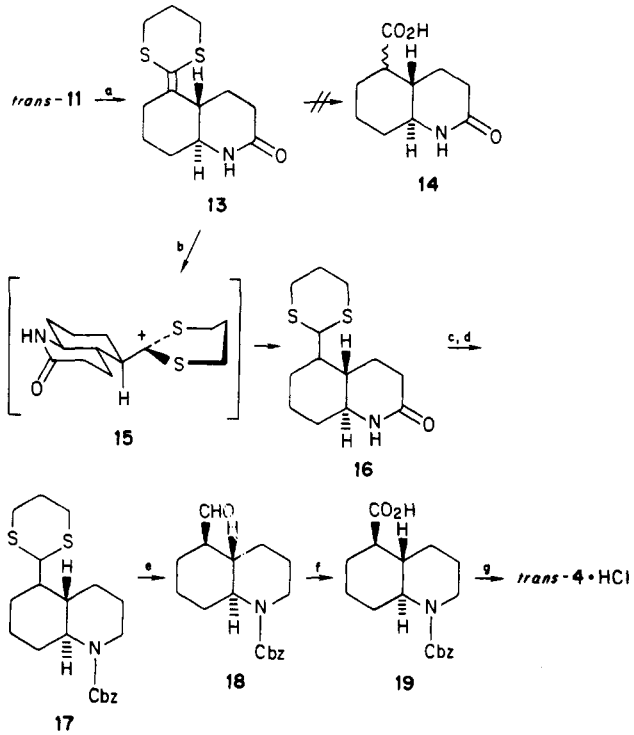
(18) Squires, R. F.; Casida, J. E.; Richardson, M.; Saederup, E. *Mol. Pharmacol.* **1983**, *23*, 326–336.
(19) Johnson, R. A.; Murray, H. C.; Reineke, L. M.; Fonken, G. S. *J. Org. Chem.* **1968**, *33*, 3207–3217. For 1-benzoyldecahydroquinolin-5-ones the cis ring juncture is thermodynamically more stable, but in closely related decahydroquinolin-4-ones the trans ring juncture is more stable [Mistryukov, E. *Izv. Akad. Nauk SSR, Otd, Khim. Nauk* **1963**, 929]. Johnson et al.[19] have prepared *trans*-decahydroquinolin-5-one by CrO_3 oxidation of the corresponding 5α-alcohol obtained by microbiological hydroxylation of 1-benzoyl-*trans*-decahydroquinoline reduction to the benzyl derivative and reductive debenzylation.
(20) A small sample of *trans*-**3** was prepared from Diels–Alder adduct I (Witiak, D. T.; Tomita, K., unpublished results). Equilibration of I[2] produced an inseparable mixture (1:2) of isomers I and II, respectively. Wittig reaction afforded the corresponding homologated products III and IV, which upon hydrogenation and reaction with 3,5-dinitrobenzoyl chloride afforded decahydroquinolines V and VI. Isomer *trans*-V could be separated by preparative TLC and hydrolysis yielded *trans*-**3**.



(a) Me_2SO, 130 °C, 10 h, 90%; (b) $Ph_3PCHCHO$, 90%; (c) H_2/Pd/C; (d) 3,5-dinitrobenzoyl chloride; (e) chromatography, 6%; (f) HCl, Δ, 53%.

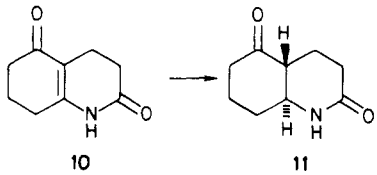
(21) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2729–2734.
(22) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2734–2742.

Scheme I[a]

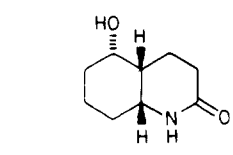


[a] a = 2 equiv of 2-lithio-2-(trimethylsilyl)-1,3-dithiane, THF; b = trifluoroacetic acid, Et_3SiH, 8 days; c = LAH, THF, Δ; d = CbzCl; e = HgO, $BF_3 \cdot Et_2O$, aqueous THF, Δ; f = Jones reagent (1.25 MCr^{6+}); g = H_2, 10% Pd/C, THF/H_2O·HCl, room temperature, 40 psi, 2 h.

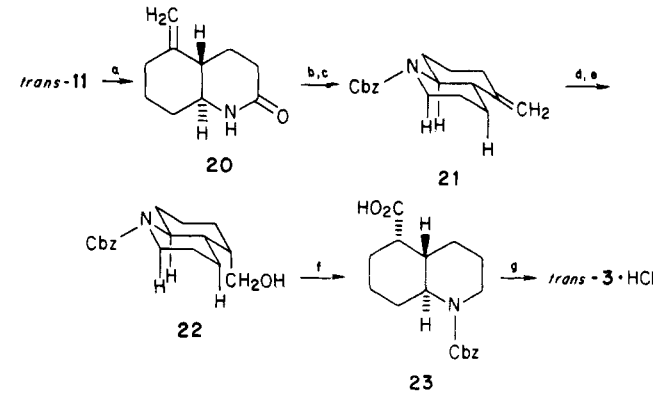
hydroquinoline-2,5-dione (11), which was obtained by reduction of known vinylogous imide **10**,[23] constructed by condensation of acrylic acid with 3-amino-2-cyclohexen-1-one by using the method of Shono et al.[24] Whereas this method provided a rapid and simple preparation of **10**, yields (50–55%) of sufficiently pure product were less than those reported (95%).[24]



trans-Decahydroquinoline-2,5-dione (**11**) has previously been obtained[25] from an equilibrium mixture of diastereomers, prepared by epimerization of the cis isomer under acidic or basic conditions. In MeOH/MeONa a trans/cis ratio of 58:42 was obtained; in TsOH/benzene the ratio was 45:55. The cis fused system had been obtained in 47.5% overall yield by hydrogenation of **10** over rhodium–alumina catalyst followed by CrO_3 oxidation of the resulting intermediate **12**. In these laboratories hydrogenation of **10** over Pd/C in MeOH containing aqueous KOH afforded a 64:36 mixture of *trans*-**11** and its cis diastereomer in yields typically ranging between 70% and 80%. The reaction was carefully monitored to prevent reduction of the ketone. The isomeric ratio was quantified by integration of the H_{8a} proton resonance signal in $CDCl_3$. For *trans*-**11** this signal appears as a deceptively simple doublet of triplets centered at δ 3.27; for the cis isomer this signal occurs as a broad singlet at δ 4.05. Fractional crystallization from H_2O afforded pure *trans*-**11**.



Scheme II[a]



[a] a = $Ph_3P^+CH_2^-$ (2 equiv) THF; b = LAH, THF; c = CbzCl; d = B_2H_6, THF; e = NaOH, H_2O_2; f = ruthenium trichloride hydrate, sodium metaperiodate,[35] CCl_4, CH_3CN, H_2O; g = H_2, 10% Pd/C, THF/H_2O HCl, room temperature, 40 psi, 2 h.

Peterson olefination[26] of *trans*-**11** with 2-lithio-2-(trimethylsilyl)-1,3-dithiane[27] (2 equiv) in dry THF afforded ketene dithioacetal **13** in 83% yield (Scheme I). However, hydrolysis to the corresponding carboxylic acids **14** using either $HgO/BF_3 \cdot Et_2O$[28] or HgO/HBF_4[29] was unsuccessful. Alternatively, the desired compounds were generated in a stepwise process. Reduction of ketene dithioacetal **13** via transfer hydrogenation[30] employing trifluoroacetic acid and triethylsilane afforded **16** in 95% yield after 8 days at room temperature. Proton NMR spectroscopy could not be employed for assigning stereochemistry at position 5 of the decahydroquinoline since the H_5 resonance signal is obscured by a 14-proton multiplet which could not be adequately simplified by proton decoupling. Ultimate conversion of **16** to *trans*-**4** coupled with a consideration of the reaction mechanism involving a sulfur-stabilized carbonium ion intermediate[30] provided the structural assignment for **16**. Thus, the charged dithianyl ring likely assumes the thermodynamically preferred equatorial position of **15** following protonation. Hydride transfer from triethylsilane leads to **16**.

Reduction of lactam **16** followed by derivatization afforded Cbz-protected amine **17** in 88% yield. Dethioketalization[31] was accomplished in 89% yield with use of red mercuric oxide and $BF_3 \cdot Et_2O$ in 15% aqueous THF. Jones oxidation of **18** yielded **19** (73%) and hydrogenolysis afforded *trans*-**4**·HCl (83%).

trans-Decahydroquinoline **11** also served as starting material for the preparation of *trans*-**3** (Scheme II). Wittig reaction employing 2 equiv of methylenetri-

(23) Bohme, E. H. W.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett.* **1965**, 2441–2444.
(24) Shono, T.; Matsumura, Y.; Kashimura, S. *J. Org. Chem.* **1981**, *46*, 3719.
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(30) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926–1929.
(31) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366–367.

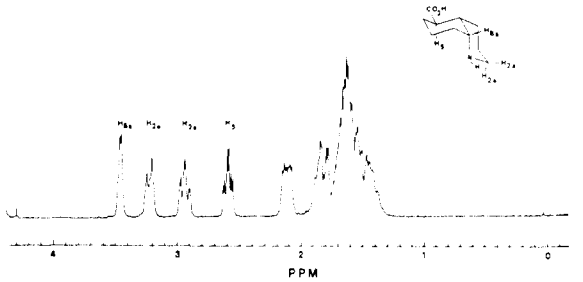

Figure 1. NMR spectrum (300 MHz) of (4aα,5α,8aα)-decahydroquinoline-5-carboxylic acid (*cis*-1).

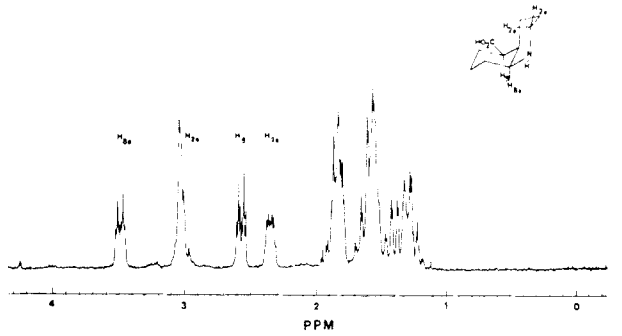

Figure 2. NMR spectrum (300 MHz) of (4aα,5β,8aα)-decahydroquinoline-5-carboxylic acid (*cis*-2).

phenylphosphorane in dry THF afforded **20** in a maximum yield of 53%. The yield could not be improved by increasing the length of the reaction time or the amount of ylide used. Reduction and amino group protection afforded carbamate **21** (95%). Diborane reduction of **21**, presumably from the least sterically hindered side of the molecule (Dreiding molecular models), provided the stereocontrol necessary for the preparation of target *trans*-**3**. Thus, hydroboration–H_2O_2 oxidation afforded the axial hydroxymethyl compound **22** in nearly quantitative yield. Interestingly, the bulky reducing agent 9-BBN (9-borabicyclo[3.3.1]nonane[32]) did not undergo reaction with exocyclic olefin **21**. Again, spectral analysis provided no information concerning stereochemistry at position 5 of **22**; confirmation of the assigned stereochemistry was obtained by ultimate conversion to *trans*-**3**.

Mild oxidative methods were sought for the conversion of **22** to **23** in order to avoid carboxyl group epimerization. Reaction of **22** with pyridinium dichromate in DMF[33] was sluggish; after 2 days and in the presence of excess reagent, the reaction mixture contained substantial quantities of starting alcohol, along with aldehyde and three additional components. Oxidation with ruthenium tetraoxide[34] was somewhat more successful in effecting conversion to axial acid **23**. No epimerized product was detected in the reaction mixture. Deprotective hydrogenolysis of crude **23** afforded *trans*-**3** hydrochloride in 45% overall yield from **22**.

^{1}H NMR Spectroscopy

Proton resonance signal assignments at 90 MHz previously were discussed[2] for *cis*-**1** and **2**. The 300-MHz spectra are recorded here (Figures 1 and 2, respectively) for comparison with spectra of the trans diastereomers **3** and **4** (Figures 3 and 4, respectively). For *trans*-**4**, the axial proton H_5 is strongly coupled to two adjacent axial protons and one equatorial proton. Hence its resonance signal appears as a deceptively simple triplet ($J \cong 11.2$ Hz) of doublets ($J \cong 3.4$ Hz) centered at δ 2.06. A similar pattern was observed for the resonance signal of H_{8a} which also results primarily from two diaxial couplings and one axial–equatorial coupling. This signal appears at δ 2.75 and is partially overlapped by the H_{2ax} resonance signal. The furthest downfield signal (δ 3.20) was assigned to the equatorial proton H_{2eq} resonance signal. The observed doublet, attributed to geminal coupling ($J \cong 12.8$ Hz), exhibits additional minor splitting and shoulders indicative of quartets. However, these couplings, owing to equatorial–axial and diequatorial interactions were too small to be accurately measured.

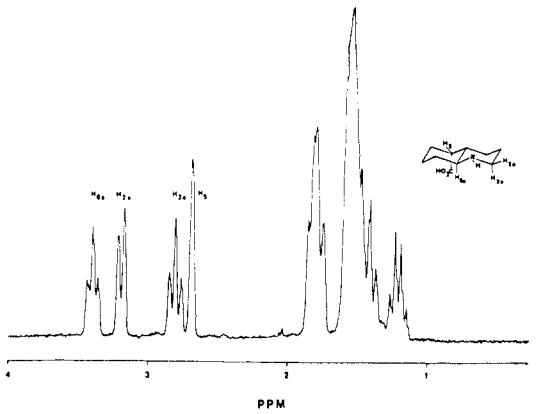

Figure 3. NMR spectrum (300 MHz) of (4aα,5β,8aβ)-decahydroquinoline-5-carboxylic acid (*trans*-**3**).

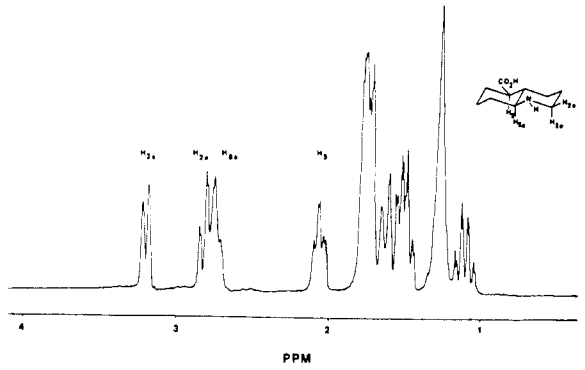

Figure 4. NMR spectrum (300 MHz) of (4aα,5α,8aβ)-decahydroquinoline-5-carboxylic acid (*trans*-**4**).

Chemical shifts and coupling constants of resonance signals assigned to H_{2eq} and H_{2ax} in *trans*-**3** are essentially the same as those of *trans*-**4**. However, H_{8a}, presumably deshielded by the axial carboxylate group, is downfield (δ 3.39) relative to the H_{8a} signal in *trans*-**4**. The resonance signal assigned to H_5 having an equatorial conformation also is downfield (δ 2.68) relative to the H_5 axial proton signal in *trans*-**4**. This broadened singlet for the H_5 resonance signal in *trans*-**3** reflects relatively smaller equatorial–axial and diequatorial couplings.

Biological Results

The effects of decahydroquinoline-5-carboxylic acids **1–4** on [^{3}H]GABA$_A$ and GABA$_B$ receptor binding to rat brain membranes are shown on Table I. Only *trans*-**4** significantly inhibited binding to these receptors, but at 100 μM the percent displacement of specifically bound [^{3}H]GABA

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(33) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399–402.
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(35) Substitution of H_5IO_6 for $NaIO_4$ led to a reduced reaction time (15 mins) but did not affect the overall yield of this transformation.

Table I. Effects of Diastereomeric Decahydroquinoline-5-carboxylic Acids on [^{3}H]GABA$_A$, [^{3}H]GABA$_B$, and *tert*-Butyl [^{35}S]Bicyclophosphorothionate (TBPS) Binding in Rat Brain Membranes and [^{3}H]GABA Uptake into Rat Brain Synaptosomes

compd (100 μM)	% displacement of specifically bound isotope: [^{3}H]GABA[a] (GABA$_A$)	[^{3}H]-GABA[b] (GABA$_B$)	[^{35}S]TBPS[c]	% inhibn of [^{3}H]GABA uptake[d]
GABA	100[e]	100[f]		95
baclofen	15	100		
picrotoxin			90[g]	
cis-1	<10	<10	<5	<5
cis-2	<10	<10	<5	15
trans-3	<10	<10	<5	<5
trans-4	43	38	<5	<5

[a] GABA$_A$ receptor binding was performed according to the method of Enna and Snyder[12] using [^{3}H]GABA as a ligand. Nonspecific binding was determined by conducting the assay in the presence of 1 mM unlabeled GABA. The results are the means of three experiments, each of which was performed in duplicate. In all cases the standard error of the means was less than 10%. [b] GABA$_B$ receptor binding was performed by using a previously reported assay.[13] The binding site was defined by incubating rat brain membranes with [^{3}H]GABA and 40 μM isoguvacine to inhibit attachment to GABA$_A$ receptor sites. Baclofen (100 μM) was used to define nonspecific binding. Values represent the means of three experiments, each of which was performed in duplicate. Standard errors were less than 20%. [c] [^{35}S]TBPS binding was assayed according to the method of Squires et al.[18] Nonspecific binding was defined as the amount of radioactivity bound in the presence of 10 μM unlabeled TBPS. Values represent the means of two experiments, each of which was performed in duplicate. [d] High-affinity [^{3}H]GABA uptake into rat brain synaptosomes was analyzed according to the method of Krogsgaard-Larsen.[16] The values are the means of two experiments. [e] The IC$_{50}$ value for GABA on GABA$_A$ binding is 20 nM. [f] The IC$_{50}$ value for GABA on GABA$_B$ binding is 80 nM. [g] The IC$_{50}$ value for picrotoxin on TBPS binding is 180 nM.

Table II. Effects of Diastereomeric Decahydroquinoline-5-carboxylic Acids on Hormone-Stimulated Cyclic AMP Formation and Baclofen-Enhanced Cyclic AMP Formation[a]

compd (100 μM)	cAMP formation, % conversion	compd (100 μM)	cAMP formation, % conversion
no addition	0.16	isoproterenol + *trans*-3	0.91
isoproterenol	0.84	isoproterenol + *trans*-4	0.84
baclofen	0.20	ISO[b] + baclofen + *cis*-1	2.59
isoproterenol + baclofen	2.56	ISO + baclofen + *cis*-2	2.81
		ISO + baclofen + *trans*-3	2.63
isoproterenol + *cis*-1	0.86	ISO + baclofen + *trans*-4	2.65
isoproterenol + *cis*-2	0.80		

[a] Cyclic AMP accumulation in rat brain cerebral cortical slices was analyzed according to the method of Shimizu et al.[14] and cyclic AMP was isolated by using the double-column method of Solomon et al.[15] The results are the means of two experiments, each of which was performed in duplicate. [b] ISO = isoproterenol.

was less than 50%. The results for *cis*-1 and 2 on GABA$_A$ receptors are in accord with previously published results. At these concentrations, GABA displaces 100% of [^{3}H]-GABA from either binding site, whereas the agonist baclofen [3-(4-ClC$_6$H$_4$)GABA] is more selective[13] for the GABA$_B$ site.

A summary of results with 1–4 on hormone-stimulated cyclic AMP formation and baclofen-enhanced cyclic AMP formation is found in Table II. None of the decahydroquinoline diastereomers enhanced either isoproterenol- or combined isoproterenol/baclofen-induced cAMP formation.[36] When assessed for their effects on [^{3}H]GABA uptake into rat brain slices (Table I), only *cis*-2 exhibited weak inhibitory activity in agreement with previous studies.[2] Furthermore, at 100 μM these compounds had no effect on [^{3}H]diazepam binding, GABA-activated diazepam binding (Table III), or [^{35}S]TBPS binding (Table I) in rat brain membranes.

Table III. Effects of Diastereomeric Decahydroquinoline-5-carboxylic Acids on [^{3}H]Diazepam Binding and GABA-Activated Diazepam Binding in Rat Brain Membranes[a]

test compd (100 μM)	[^{3}H]diazepam, fmol spec bound/mg of protein
[^{3}H]diazepam	29.3
[^{3}H]diazepam + *cis*-1	31.9
[^{3}H]diazepam + *cis*-2	32.0
[^{3}H]diazepam + *trans*-3	28.8
[^{3}H]diazepam + *trans*-4	35.0
[^{3}H]diazepam + GABA	55.4
[^{3}H]diazepam + GABA + *cis*-1	55.3
[^{3}H]diazepam + GABA + *cis*-2	59.4
[^{3}H]diazepam + GABA + *trans*-3	59.1
[^{3}H]diazepam + GABA + *trans*-4	65.5

[a] [^{3}H]Diazepam binding and GABA-activated diazepam binding were analyzed according to the method of Tallman et al.[17] Nonspecific binding was determined in the presence of 1 μM unlabeled diazepam. The results are the means of two experiments, each of which was performed in duplicate.

Table IV. Effect of ICV Administration of *trans*-Decahydroquinolines 3 and 4 on Mice[a]

treatment groups	tonic-clonic seizure[b]	duration of seizure, min (mean ± SEM)
saline	0/6	
trans-3		
100 μg	5/5[c]	26.5 ± 1.4
50 μg	5/5[c]	9.5 ± 0.6
25 μg	0/5	
trans-4		
100 μg	5/5[c]	11.7 ± 0.2
50 μg	1/6	0.8 ± 0.6
25 μg	0/5	

[a] Under halothane anesthesia, saline, *trans*-3 or *trans*-4 was injected in a volume of 4 μL into the left ventricle of the mouse. Animals were placed into a 1-L beaker and observed for seizure activities 2 min post ICV drug injection; behavioral changes were observed for 40 min. [b] Ratio indicates the number of mice showing convulsant activity to the number of mice tested. Seizures were considered present when tonic-clonic convulsions occurred and the mouse fell on its flank. [c] Significantly different from control, $p < 0.05$ (χ square test).

ICV administration of *trans*-3 or 4 produced convulsant activity in mice (Table IV). Animals treated with *trans*-3 (50 and 100 μg) and *trans*-4 (100 μg) exhibited tonic-clonic convulsions within 3 min after ICV injection. Unlike *cis*-1,[3] neither agent was lethal at these doses. There was no obvious motor impairment during a 40-min postictal observation period.

The effect of diazepam pretreatment in reversing the seizure activities induced by *trans*-3 or 4 is shown in Table V. Mice appeared sedated 7 min after the administration (ip) of diazepam (2–10 mg/kg). Five minutes following a 10 mg/kg dose the mice were clearly ataxic. Only at this dose of diazepam was the seizure activity produced by ICV administration of 100 μg of *trans*-4 abolished. Diazepam (10 mg/kg) pretreatment was not effective in abolishing

(36) Karbon, E. W.; Enna, S. J. *Mol. Pharmacol.* **1985**, *27*, 53–59.

Table V. Effect of Diazepam Pretreatment in Reversing the Seizure Activities Induced by *trans*-Decahydroquinolines **3** and **4**[a]

treatment groups	tonic-clonic seizure[b]
(1) saline (ip) + saline (ICV)	0/5
(2) saline (ip) + *trans*-**3** (100 μg, ICV)	5/5[c]
(3) diazepam (2 mg/kg, ip) + *trans*-**3** (100 μg, ICV)	5/5[c]
(4) diazepam (5 mg/kg, ip) + *trans*-**3** (100 μg, ICV)	4/4[c]
(5) diazepam (10 mg/kg, ip) + *trans*-**3** (50 μg, ICV)	0/5[c]
(6) saline (ip) + *trans*-**4** (100 μg, ICV)	5/5[c]
(7) diazepam (2 mg/kg, ip) + *trans*-**4** (100 μg, ICV)	4/4[c]
(8) diazepam (5 mg/kg, ip) + *trans*-**4** (100 μg, ICV)	5/5[c]
(9) diazepam (10 mg/kg, ip) + *trans*-**4** (100 μg, ICV)	0/6

[a] Animals were pretreated with diazepam (2–10 mg/kg, ip) 10 min prior to the icv administration of various agents. Diazepam (Hoffmann-La Roche Inc.) was administered in a volume of 0.1 mL/10 g of body weight of mice. Animals were observed for convulsant activities for 40 min post ICV drug injection. [b] Ratio indicates the number of mice showing the indicated behavior to the total number of mice tested. [c] Significantly different from the control group, $p < 0.05$ (χ square test).

seizures produced by 100 μg of *trans*-**3** but did antagonize seizures induced by 50 μg of *trans*-**3**.

Discussion

Previously we suggested[3] that *cis*-**1** may act indirectly as a partial GABA agonist in vivo and that at higher concentrations both *cis*-**1** and **2** exhibit properties of GABA antagonists, but that this effect cannot be explained by an interaction with the classical $GABA_A$ binding site. Results communicated in this article confirm that the cis decahydroquinolines **1** and **2** have a low affinity for either $GABA_A$ or $GABA_B$ binding sites in vitro. Additionally, *trans*-**3** had no measurable affinity for these sites in vitro. Although *trans*-**4** (100 μM) inhibited [^{3}H]GABA binding to $GABA_A$ and $GABA_B$ receptors in rat brain membranes by 43% and 38%, respectively, this interaction appears weak compared to standard agents on this site.[36] Additionally, at 100 μM none of the four isomers influenced either benzodiazepine binding or GABA-activated benzodiazepine binding, with the latter being a measure of $GABA_A$ receptor activity.[17] These compounds had little affinity for GABA transport carriers as no significant inhibition of GABA uptake was observed at 100 μM. Lack of affinity for the [^{35}S]TBPS binding site[18] suggests that these agents do not interact with the picrotoxinin components of $GABA_A$ receptors in vitro.

Nonetheless, the CNS excitatory effects of *cis*-**1** and **2**, like those of picrotoxinin, are completely reversed by valproic acid, a GABA transaminase inhibitor, suggesting that in vivo they may interfere with some aspect of GABA-mediated transmission.[3] However, considering the negligible binding activities of the cis analogues as well as *trans*-**3** in vitro in light of the demonstrated positive correlation between receptor binding in vitro and activity in vivo of other GABA analogues,[37] it does not seem likely that these compounds are acting as antagonists at the GABA receptors that are currently identifiable with binding assays. If the CNS excitatory responses observed after ICV administration are in fact GABA related, it is conceivable that they may be the result of a decrease in GABA release or synthesis or an interaction with a pharmacologically distinct subset of GABA receptors. Alternatively, the brain membrane preparations used in these binding assays may contain altered receptors such that the bulky zwitterionic decahydroquinoline-5-carboxylic acids are unable to fit properly although they are capable of binding to GABA receptors in vivo.

Clearly, these isomers have no effect on the ability of baclofen to potentiate isoproterenol-stimulated cyclic AMP formation. It is not likely that these isomers interact with $GABA_B$ receptors in vivo. The finding that diazepam reverses the convulsant activity of both *trans*-**4** and *trans*-**3** is not necessarily a reflection of GABA antagonist activity in vivo. Of the four diastereomers, *trans*-**4** is the only one that inhibits [^{3}H]GABA binding to brain membrane preparations. It is of interest that *trans*-**3** and *cis*-**1** are the most potent convulsants in this series and that the zwitterionic topography found in *trans*-**3** is mimicked in **1b**. Future studies will concentrate on investigating the stereoselective CNS effects of amino and carboxylic acid zwitterionic topographies intrinsic to the four decahydroquinoline-5-carboxylic acids.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded with a Beckman Model 4230 spectrophotometer. Nuclear magnetic resonance spectra were recorded with either a Bruker WP-80, HX-90E, or WM-300 MHz spectrophotometer. Me_4Si ($CDCl_3$, Me_2SO) was used as internal standard. Mass spectra were recorded with a DuPont Model 21-491 mass spectrometer with a Model 21-094 data system. High-resolution mass spectra were obtained with a Kratos MS-30 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

(4aα,5β,8aβ)-Decahydroquinoline-5-carboxylic Acid (*trans*-3) Hydrochloride. A solution of **23** (77 mg, 0.24 mmol) in 20 mL of THF/H_2O (1:1) containing 0.020 mL of concentrated HCl was hydrogenated over 25 mg of 10% Pd/C at room temperature and 40 psi for 2 h. After filtration, the solvent was removed under reduced pressure and the residue was dissolved in a minimal amount of MeOH. This solution was passed through a small plug of Celite and concentrated. The residual semisolid was recrystallized from MeOH/Me_2CO, affording 34 mg (45.6%) of *trans*-**3** as white crystals: mp 315–320 °C dec; IR (KBr) 3400–2200, 1720, 1590 cm^{-1}; NMR (D_2O, 300 MHz) δ 1.1–1.9 (m, 11 H), 2.68 (br s, 1 H, 5-H), 2.79 (br dt, 1 H, $J_{ea} \cong 2.5$ Hz, $J_{gem} \cong J_{aa} \cong 12$–13 Hz, 2ax-H), 3.19 (d, 1 H, $J_{gem} \cong 12.3$ Hz, 2eq-H), 3.39 (br dt, 1 H, $J \cong 3.4$ and 11.4 Hz, 8a-H) with 4.30 (HOD). Anal. ($C_{10}H_{18}ClNO_2$) C, H, N, Cl.

(4aα,5α,8aβ)-Decahydroquinoline-5-carboxylic Acid (*trans*-4) Hydrochloride. A solution of **19** (375 mg, 1.183 mmol) in 60 mL of THF/H_2O (1:1) containing 0.4 mL of 10% HCl solution was hydrogenated over 125 mg of 10% Pd/C at room temperature and 40 psi for 2 h. After filtration, the solvent was removed under pressure and the residue was dissolved in MeOH. The solution was passed through a small plug of Celite and concentrated. The residual semisolid was recrystallized from MeOH/Et_2O, affording 216 mg (83.2%) of *trans*-**4** as off-white granules: mp 275–280 °C dec; IR (KBr) 3300–2300, 1730, 1560 cm^{-1}; NMR (D_2O, 300 MHz) δ 1.0–1.8 (m, 11 H), 2.06 (dt, 1 H, $J \cong 3.4$ and 11.2 Hz, 5-H), 2.6–2.9 (m, 2 H, 8a-H, 2ax-H), 3.20 (br d, 1 H, $J \cong 12.8$ Hz, 2eq-H), with 6.30 (s, HOD). Anal. ($C_{10}H_{18}ClNO_2$) C, H, Cl, N.

4,6,7,8-Tetrahydro-2,5(1*H*,3*H*)-quinolinedione (10). The method of Shono et al.[24] was employed, affording **10** in 54% yield as a very lightly colored green-yellow solid: mp 198–200 °C (lit.[23] mp 200–201 °C; lit.[24] mp 194–195 °C); IR (KBr) 3200, 3120, 1695, 1635, 820 cm^{-1}; MS, *m/e* 165 (M^+).

***trans*-Hexahydro-2,5(1*H*,3*H*)-quinolinedione (11).** A solution containing **10** (1.0 g, 6.06 mmol), 10% aqueous KOH (1 mL), and MeOH (100 mL) was hydrogenated over 300 mg of 10% Pd/C at room temperature and 40 psi for 2 h. The solution was acidified to pH 2 with 10% HCl solution, filtered, and concentrated under reduced pressure to yield a solid. $CHCl_3$ (150 mL)

(37) Olsen, R. W.; Ticku, M. K.; Greenlee, D.; Van Ness, P. In "GABA-Neurotransmitters: Pharmacochemical, Biochemical and Pharmacological Aspects"; Krogsgaard-Larson, P., Scheel-Kruger, J., Kofod, H., Eds.; Academic Press: New York, 1979; pp 165–178.

was added and the mixture shaken and passed through a small plug of Celite. The $CHCl_3$ was removed under reduced pressure, producing a white solid which was washed with Me_2CO to afford 828 mg (81.8%) of a mixture (64:36) of **11** and its cis diastereomer, respectively. Isomer **11** was separated by fractional crystallization (H_2O) affording colorless needles: mp 229–230 °C dec; IR (KBr) 3190, 3060, 1710, 1650, 830 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.2–2.7 (m, 11 H), 3.27 (dt, 1 H, $J \cong 3.3$ and 10.5 Hz, 8a-H), 7.0 (br s, 1 H, NH); MS, m/e 167 (M^+). Anal. ($C_9H_{13}NO_2$) C, H, N.

***trans*-5-(1,3-Dithian-2-ylidene)octahydro-2(1*H*)-quinolinone (13).** To an ice-cooled solution of 2-(trimethylsilyl)-1,3-dithiane (1.15 g, 0.006 mol) in dry THF (25 mL) was added *n*-BuLi [1.55 M in hexane (3.75 mL, 0.006 mol)]. After the mixture was stirred for $^1/_2$ at 0 °C, solid **11** (0.500 g, 0.003 mol) was added. The reaction mixture was allowed to warm to room temperature and stirring was continued for 36 h after which time the mixture was quenched with H_2O (25 mL) and extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure, affording a solid/oil mixture. This mixture was washed with hexane, affording 672 mg (83.5%) of **13** as white needles (EtOH): mp 222–229 °C dec; IR (KBr) 3180, 3040, 2920, 2850, 1645 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.2–2.7 (m, 14 H), 2.7–3.1 [m, 4 H, 2(CH_2S)], 3.35 (dt, 1 *H*, $J \cong 3.7$ and 10.5 Hz, 8a-H), 5.95 (br s, 1 H, NH); MS, m/e 269 (M^+). Anal. ($C_{13}H_{19}NOS_2$) C, H, N, S.

(4aα,5α,8aβ)-5-(1,3-Dithian-2-yl)octahydro-2(1*H*)-quinolinone (16). A solution of **13** (925 mg, 3.44 mmol), triethylsilane (1 mL), and trifluoroacetic acid (2.0 mL) in CH_2Cl_2 (10 mL) was stirred at room temperature for 8 days. The reaction mixture was made alkaline with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried ($CaSO_4$), filtered, and concentrated under reduced pressure, affording 890 mg (95.4%) of **16** as fine white needles (EtOH): mp 222–223 °C; IR (KBr) 3150, 3030, 2900, 1640 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.2–2.6 (m, 14 H), 2.7–3.2 [m, 5 H, 8a-H, 2 (CH_2S)], 4.38 (s, 1 H, SCHS), 5.92 (br s, 1 H, NH); MS, m/e 271 (M^+). Anal. ($C_{13}H_{21}NOS_2$) C, H, N, S.

Phenylmethyl (4aα,5α,8aβ)-5-(1,3-Dithian-2-yl)octahydro-1(2*H*)-quinolinecarboxylate (17). A mixture of **16** (900 mg, 3.32 mmol) and $LiAlH_4$ (505 mg, 13.28 mmol) in 100 mL of dry THF was refluxed under N_2. After 20 h the reaction mixture was cooled to room temperature, carefully quenched with $Na_2SO_4 \cdot 10H_2O$, and filtered. The filtered aluminum salts were washed with hot THF and the combined filtrates were concentrated under reduced pressure to afford 898 mg of a viscous oil containing **(4aα,5α,8aβ)-5-(1,3-dithian-2-yl)decahydroquinoline.** This crude compound was taken up in 25 mL of THF to which 15 mL of 10 aqueous KOH solution subsequently was added. Benzyl chloroformate (850 mg, 4.98 mmol) was then added to this biphasic solution which was vigorously stirred for 2 h. The mixture was acidified with 10% HCl, extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure, affording 2.3 g of a light yellow oil. The oil was chromatographed on silica gel (column) by elution with $CHCl_3$, yielding 1.14 g (88.1%) of **17** as a viscous, undistillable, colorless oil: IR (Neat) 2930, 2890, 2855, 1690, 750, 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.8–2.3 (m, 14 H), 2.7–3.0 [m, 4 H, 2(S-CH_2)], 3.1–3.4 (m, 2 H, 2ax-H, 8a-H), 3.73 (observed center) (ddd, 1 H, $J \cong 3.5$, 6.2 and 13.8 Hz, 2eq-H), 4.36 (s, 1 H, SCHS), 5.12 (s, 2 H, OCH_2), 7.34 (s, 5 H, phenyl); MS, m/e 391 (M^+). Anal. ($C_{21}H_{29}NO_2S_2$) C, H, N, S.

Phenylmethyl (4aα,5α,8aβ)-5-Formyloctahydro-1(2*H*)-quinolinecarboxylate (18). To a vigorously stirred suspension of red HgO (445 mg, 2.046 mmol) and $BF_3 \cdot Et_2O$ (290 mg, 2.046 mmol) in 15% aqueous THF (10 mL) was added a solution of **17** (400 mg, 1.023 mmol) in 2 mL of THF. After refluxing for 0.5 h the HgO dissolved and the reaction mixture turned colorless. Refluxing was continued for 24 h during which time a grey precipitate formed. The reaction mixture was cooled to room temperature and Et_2O (10 mL) was added. The coagulated precipitate was triturated and washed with Et_2O, and the combined washings were concentrated to a volume of 5 mL. H_2O (10 mL) was added and the mixture was extracted with $CHCl_3$, dried ($MgSO_4$), and concentrated under reduced pressure to afford 290 mg of a colorless oil. The oil was chromatographed on silica gel (column) by elution with $CHCl_3$, affording 275 mg (89.3%) of **18** as a colorless oil: bp 115 °C (0.01–0.05 mm; micro distillation); IR (neat) 2930, 2855, 2700, 1720, 1690, 745, 690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 0.8–2.3 (m, 12 H), 3.18 (dt, 1 H, $J \cong 3.2$ and 10.3 Hz, 8a-H), 3.3–3.8 (m, 2 H, NCH_2), 5.13 (s, 2 H, OCH_2), 7.34 (s, 5 H, phenyl), 9.56 (d, 1 H, $J \cong 3.2$ Hz, CHO). Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(4aα,5α,8aβ)-Octahydro-1,5(2*H*)-quinolinedicarboxylic Acid 1-Phenylmethyl Ester (19). To a cooled solution (ice bath) of **18** (175 mg, 0.581 mmol) in Me_2CO (15 mL) was added Jones reagent [diluted to 1.25 M Cr(VI)] dropwise until the orange color of the reagent persisted. After the solution was stirred for an additional 0.5 h, the excess chromic acid was quenched with *i*-PrOH and the solution decanted. The chromium salts were triturated with Me_2CO (five times) and the combined washings were concentrated under reduced pressure. The residue was taken up in a saturated Na_2CO_3 solution and extracted with Et_2O. The aqueous layer was acidified with diluted H_2SO_4 solution and extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated under reduced pressure to afford 161 mg of a colorless oil which solidified on standing overnight. Recrystallization (Me_2CO/hexane) yielded 135 mg (73.2%) of **19** as fine colorless plates: mp 124–125 °C; IR (KBr) 3400–2400, 1700, 1680, 740, 695 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.0–2.3 (m, 12 H), 3.0–3.5 (m, 2 H, 8a-H, 2ax-H), 3.7 (observed center) (ddd, 1 H, $J \cong 3.3$, 6.0 and 13.5 Hz, 2eq-H), 5.13 (s, 2 H, OCH_2), 7.34 (s, 5 H, phenyl), 9.0 (br s, 1 H, CO_2H); MS, m/e 317 (M^+). Anal. ($C_{18}H_{23}NO_4$) C, H, N.

***trans*-Octahydro-5-methylene-2(1*H*)-quinolinone (20).** To a suspension of methyltriphenylphosphonium iodide (2.420 g, 5.988 mmol) in 50 mL of THF was added 1.6 M of *n*-BuLi (3.75 mL, 5.988 mmol). The resulting solution was stirred under N_2 at room temperature for 4 h. Solid **11** (500 mg, 2.994 mmol) was added and the mixture refluxed for 3 h. After the mixture cooled to room temperature, H_2O (25 mL) was added and the solution extracted with Et_2O, dried ($MgSO_4$), and concentrated under reduced pressure, affording 1.23 g of a yellow solid/oil mixture. Purification by flash chromatography using EtOAc as eluent afforded 264 mg (53.4%) of **20** as white needles ($CHCl_3$/hexane): mp 154.5–156 °C; IR (KBr) 3190, 3080, 3060, 2940, 2870, 1690, 1660 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.0–2.6 (m, 11 H), 2.95 (dt, 1 H, $J \cong 3.3$ and 10.0 Hz, 8a-H), 4.75 [d, with small (~1 Hz) allylic coupling, 2 H, $J = 13.0$ Hz, vinyl H], 6.06 (br s, 1 H, NH); MS, m/e 165 (M^+). Anal. ($C_{10}H_{15}NO$) C, H, N.

Phenylmethyl *trans*-Octahydro-5-methylene-1(2*H*)-quinolinecarboxylate (21). A mixture of **20** (260 mg, 1.576 mmol) and $LiAlH_4$ (240 mg, 6.30 mmol) in 50 mL of dry THF was refluxed for 5 h under N_2. After cooling to room temperature, the reaction mixture was carefully quenched with $Na_2SO_4 \cdot 10H_2O$ and filtered. The aluminum salts were washed with hot THF and the combined filtrates were concentrated under reduced pressure, affording 240 mg of a solid containing *trans*-decahydro-5-methylenequinoline. This crude compound was dissolved in 10 mL of THF followed by 2 mL of 10% aqueous KOH. Benzyl chloroformate (540 mg, 3.15 mmol) was then added and the resulting biphasic solution was stirred vigorously for 1 h. H_2O (10 mL) was added and the mixture extracted with Et_2O. The organic layer was washed with 10% HCl solution, dried ($MgSO_4$), and concentrated under reduced pressure to give a colorless oil which was chromatographed on silica gel (column) by elution with $CHCl_3$, yielding 428 mg (95.3%) of **21** as a colorless oil: IR (Neat) 2940, 2865, 1700, 1650, 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.1–2.5 (m, 11 H), 3.0–3.5 (m, 2 H, 2ax-H, 8a-H), 3.80 (observed center) (ddd, 1 H, $J \cong 2.5$, 6.5 and 13.5 Hz, 2eq-H), 4.62 [d, with small (~1 Hz) allylic coupling, 2 H, $J \cong 16.5$ Hz, vinyl H], 5.13 (s, 2 H, OCH_2), 7.33 (s, 5 H, phenyl); MS, m/e 285 (M^+). Anal. ($C_{18}H_{23}NO_2$) C, H, N.

Phenylmethyl (4aα,5β,8aβ)-Octahydro-5-(hydroxymethyl)-1(2*H*)-quinolinecarboxylate (22). To a cooled (dry ice) solution of **21** (380 mg, 1.33 mmol) in dry THF (20 mL) was added B_2H_6 [0.98 M in THF (2 mL, 1.96 mmol)]. The mixture was allowed to warm to room temperature and stirring was maintained for 1 h after which time 6 N NaOH solution (5 mL) was slowly added. H_2O_2 (30%; 3.5 mL) was added and the resulting solution was stirred vigorously overnight. K_2CO_3 was added to saturate the aqueous phase and the mixture was extracted with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and

concentrated under reduced pressure to afford 436 mg of a colorless oil. Purification by flash chromatography using $CHCl_3$ as eluent gave 400 mg (99%) of **22** as a colorless, viscous oil: IR (neat) 3600–3100, 2930, 2870, 1680, 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.0–2.2 (m, 12 H), 2.8–4.0 (m, 6 H), 5.12 (s, 2 H, CH_2Ph), 7.34 (s, 5 H, phenyl); MS, *m/e* calcd (M^+) 303.1834, obsd 303.1856.

(4aα,5β,8aβ)-Octahydro-1,5(2*H*)-quinolinedicarboxylic Acid 1-Phenylmethyl Ester (23). To a biphasic mixture of **22** (103 mg, 0.340 mmol) and $NaIO_4$ (255 mg, 1.190 mmol)[35] in CCl_4 (1.5 mL), CH_3CN (1.5 mL), and H_2O (2.25 mL) was added $RuCl_3 \cdot 3H_2O$ (2 mg, 2.2 mol %). After the mixture was stirred vigorously for 2 h, CH_2Cl_2 (10 mL) was added, and the solvent layers were separated. The aqueous layer was extracted (three times) with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was dissolved in Et_2O, passed through a small plug of Celite, and concentrated under reduced pressure, affording 99 mg of an oil. Purification by preparative TLC ($CHCl_3$/HOAc, 100:2) produced 77 mg of crude **23** as a viscous oil which was used directly without further purification.

Acknowledgment. FT NMR 300-MHz spectra were produced at The Ohio State University Chemical Instrumentation Center using a Bruker WM-300 spectrometer funded in part by NIH Grant No. 1-S10-RR01458-01A1. Spectra were obtained by Dr. C. E. Cottrell.

Registry No. *trans*-**3**, 98761-59-2; *trans*-**3**·HCl, 98761-61-6; *trans*-**4**, 98761-62-7; *trans*-**4**·HCl, 98761-63-8; **10**, 5057-12-5; **11**, 70075-68-2; **13**, 98761-65-0; **16**, 98761-66-1; **17**, 98761-67-2; **18**, 98761-69-4; **19**, 98761-64-9; **20**, 98761-70-7; **21**, 98761-71-8; **22**, 98761-72-9; **23**, 98761-60-5; I, 77823-89-3; II, 98819-45-5; III, 98819-46-6; IV, 98819-47-7; V, 98761-73-0; VI, 98761-74-1; $Ph_3PCHCHO$, 2136-75-6; 2-(trimethylsilyl)-1,3-dithiane, 13411-42-2; (4aα,5α,8aα)-5-(1,3-dithian-2-yl)decahydroquinoline, 98761-68-3.

Neuroleptic Activity of Chiral *trans*-Hexahydro-γ-carbolines†

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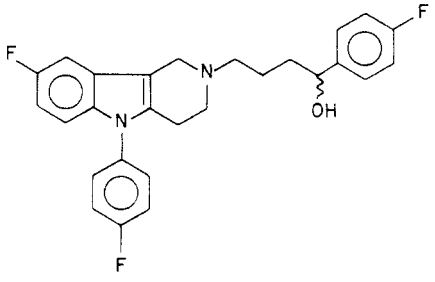
A series of *trans*-8-fluoro-5-(4-fluorophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indoles with various N-2 substituents has been prepared and tested for neuroleptic activity ([^{3}H]spiroperidol binding and amphetamine antagonism). Several members of this series showed exceptional in vivo potency, especially the hydantoin derivatives **27–30**. Resolution into the enantiomers showed that neuroleptic activity is associated with the 4a*S*,9b*S* absolute configuration. These rigid neuroleptics have been correlated with other rigid neuroleptics [(+)-dexclamol, Ro 22-1319] and can serve to further define the topography of the dopamine receptor.

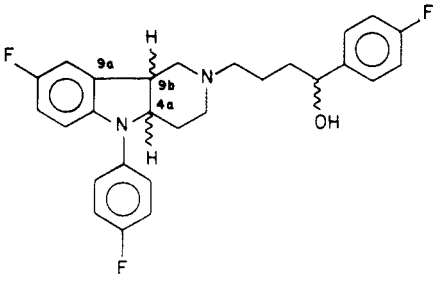
Previous work from these laboratories has shown that the tetrahydro-γ-carboline derivative flutroline (**1**; CP-36,584; 8-fluoro-5-(4-fluorophenyl)-2-[4-hydroxy-4-(4-fluorophenyl)butyl]-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]-indole) is a potent neuroleptic agent in animal models, apparently due to blockade of dopamine receptors in the central nervous system.[1] Reduction of the 4a,9b double



1 (flutroline)

bond of flutroline with borane resulted in the formation of a 1:1 mixture of two *trans*-hexahydro-γ-carboline diastereomers. These were separated by crystallization and subsequently resolved as the L-phenylalanine esters into their respective enantiomers **2a** to **2d**.[2] Interestingly, neuroleptic activity appeared to residue exclusively in two of these isomers, **2a** and **2c**, their in vitro activity (inhibition of spiroperidol binding) approaching that of haloperidol (**3**, Table I) and their in vivo activity (amphetamine antagonism) greatly surpassing that of haloperidol, especially at later time points. These findings made it im-

Table I. Activity of Flutroline and Its Four *trans*-Hexahydro-γ-carboline Reduction Products



2a–d

no.	$[\alpha]^{20}_D$, deg	inhibn of [^{3}H]-spiroperidol binding:[a] IC_{50}, nM	antagonism of amphetamine (rat):[b] ED_{50}, mg/kg sc 1 h	5 h	24 h
2a	+3.1	25	0.21	0.05	0.02
2b	−2.7	350	>10	5.7	>10
2c	+32.2	22	0.05	0.02	0.02
2d	−33.0	1800	>10	18.1	>10
1 (flutroline)		12 ± 1 (7)	1.0	0.15	2.2
3 (haloperidol)		9	0.66	0.75	>10
4 (penfluridol)		62	~32	2.4	3.9[c]

[a] IC_{50} values were determined on rat striatal membrane using 0.5 nM radioligand. Entries are based on one to two determinations. For multiple determinations, mean IC_{50} ± SE are given with number of determinations in parentheses. [b] 5 mg/kg ip *d*-amphetamine sulfate was administered to rats at 1, 5, 24 h after test drug (N = 5). [c] The ED_{50} of **4** at 48 h was ~32 mg/kg. This time course is consistent with the one observed after po dosing of **4** by Janssen et al., *Eur. J. Pharmacol.* **1970**, *11*, 139.

† For simplicity's sake, the common name γ-carboline is used in general throughout this paper instead of 1*H*-pyrido[4,3-*b*]indole.

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