72371-40-5; **63**, 98977-99-2; **64**, 98978-00-8; **65**, 98978-01-9; **66**, 65473-12-3; **67**, 79416-72-1; **68**, 98978-02-0; **69**, 98978-03-1; **70**, 98978-04-2; **71**, 98978-05-3; **72**, 98978-06-4; **73**, 98978-07-5; **74**, 98978-08-6; **75**, 98978-09-7; **76**, 70809-53-9; **77**, 98978-10-0; **78**, 98978-11-1; **79**, 98978-12-2; **80**, 92525-78-5; **81**, 98978-13-3; **82**, 98978-14-4; (*E*)-**83**, 98978-15-5; (*Z*)-**83**, 98978-58-6; **84**, 98978-16-6; **85**, 98978-17-7; **86**, 70809-51-7; **87**, 98978-18-8; **88**, 98978-19-9; **89**, 98978-20-2; **90**, 14489-75-9; **91**, 76532-34-8; **92**, 98978-21-3; **93**, 14489-84-0; **94**, 7182-94-7; **95**, 98978-22-4; **96**, 98978-23-5; **97**, 98978-24-6; **98**, 98978-25-7; **99**, 98978-26-8; **100**, 98978-27-9; **101**, 65473-20-3; **102**, 98978-28-0; **103**, 98978-29-1; **104**, 98978-30-4; **105**, 98978-31-5; **106**, 98978-32-6; **107**, 98978-33-7; **108**, 98978-34-8; **109**, 65473-19-0; **110**, 98978-35-9; **111**, 98978-36-0; **112**, 98978-37-1; **113**, 98978-38-2; **114**, 98978-39-3; **115**, 98978-40-6; **116**, 98978-41-7; **117**, 98978-42-8; **118**, 98978-43-9; **120**, 98978-44-0; **121**, 98978-45-1; **122**, 98978-46-2; **123**, 98978-47-3; **124**, 98978-48-4; **125**, 98978-49-5; **126**, 98978-50-8; **127**, 98978-51-9; $MeNH_2$, 74-89-5; (*E*)-PhCH=$CHCH_2NH_2$, 4335-60-8; Ph_2CHNH_2, 91-00-9; PhNHEt, 64-04-0; Ph_3P=CHCHO, 2136-75-6; $PhCH_2NHMe$, 103-67-3; $Br(CH_2)_3Ph$, 637-59-2; (*E*)-PhCH=$CHCH_2Br$, 26146-77-0; (*E*)-PhCH=$CHCH_2NHMe$, 60960-88-5; CH_2=CHCH=CHC(O)OMe, 1515-75-9; *i*-PrI, 75-30-9; CH_2=$CHCH_2Br$, 106-95-6; $PhCH_2Cl$, 100-44-7; $PhC(O)CH_2Br$, 70-11-1; 1-naphthalenemethanamine, 118-31-0; cinnamaldehyde, 104-55-2; α-methylcinnamaldehyde, 101-39-3; 2-methoxy-1-naphthaldehyde, 5392-12-1; 1-naphthaldehyde, 66-77-3; cyclohexylamine, 108-91-8; aniline, 62-53-3; (*E*)-*N*-(3-phenyl-2-propenyl)-1-naphthalenamine, 98978-53-1; 2-(1-naphthyl)ethanamine, 4735-50-6; 5-phenyl-2,4-pentadienal, 13466-46-5; 6-methoxy-1-naphthalenemethanamine hydrochloride, 98978-54-2; 6-methoxynaphthalene-1-carbonitrile, 77029-01-7; 1,2,3,4-tetrahydro-1-naphthalenemethanamine, 91245-72-6; 1,2,3,4-tetrahydro-1-naphthalenamine, 2217-40-5; 3,4-dihydronaphthalene-1-carboxaldehyde, 93340-32-0; 3,4-dihydronaphthalene-1-carbonitrile, 73599-59-4; anthracene-9-carboxaldehyde, 642-31-9; phenanthrene-9-carboxaldehyde, 4707-71-5; 1-methylindole-3-carboxaldehyde, 19012-03-4; chinoline-4-carboxaldehyde, 4363-93-3; 3-benzo[*b*]thiophenemethanamine, 40615-04-1; benzalacetone, 122-57-6; *trans*-2-phenyl-1-carbethoxycyclopropane, 946-39-4; (*E*)-3-(2-thienyl)-2-propenal, 39511-07-4; (*E*)-3-(3-thienyl)-2-propenal, 3216-40-8; (*E*)-3-(2-furyl)-2-propenal, 39511-08-5; (*E*)-3-(1-methylpyrrol-2-yl)-2-propenal, 87234-31-9; (*E*)-3-(4-pyridinyl)-2-propenal, 32986-66-6; (*E*)-3-(2-pyridinyl)-2-propenal, 28823-16-7; 3-cyclohexene-1-carboxaldehyde, 100-50-5; acetophenone, 98-86-2; 4-fluoroacetophenone, 403-42-9; 2-fluoroacetophenone, 450-95-3; 4-chloroacetophenone, 99-91-2; 2-chloroacetophenone, 532-27-4; 4-methylacetophenone, 122-00-9; 4-methoxyacetophenone, 100-06-1; *N*-methyl-2-naphthalenemethanamine, 76532-33-7; *N*-methyl-1-(1-naphthyl)ethanamine, 98978-55-3; (*E*,*E*)-5-carbethoxy-2,4-pentadienal, 6071-66-5; triethyl phosphonoacetate, 867-13-0; 1-ethynylcyclohexene, 931-49-7; ethynylcyclohexane, 931-48-6; 1-ethynylcyclopentene, 1610-13-5; 1-ethynylcycloheptene, 2809-83-8; ethynylbenzene, 536-74-3; (*E*)-1-bromo-4-phenyl-3-butene, 7515-41-5; (*E*)-1-iodo-4-phenyl-2-butene, 52534-83-5; *N*-methyl-4-methoxy-1-naphthalenemethanamine, 76532-35-9; *N*-methyl-5,6,7,8-tetrahydro-1-naphthalenemethanamine, 17450-64-5; 3-(chloromethyl)-1*H*-indene, 98978-57-5; 3-(hydroxymethyl)-1*H*-indene, 2471-87-6; bicyclo[2.2.1]hept-2-ene, 498-66-8; 4-(chloromethyl)-*s*-hydrindacene, 65935-64-0; 4-(chloromethyl)-2*H*-1-benzopyran, 15877-26-6; *N*-methyl-3-benzo[*b*]furanmethanamine, 78629-16-0; *N*-ethyl-1-naphthalenemethanamine, 14489-76-0; 1-(chloromethyl)naphthalene, 86-52-2; crotyl bromide, 4784-77-4; 3-bromoacrylonitrile, 52039-20-0; ethyl 4-bromocrotonate, 6065-32-3; *n*-pentyl 4-bromocrotonate, 59424-98-5; *n*-pentyl crotonate, 25415-76-3; benzyl 4-bromocrotonate, 60343-31-9; benzyl crotonate, 65416-24-2; 1-(hydroxymethyl)naphthalene, 4780-79-4; 1-naphthoyl chloride, 879-18-5; cinnamoyl chloride, 102-92-1; 1-(mercaptomethyl)naphthalene, 5254-86-4; 4-[*N*-methyl-*N*-(1-naphthylmethyl)amino]-2-phenyl-2-butanol, 98978-59-7; benzo[*b*]thiophene-4-acetic acid, 2635-75-8.

Synthesis of Alkyl-Substituted Arecoline Derivatives as γ-Aminobutyric Acid Uptake Inhibitors

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Received March 11, 1985

A series of *N*-methyltetrahydropyridine-3-carboxylic acids and methyl esters have been synthesized and biologically evaluated. Arecoline (**6**) was lithiated with LDA in THF to give **7**, which was treated with various alkyl halides to afford exclusively the α-substituted products **8a–g**. Thermodynamic reaction of **7** with carbonyl compounds gave the corresponding 5-substituted arecoline derivatives **10a–q**. When phenyldiazonium tetrafluoroborate was used as electrophile, **8h** and **9** were obtained. The relative stereochemistry of **10j–o** was established by ^{1}H NMR spectroscopy. Compound **12** was obtained by condensation of the silylketene acetal **11** with *N*-acetylindoxyl. Dehydration of **10a–c** yielded **14a–c**, respectively. Deprotection of the esters **14a**, **14c**, and **15** followed by chromatography on an ion-exchange resin gave the amino acids **16a**, **16c**, and **16d**. The alcohol **17** was obtained by $LiAlH_4$ reduction of the corresponding ester **14c**. The amino acid **16c** displayed a marked inhibitory effect on the synaptosomal uptake of γ-amino[^{3}H]butyric acid ([^{3}H]GABA). The type of inhibition was competitive with a K_i of 12.9 μM. Compound **16d** also inhibited [^{3}H]GABA uptake but was about 10 times weaker than **16c**. None of the biologically tested compounds (**8a–g**, **9**, **10a–q**, **12**, **14a–c**, **16a–d**, **17**) showed any effect in binding studies using [^{3}H]GABA as ligand.

Growing interest in the pharmacology of GABA (γ-aminobutyric acid) has been stimulated by findings linking this amino acid to certain psychiatric and neurological diseases.[2-4] Therefore, particular interest has been directed to compounds that interact with the neuronal and glial GABA-uptake system or the postsynaptic GABA receptors.[5-7]

For instance, (*RS*)-piperidine-3-carboxylic acid (nipecotic acid) (**1**) and 1,2,5,6-tetrahydropyridine-3-carboxylic acid (guvacine) (**2**) have been shown to be potent inhibitors of the GABA-uptake process,[6,8,9] whereas the isomeric compounds piperidine-4-carboxylic acid (isonipecotic acid) (**3**)

[†] Institute of Pharmaceutical Chemistry.
[‡] Institute of Pharmacology.

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Scheme I. Structures of Some Heterocyclic GABA Agonists and GABA-Uptake Inhibitors

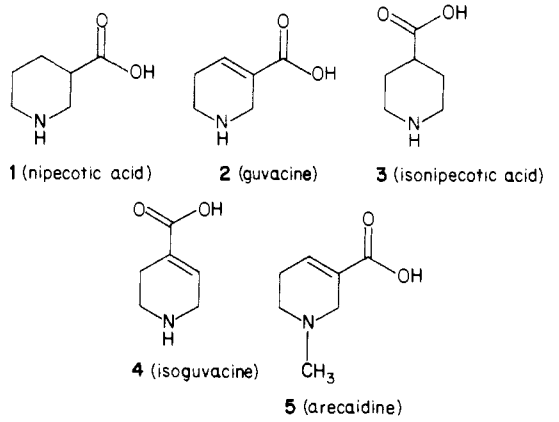

Table I. Reaction of 7 with Electrophiles (RX)

electrophile (RX)	R	product	yield, %
ammonium chloride	H	**8a**[a]	91
iodomethane	CH_3	**8b**	94
benzyl chloride	$C_6H_5CH_2$	**8c**	89
allyl bromide	CH_2=$CHCH_2$	**8d**	93
1-bromo-2-phenylethane	$C_6H_5CH_2CH_2$	**8e**	93
1-bromo-1-phenylethane	$C_6H_5CH(CH_3)$	**8f**	89[b]
tricarbonylchromium–fluorobenzene/I_2[c]	C_6H_5	**8g**	75

[a] See ref 19. [b] Diastereomeric ratio = 1/1. [c] See ref 30.

and 1,2,5,6-tetrahydropyridine-4-carboxylic acid (isoguvacine) (4) exhibit a specific agonist activity at postsynaptic GABA receptors[9-12] (Scheme I).

In addition, a variety of cyclic amino acids related to nipecotic acid (1), including amino, mercapto, hydroxy, and epoxy derivatives have been synthesized and tested for GABA-uptake inhibition or receptor interaction.[13-18] Likewise, the synthesis of guvacine analogues, represented by 3-alkyl-1,2,3,6-tetrahydropyridine-3-carboxylic acids,[19] 5-methylguvacine,[17] and N-alkylated guvacine derivatives,[20] has led to substances capable of inhibiting the GABA-uptake system.

However, little information is available about derivatives of arecaidine (*N*-methylguvacine) (5). Therefore, the present paper describes the synthesis of a series of *N*-methyltetrahydropyridine-3-carboxylic acids and methyl esters and the effects of these compounds on synaptosomal [^{3}H]GABA uptake and on the binding of [^{3}H]GABA to a brain membrane preparation.

Table II. Reaction of 7 with Carbonyl Compounds

electrophile (R^1COR^2)	R^1, R^2	product	yield, %	diast ratio
acetone	CH_3, CH_3	**10a**	52	
cyclohexanone	$-(CH_2)_5-$	**10b**	48	
benzophenone	C_6H_5, C_6H_5	**10c**	95	
2-benzoylpyridine	NC_5H_4, C_6H_5	**10d/10e**	42/26	1/1
3-benzoylpyridine	NC_5H_4, C_6H_5	**10f/10g**	40/38	1/1
4-benzoylpyridine	NC_5H_4, C_6H_5	**10h/10i**	62/19	3/1
acetophenone	CH_3, C_6H_5	**10j/10k**	33/15	3/1
cyclohexyl phenyl ketone	C_6H_{11}, C_6H_5	**10l/10m**	27/30	1/1
benzaldehyde	H, C_6H_5	**10n/10o**	45[a]	1/3
isatin	$-C_6H_4NHCO-$	**10p/10q**	40/8	1/1
N-acetylindoxyl[b]	$-C_6H_4N(CH_3CO)CH_2-$	**10r**	0	

[a] Only the major diastereomer could be separated from the mixture. [b] See ref 33.

Chemistry and Spectroscopy. The regioselective substitution of α,β-unsaturated esters via their enolates is a well-established method for introduction of alkyl substituents either in the α- or γ-position of the ester function. While α-alkylation is a kinetically controlled reaction,[21,22] the γ-substituted products are obtained under thermodynamic conditions.[23-29] When the lithium enolate of arecoline (7), obtained by treatment of arecoline (6) with LDA in THF, was reacted with various alkyl halides, exclusively α-substituted products were obtained (Table I and Scheme II). In the crude reaction mixture no γ-alkylated derivatives were detected by ^{1}H NMR spectroscopy except when phenyldiazonium tetrafluoroborate was used as electrophile. In this case a mixture of the 3-phenyldiazo derivative **8h** and 5-(phenylhydrazono)arecoline (9) was obtained. However, the 3-phenyl-substituted product **8g** was not formed. This was established by comparison with the product **8g**, afforded by treatment of 7 with tricarbonylchromium–fluorobenzene[30] according to a procedure reported by Semmelhack.[31]

Thermodynamic reaction of 7 with the aldehydes or ketones listed in Table II gave the expected γ-products in moderate to good yields. ^{1}H NMR spectroscopy of the crude reaction mixtures showed a high regioselectivity. However, the diastereomeric ratio of the products obtained by reaction of unsymmetrical carbonyl compounds with 7 was low and in no case better than 3/1. With the exception of **10n** and **10o**, a separation of the diastereomers was achieved.

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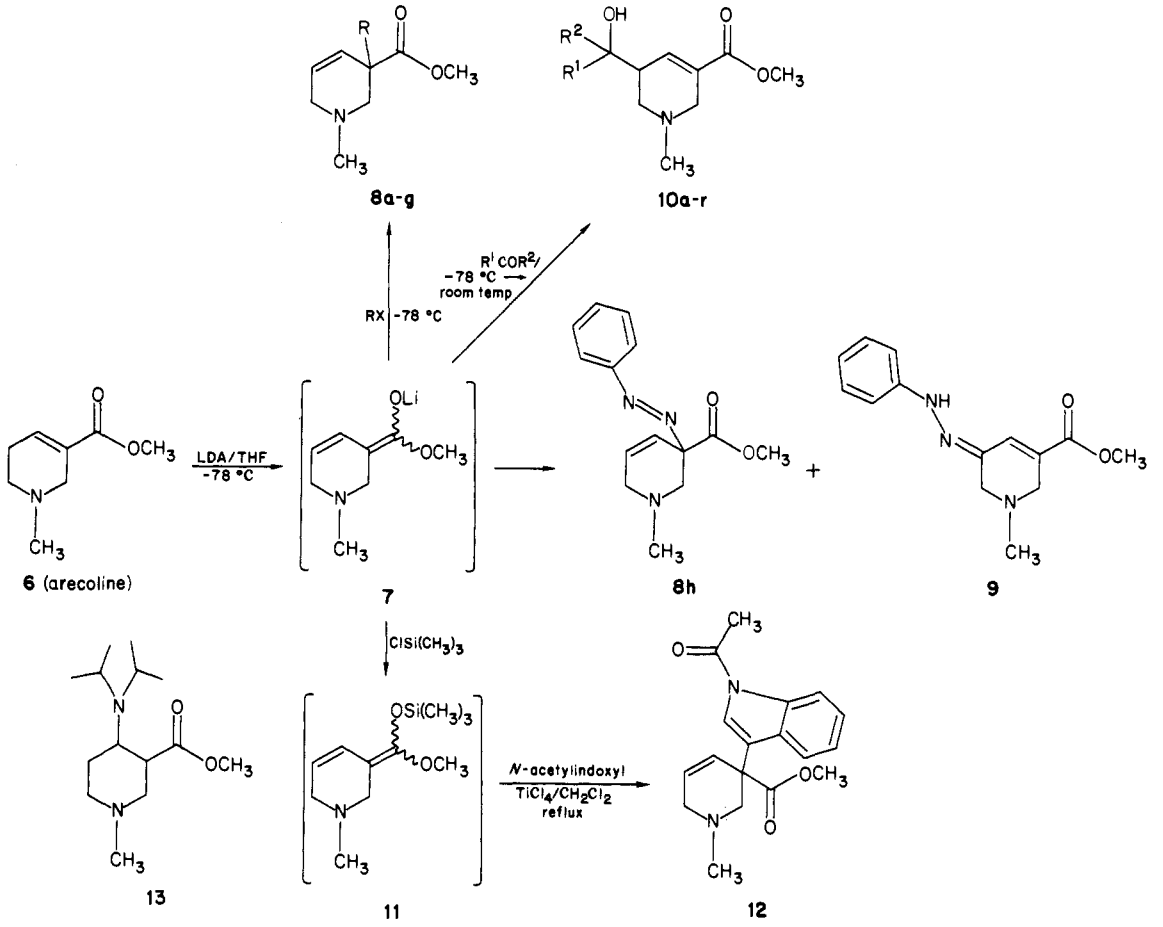
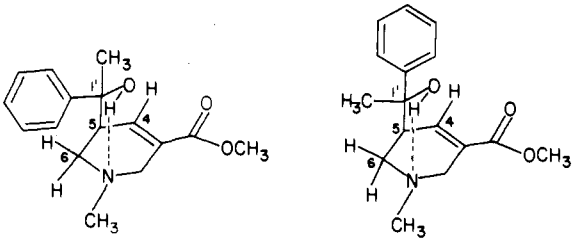
Scheme II



The relative configurations of **10j** and **10k** were investigated by ^{1}H NMR spectroscopy. NOE measurement of **10j** indicates a vicinity of the methyl group C-2′ to the olefinic proton on C-4, whereas the signal of one of the two protons on C-6 is shifted to higher field (δ 2.48) because of the influence of the phenyl group. We think that the molecule is fixed in this position by a hydrogen bond between the hydroxy group and the nitrogen atom. Thus, when the ^{1}H NMR of **10j** was measured in $CDCl_3$ or Me_2SO-d_6, no significant change on the chemical shifts of the influenced protons was obtained. Either acetylation of **10j** or recording the spectra in pyridine-d_5[32] leads to a break of the hydrogen bond, probably due to a change of the substituent from the pseudoaxial position to the pseudoequatorial one. In agreement with this proposal the diasteromer **10k** shows a NOE on the proton on C-6 when the protons of the methyl group C-2′ are irradiated. In addition, the signal of the proton on C-4 is moved upfield (δ 6.40). Also, acetylation or recording the spectra in pyridine-d_5 eliminates these effects. The relative position of the two chiral centers C-5 and C-1′ in **10j** and **10k** is outlined in Scheme III. Owing to the similar shift differences of the protons on C-4 and C-6 in the diastereomers **10l–o**, we suggest a stereochemistry of these compounds according to **10j** and **10k**. A determination of the relative position of the chiral centers in the compounds **10d–i**, **10p**, and **10q** by ^{1}H NMR spectroscopy was not possible. Interestingly, the isomers **10d** and **10e** could not be separated by chromatography but could be by selective hydrolysis. When the diastereomeric mixture of **10d** and **10e** was refluxed in 1 N HCl for 45 min, only **10e** was hydrolyzed.

Scheme III. Relative Configurations of 10j and 10k



After removal of the remaining ester **10d** by extraction of the alkalined solution with methylene chloride, **10e** was accomplished by reesterification with dry HCl in methanol at 0 °C. Dehydration of the tertiary alcohol was not observed.

The yields of the described γ-alkylated products depend on the acidity of the α-protons of the used carbonyl compounds. Thus, *N*-acetylindoxyl, which in solution exists mainly as the ketone tautomer,[33] gave no addition product under these conditions. To circumvent this problem, *N*-acetylindoxyl was reacted with the silylketene acetal **11**, which was obtained by treating the enolate **7** with chlorotrimethylsilane. Although Lewis acid promoted alkylations of silylketene acetals of α,β-unsaturated esters are reported to give mainly γ-substituted products,[25,26] in this case we exclusively obtained the α-derivative **12**. Probably due to the great aromatization tendency of the intermediate aldol, the isomerization to the favored γ-product **10r** was impossible (Scheme II). An undesired minor product

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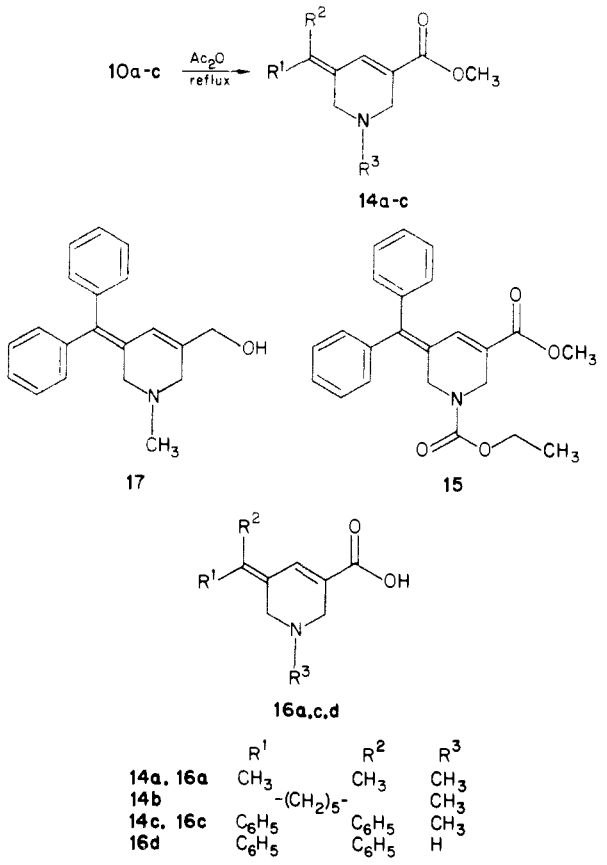
Scheme IV



	R^1	R^2	R^3
14a, 16a	CH_3	CH_3	CH_3
14b	$-(CH_2)_5-$		CH_3
14c, 16c	C_6H_5	C_6H_5	CH_3
16d	C_6H_5	C_6H_5	H

of all these reactions was identified as the Michael-type addition product **13**. When HMPA was added to the LDA solution prior to enolate formation, **13** was not found. Because of the low yield of **13** (5% estimated by ^1H NMR spectroscopy) and the toxicity of HMPA we tried to work without the use of it except in those cases where the side product could not be eliminated by usual purification methods.

Dehydration of **10a–c** (the reaction products of **7** with symmetrical carbonyl compounds) was afforded by refluxing them in acetic anhydride for a short time. To obtain substances with an acidic function instead of the ester moiety, **14a**, **14c**, and **15** were hydrolyzed with HBr/CH_3COOH and chromatographed on Dowex 50 WX 8 ion-exchange resin to give **16a**, **16c**, and **16d**, respectively. $LiAlH_4$ reduction of **14c** led to the amino alcohol **17** (Scheme IV).

Pharmacological Evaluation. Uptake Experiments. In the range of concentrations of [^{3}H]GABA used in our experiments the incorporation of radioactivity was a linear function of time for at least 4 min. Therefore, the uptake rate during 4-min incubations was chosen for the estimation of kinetic constants. The kinetic analysis was performed with use of at least eight concentrations of [^{3}H]-GABA ranging from 1.3 to 40 μM. The apparent affinity constant (K_M) for GABA was 4.3 ± 0.4 μM (n = 4; all values $\bar{x}$ ± SEM) and the maximal initial uptake velocity (V_{max}) was 881 ± 113.3 pmol mg^{-1} min^{-1} (n = 4). In a first step, all compounds tested (**8a–g**, **9**, **10a–q**, **12**, **14a–c**, **16a–d**, and **17**) were used at a concentration of 10 μM in the presence of 0.1 μM [^{3}H]GABA. A substance that did not exhibit any effect under these conditions was not investigated further. As compounds **16c** and **16d** proved to be active at this point, their respective inhibition constants (K_i) were determined in comparison to nipecotic acid (**1**), a known potent inhibitor of GABA uptake.[9,14] The K_i of

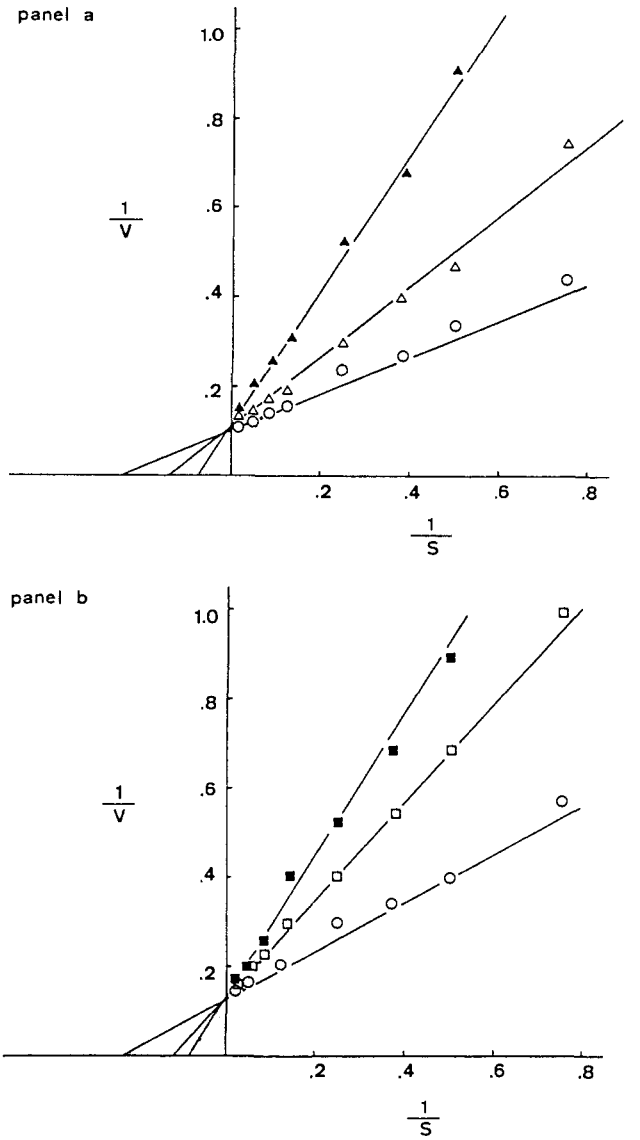


Figure 1. Lineweaver–Burk plot of the inhibition by **16c** and **16d** of synaptosomal [^{3}H]GABA uptake. Ordinates: $1/v$, (pmol × mg^{-1} × min^{-1}) × 10^2. Abscissae: $1/s$ (1μM)$^{-1}$. Panel a: uptake of [^{3}H]GABA in the absence (○) or presence of **16c**, 10^{-5} M (△) and 3×10^{-5} M (▲). Panel b: uptake of [^{3}H]GABA in the absence (○) or presence of **16d**, 10^{-4} M (□) and 2×10^{-4} M (■). Points are the means of two to three experiments run in triplicate.

16c was 12.9 ± 1.59 μM (n = 3), of **16d** 104 ± 19.8 μM (n = 3), and of **1** 3.8 ± 0.16 μM (n = 3), respectively. As shown in Figure 1, graphical analyses of the data according to Lineweaver and Burk[34] revealed a competitive-type inhibition for both **16c** and **16d**.

Binding Experiments. The specific binding of [^{3}H]-GABA at 5 nM was 261 ± 12.1 fmol/mg of membrane protein (n = 12). None of the tested compounds showed any inhibition of binding up to a concentration of 30 μM. In contrast, unlabeled GABA displaced the binding with a IC_{50} of 22 ± 3.1 nM (n = 3).

Discussion

The present data confirm the notion that derivatives of **2** do not possess activity on central GABA receptors as none of the tested compounds displayed interference with [^{3}H]GABA binding. In contrast, guvacine derivatives are known to inhibit the uptake of GABA in various experi-

(34) Lineweaver, H.; Burk, D. *J. Am. Chem. Soc.* **1934**, *56*, 658.

mental systems.[9,14] For instance, nipecotic acid (1) is one of the most potent compounds in this respect.[8,13] Of the substances shown in this report the arecaidine derivative **16c** exhibited a marked competitive inhibition of [^{3}H]-GABA uptake with a K_i that was in the same order of magnitude as that of 1. Thereby the benzhydrylidene substitution in position 5 of the piperidine ring proved to be critical, since the isopropylidene derivative **16a** did not inhibit [^{3}H]GABA uptake.

As guvacine (2) has been shown to be a stronger GABA-uptake inhibitor than arecaidine (5),[8] it was decided to synthesize the corresponding N-dealkylated product of **16c**, **16d**. This compound still inhibited competitively [^{3}H]GABA uptake, but its K_i was about 10 times higher. In contrast to the free amino acids **16c** and **16d**, all ester compounds (**8a–g**, **9**, **10a–q**, **12**, **14a–c**) and the alcohol **17** did not exhibit any inhibitory effect. This is in accordance with published data emphasizing the importance of an acidic proton in the molecule.[6,8]

In conclusion, the present data show that introduction of a benzhydrylidene group in the position 5 of the piperidine ring of arecaidine results in a potent inhibitor of synaptosomal [^{3}H]GABA uptake. Experimental work is in progress to synthesize a series of 5-substituted *N*-methylpiperidine-3-carboxylic acids to obtain further compounds with strong inhibitory action on the GABA-uptake system.

Experimental Section

Chemistry. Melting points, determined with a Kofler melting point microscope, are uncorrected. Analyses, indicated by elemental symbols, were within ±0.4% of the theoretical values and were performed by Dr. Zak, Institute of Physical Chemistry, University of Vienna. TLC was accomplished with silica gel F_{254} plates (Merck). For spectral data a Perkin-Elmer infrared spectrophotometer (Model 298), a Hewlett Packard UV spectrophotometer (Model HP 8451 A), a Varian EM 390 90 MHz ^{1}H NMR instrument were used. The ^{1}H NMR spectra were recorded with Me_4Si as internal standard, except for the compounds dissolved in D_2O, where sodium 3-(trimethylsilyl)-propanesulfonate was used. The NOE measurements were obtained on a Bruker WM 250 instrument and were performed by Dr. Silhan, Institute of Organic Chemistry, University of Vienna. The mass spectra (EI) were measured on a Varian-MAT 111 by Dr. Nikiforov, Institute of Organic Chemistry, University of Vienna. For the UV spectra the substances were dissolved in physiological salt solution (see Pharmacology).

THF was dried over Na/benzophenone under Ar. All reagents were purified before use as described earlier.[35] LDA was generated in situ under dry Ar by adding a solution of *n*-butyllithium in hexane (3.64 mL of 1.4 M, 5.1 mmol) to a solution of diisopropylamine (0.72 mL, 5.1 mmol) in anhydrous THF at −78 °C (dry ice/acetone) and maintained at this temperature for 10 min. (The two cases where HMPA was used as a cosolvent are indicated.)

Lithiation of Arecoline (6) and Reaction with Electrophiles. Commercial available arecoline hydrobromide (Fluka) was dissolved in water. The solution was saturated with Na_2CO_3 and the free amine was extracted into CH_2Cl_2. After drying the organic phase over Na_2SO_4 and evaporation in vacuo, the resulting yellow oil was distilled in a Kugelrohr apparatus at 80 °C oven temperature (0.5 torr). The pure base (0.74 mL, 5 mmol) was added to a solution of 5.1 mmol of LDA in THF via a syringe at −78 °C over a period of 5 min. At this temperature the lithiation was complete within 10 min. After quenching of the enolate with various electrophiles, the mixture was allowed to stir at the temperature *T* for a reaction time RT (see individual compounds). Unless stated otherwise, the reaction mixtures were worked up as follows.

(35) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R., Eds. "Purification of Laboratory Chemicals"; Pergamon Press: Frankfurt, 1980.

To the solution was added a saturated aqueous solution of NH_4Cl. After extraction with ether (three times), the combined ethereal solutions were washed with 1N HCl (four times). The washings were combined, alkalined with 2 N NH_3, and extracted with CH_2Cl_2 (three times). After drying of the solvent over Na_2SO_4, it was evaporated in vacuo.

(3*RS*)-Methyl 1-Methyl-1,2,3,6-tetrahydropyridine-3-carboxylate (8a). Before lithiation of **6**, HMPA (0.89 mL, 5.1 mmol) was added to the LDA solution (prepared in 10 mL of THF) and the resulting mixture was allowed to stir for 30 min at −78 °C. Electrophile: H^+ ion from the NH_4Cl solution. The pure **8a** (705 mg, 91%) was obtained as a yellow oil after distillation of the crude product in a Kugelrohr apparatus at 100 °C oven temperature (0.5 torr): IR (film) 1735 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.85 (2 H, m), 3.70 (3 H, s), 3.42–2.68 (5 H, m), 2.32 (3 H, s); MS, *m/e* 155 (M^+, 26), 156 (3); UV 210 nm (log ε 0.24).

(3*RS*)-Methyl 1,3-Dimethyl-1,2,3,6-tetrahydropyridine-3-carboxylate (8b). Before lithiation of **6**, HMPA (0.89 mL, 5.1 mmol) was added to the LDA solution (prepared in 10 mL of THF) and the mixture was allowed to stir for 30 min at −78 °C. Electrophile: iodomethane (0.32 mL, 5.1 mmol). RT: 10 min. *T*: −78 °C. The pure **8b** (794 mg, 94%) was obtained after distillation of the crude product in a Kugelrohr apparatus at 120 °C oven temperature (0.5 torr) as a colorless liquid: IR (film) 1735 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.78 (2 H, m), 3.70 (3 H, s), 3.15–2.05 (4 H, m), 2.30 (3 H, s), 1.23 (3 H, s); MS, *m/e* 169 (M^+, 36), 170 (4); UV 214 nm (log ε 0.13).

(3*RS*)-Methyl 3-Benzyl-1-methyl-1,2,3,6-tetrahydropyridine-3-carboxylate (8c). The solution of the enolate in 10 mL of THF was quenched with benzyl chloride (0.59 mL, 5.1 mmol). RT: 10 min. *T*: −78 °C. Yield: 1.09 g (89%)/colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.35–7.0 (5 H, m), 5.81 (2 H, br s), 3.60 (3 H, s), 2.95 (2 H, s), 2.90–2.30 (4 H, m), 2.30 (3 H, s); MS, *m/e* 245 (M^+, 60), 246 (10). An analytical sample was purified by recrystallization of **8c·HCl** from methanol/ethyl acetate: mp 202–206 °C dec; IR (KBr) 1730 (s) cm^{-1}; UV 210 nm (log ε 0.74). Anal. ($C_{15}H_{20}NO_2Cl$) C, H, N.

(3*RS*)-Methyl 3-Allyl-1-methyl-1,2,3,6-tetrahydropyridine-3-carboxylate (8d). The solution of the enolate in 10 mL of THF was quenched with allyl bromide (0.44 mL, 5.1 mmol). RT: 20 min. *T*: −78 °C. Yield: 907 mg (93%)/colorless oil. ^{1}H NMR ($CDCl_3$) δ 5.90–5.42 (3 H, m), 5.18–4.88 (2 H, m), 3.70 (3 H, s), 3.12–2.13 (6 H, m), 2.30 (3 H, s); MS, *m/e* 195 (M^+, 16), 196 (2). An analytical sample was purified by recrystallization of **8d·HCl** from water/acetone: mp 141–149 °C dec; IR (KBr) 1735 (s) cm^{-1}; UV 210 nm (log ε 0.10). Anal. ($C_{11}H_{18}NO_2Cl$) C, H, N.

(3*RS*)-Methyl 1-Methyl-3-phenethyl-1,2,3,6-tetrahydropyridine-3-carboxylate (8e). The solution of the enolate in 10 mL of THF was quenched with 1-bromo-2-phenylethane (0.70 mL, 5.1 mmol). RT: 30 min. *T*: room temperature. Yield: 1.21 g (93%)/colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.40–7.11 (5 H, m), 6.02–5.73 (2 H, m), 3.70 (3 H, s), 3.18–1.75 (8 H, m), 2.30 (3 H, s); MS, *m/e* 259 (M^+, 0.8), 260 (0.3). An analytical sample was purified by recrystallization of **8e·HCl** from water/acetone: mp 171–180 °C dec; IR (KBr) 1730 (s) cm^{-1}; UV 210 nm (log ε 0.73). Anal. ($C_{16}H_{22}NO_2Cl$) C, H, N.

Methyl 1-Methyl-3-(1′-phenylethyl)-1,2,3,6-tetrahydropyridine-3-carboxylate (8f). The solution of the enolate in 10 mL of THF was quenched with 1-bromo-1-phenylethane (0.70 mL, 5.1 mmol). RT: 30 min. *T*: room temperature. TLC (eluent: ethyl acetate) gave the diastereomeric mixture (1/1) **8f** (1.15 g, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.40–7.06 (5 H, m), 6.11–5.69 (2 H, m), 3.64, 3.50 (3 H, s), 3.32–2.10 (5 H, m), 2.30, 2.26 (3 H, s), 1.35, 1.34 (3 H, d, J = 7.5 Hz); MS, *m/e* 259 (M^+, 27), 260 (5). An analytical sample was purified by recrystallization of **8f·HCl** from water/acetone: IR (KBr) 1730 (s) cm^{-1}; UV 210 nm (log ε 0.80). Anal. ($C_{16}H_{22}NO_2Cl$) C, H, N.

(3*RS*)-Methyl 1-Methyl-3-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (8g). To the solution of the enolate in 50 mL of THF was added a solution of tricarbonylchromium fluorobenzene[80] (1.184 g, 5.1 mmol) in 10 mL of THF and the solution stirred at room temperature for 2 h. After cooling of the solution to −78 °C, a solution of iodine (5 g, 20 mmol) in 13 mL of THF was added and stirring was continued for a further 4 h at room temperature. The reaction mixture was poured into 60

mL of an ice-cold 30% (w/v) solution of K_2CO_3 in water and was worked up as described above except the ethereal solutions were combined and washed with a 10% (w/v) $Na_2S_2O_3$ solution before extracting with 1 N HCl.[31] TLC (alumina, Merck; eluents: benzene/methanol = 9/1 (v/v)) gave **8g** (866 mg, 75%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.38 (5 H, br s), 6.30–5.90 (2 H, m), 3.72 (3 H, s), 3.41 (1 H, d, J = 13 Hz), 3.16 (1 H, dd, J_{gem} = 16 Hz, J = 0.3 Hz), 2.79 ((1 H, dd, J_{gem} = 16 Hz, J = 0.2 Hz), 2.40–2.19 (1 H, m), 2.32 (3 H, s); MS, m/e 231 (M^+, 30), 232 (5). An analytical sample was prepared by recrystallization of **8g·HCl** from water/acetone: mp 186–187 °C dec; IR (KBr) 1735 (s) cm^{-1}; UV 210 nm (log ϵ 0.82). Anal. ($C_{14}H_{18}NO_2Cl$) C, H, N.

(3*RS*)-Methyl 1-Methyl-3-(phenyldiazo)-1,2,3,6-tetrahydropyridine-3-carboxylate (8h) and Methyl 1-Methyl-5-(phenylhydrazono)-1,2,5,6-tetrahydropyridine-3-carboxylate (9). The solution of the enolate was quenched with phenyldiazonium tetrafluoroborate[36] (979 mg, 5.1 mmol). RT: 60 min. T: room temperature. TLC (eluents: ethyl acetate/CH_2Cl_2 = 9/1 (v/v)) gave after elution of the upper layer **8h** (337 mg, 26%) as a yellow oil: IR (film) 1735 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85–7.28 (5 H, m), 6.12 (2 H, m), 3.73 (3 H, s), 3.41–2.90 (4 H, m), 2.40 (3 H, s); MS, m/e 154 (M^+ – 105, 30), 155 (4). Elution of the lower layer gave **9** (130 mg, 10%) as yellow crystals. An analytical sample was recrystallized from ethyl acetate/light petroleum: mp 155 °C dec; IR (KBr) 1695 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (1 H, br s), 7.44–6.83 (6 H, m), 3.77 (3 H, s), 3.41–3.30 (4 H, m), 2.48 (3 H, s); MS, m/e 259 (M^+, 47), 260 (8); UV 208 nm (log ϵ 1.06), 250 nm (log ϵ 1.07), 366 nm (log ϵ 2.20). Anal. ($C_{14}H_{17}N_3O_2$) C, H, N.

(5*RS*)-Methyl 5-(1′-Hydroxyisopropyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10a). The solution of the enolate in 3 mL of THF was quenched with acetone (0.38 mL, 5.1 mmol). RT: 120 min. T: room temperature. Ater workup, arecoline (**6**) was distilled off from the remaining oil in vacuo and the resulting gum was treated with ethyl acetate to give **10a** (556 mg, 52%) as colorless crystals: mp 107–108 °C; IR (KBr) 1715 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19 (1 H, m), 5.05 (1 H, br s), 3.72 (3 H, s), 3.59–2.19 (5 H, m), 2.39 (3 H, s), 1.30 (3 H, s), 1.28 (3 H, s); MS, m/e 213 (M^+, 47), 214 (6); UV 218 nm (log ϵ 1.03). Anal. ($C_{11}H_{19}NO_3$) C, H, N.

(5*RS*)-Methyl 5-(1′-Hydroxycyclohexyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10b). The solution of the enolate in 3 mL of THF was quenched with cyclohexanone (0.53 mL, 5.1 mmol). RT: 120 min. T: room temperature. After workup, arecoline (**6**) was distilled off from the remaining oil in vacuo and the resulting gum was treated with ethyl acetate to give **10b** (607 mg, 48%) as colorless crystals: mp 110–111 °C; IR (KBr) 1715 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20 (1 H, m), 4.93 (1 H, br s), 3.76 (3 H, s), 3.62–2.14 (5 H, m), 2.36 (3 H, s), 1.90–1.30 (10 H, m); MS, m/e 253 (M^+, 18), 254 (3); UV 220 nm (log ϵ 1.05). Anal. ($C_{14}H_{23}NO_3$) C, H, N.

(5*RS*)-Methyl 5-(1′-Hydroxybenzhydryl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10c). The solution of the enolate in 10 mL of THF was quenched with a solution of benzophenone (930 mg, 5.1 mmol) in 3 ml of THF. RT: 30 min. T: room temperature. Recrystallization of the crude product from ethyl acetate afforded **10c** (1.6 g, 95%) as colorless crystals: mp 137–139 °C; IR (KBr) 1720 (s) cm^{-1}; ^{1}H NMR δ = 7.71–7.07 (11 H, m), 6.84 (1 H, m), 3.66–2.12 (5 H, m), 3.62 (3 H, s), 2.22 (3 H, s); MS, m/e 337 (M^+, 8), 338 (2); UV 222 nm (log ϵ 1.65). Anal. ($C_{21}H_{23}NO_3$) C, H, N.

Methyl 5-(1′-Hydroxy-1′-pyrid-2-ylbenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10d and 10e). The solution of the enolate in 10 mL of THF was quenched with a solution of 2-benzoylpyridine (933 mg, 5.1 mmol) in 3 mL of THF. RT: 60 min. T: room temperature. A 338-mg (1 mmol) sample of the diastereomeric mixture (1/1) was dissolved in 10 mL of 1 N HCl and refluxed for 45 min. After cooling of the solution to room temperature, it was alkalined with 6 N NH_3 and extracted twice with CH_2Cl_2. Drying of the organic layer over Na_2SO_4, evaporation in vacuo, and recrystallization of the crude product from 2-propanole yielded **10d** (142 mg, 42%) as colorless crystals: mp 140–146 °C; IR (KBr) 1705 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.70 (1 H, m), 7.98–7.02 (9 H, m), 6.90 (1 H, m), 4.05–2.12 (5 H, m), 3.66 (3 H, s), 2.28 (3 H, s); MS, m/e 185 (M^+ – 153, 97), 186 (13); UV 210 nm (log ϵ 1.12), 266 (log ϵ 0.59). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N. The remaining aqueous layer was evaporated in vacuo and the residue was dissolved in 10 mL of methanol. Then the solution was saturated with HCl gas at 0 °C and was allowed to stand overnight at room temperature. Most of the solvent was removed in vacuo and the crude product was suspended in 20 mL of CH_2Cl_2. Then the organic phase was washed with 2 N NH_3 and evaporated in vacuo and the residue was recrystallized from ethyl acetate/light petroleum to afford **10e** (88 mg, 26%) as colorless crystals: mp 111–119 °C; IR (KBr) 1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.61 (1 H, m), 7.95–7.00 (9 H, m), 6.66 (1 H, m), 4.05 (1 H, m), 3.78–2.18 (4 H, m), 3.64 (3 H, s), 2.21 (3 H, s); MS, m/e 185 (M^+ – 153, 100), 186 (13); UV 210 nm (log ϵ 1.19), 266 (log ϵ 0.56). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

Methyl 5-(1′-Hydroxy-1′-pyrid-3-ylbenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10f and 10g). The solution of the enolate in 10 mL of THF was quenched with a solution of 3-benzoylpyridine (933 mg, 5.1 mmol) in 3 mL of THF. RT: 30 min. T: room temperature. The diastereomeric mixture (1/1) was separated by TLC (eluents: ethyl acetate/CH_2Cl_2=2/1 (v/v)). Elution of the upper layer and recrystallization from ethyl acetate/light petroleum afforded **10f** (676 mg, 40%) as colorless crystals: mp 144–146 °C; IR (KBr) 1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.89 (1 H, m), 8.49 (1 H, m), 7.98–7.12 (8 H, m), 6.80 (1 H, m), 3.81–2.18 (5 H, m), 3.70 (3 H, s), 2.30 (3 H, s); MS, m/e 338 (M^+, 5), 339 (1); UV 222 nm (log ϵ 1.68). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N. Elution of the lower layer and recrystallization from acetone afforded **10g** (642 mg, 38%) as colorless crystals: mp 130–131 °C; IR (KBr) 1715 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.92 (1 H, m), 8.52 (1 H, m), 7.99 (1 H, m), 7.61–7.18 (7 H, m), 6.78 (1 H, m), 3.80–2.18 (5 H, m), 3.69 (3 H, s), 2.29 (3 H, s); MS, m/e 338 (M^+, 8), 339 (2); UV 222 nm (log ϵ 1.72). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

Methyl 5-(1′-Hydroxy-1′-pyrid-4-ylbenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10h and 10i). The solution of the enolate in 10 mL of THF was quenched with a solution of 4-benzoylpyridine (933 mg, 5.1 mmol) in 3 mL of THF. RT: 30 min. T: room temperature. The diastereomeric mixture (**10h**/**10i** = 3/1) was separated by TLC (eluents: ethyl acetate/CH_2Cl_2 = 75/15 (v/v)). Elution of the upper layer and recrystallization from acetone afforded **10h** (1.05 g, 62%) as colorless crystals: mp 142–143 °C; IR (KBr) 1720 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.55 (2 H, m), 7.70–7.21 (8 H, m), 6.69 (1 H, m), 3.80–2.11 (5 H, m), 3.68 (3 H, s), 2.22 (3 H, s); MS, m/e 338 (M^+, 10), 339 (2); UV 222 nm (log ϵ 1.64). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N. Elution of the lower layer and recrystallization from ethyl acetate/light petroleum afforded **10i** (321 mg, 19%) as colorless crystals: mp 159–160 °C; IR (KBr) 1715 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.61 (2 H, m), 7.66–7.18 (8 H, m), 6.80 (1 H, m), 3.82–2.19 (5 H, m), 3.67 (3 H, s), 2.29 (3 H, s); MS, m/e 338 (M^+, 5), 339 (1); UV 222 nm (log ϵ 1.74). Anal. ($C_{20}H_{22}N_2O_3$) C, H, N.

(5*RS*,1′*RS*)- and (5*RS*,1′*SR*)-Methyl 5-(1′-Hydroxy-1′-methylbenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10j and 10k). The solution of the enolate in 3 mL of THF was quenched with acetophenone (0.60 mL, 5.1 mmol). RT: 120 min. T: room temperature. The diastereomeric mixture (**10j**/**10k** = 3/1) was separated by TLC (eluents: ethyl acetate/CH_2Cl_2 = 1/1 (v/v)). Elution of the upper layer afforded **10j** (454 mg, 33%) as a pale yellow oil: IR (film) 1720 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56–7.21 (6 H, m), 3.79 (3 H, s), 3.63 (1 H, d, J_{AB} = 18 Hz), 2.75 (1 H, d, J_{AB} = 18 Hz), 2.66 (1 H, br s), 2.48 (1 H, d, J_{AB} = 12 Hz), 2.25 (3 H, s), 2.06 (1 H, dd, J_{AB} = 12 Hz, J = 4 Hz), 1.56 (3 H, s); ^{1}H NMR (250 MHz, Me_2SO-d_6) δ 7.55–7.18 (5 H, m), 7.08 (1 H, br s), 5.76 (1 H, br s), 3.68 (3 H, s), 2.99 (2 H, br s), 2.82 (1 H, br s), 2.18 (3 H, s), 2.26–2.08 (2 H, m), 1.51 (3 H, s); ^{1}H NMR (pyridine-d_5) δ 7.56–7.07 (6 H, m), 6.67 (1 H, br s), 3.76 (3 H, s), 3.33 (1 H, d, J_{AB} = 18 Hz), 2.83 (2 H, m), 2.43 (1 H, dd, J_{AB} = 12 Hz, J = 3.5 Hz), 2.10 (1 H, m), 2.04 (3 H, s), 1.62 (3 H, s); MS, m/e 275 (M^+, 20), 276 (4); UV 218 nm (log ϵ 1.38). Elution of the lower layer afforded **10k** (206 mg, 15%) as a pale yellow oil: IR (film) 1715 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48–7.20 (5 H, m), 6.40 (1 H, m), 3.64 (3 H, s), 3.56 (1 H, d, J_{AB} = 16 Hz), 3.23 (1 H, d, J_{AB} = 12.5 Hz), 2.80 (1 H, dd,

(36) Dunker, M. F. W.; Starkey, E. B.; Jenkins, G. L. *J. Am. Chem. Soc.* **1936**, *58*, 2308.

J_{AB} = 16 Hz, J = 5 Hz), 2.65 (1 H, br s), 2.45 (3 H, s), 2.40 (1 H, dd, J_{AB} = 12.5 Hz, J = 4 Hz), 1.65 (3 H, s); ^{1}H NMR (250 MHz, Me_2SO-d_6) δ 7.55–7.19 (5 H, m), 6.71 (1 H, br s), 5.48 (1 H, br s), 3.65 (3 H, s), 3.16 (1 H, d, J_{AB} = 16 Hz), 2.82 (2 H, m), 2.32 (1 H, m), 2.29 (3 H, s), 1.46 (3 H, s); ^{1}H NMR (pyridine-d_5) δ 7.53–6.95 (6 H, m), 5.80 (1 H, br s), 3.50 (3 H, s), 3.10 (2 H, m), 2.97 (1 H, m), 2.57 (2 H, m), 2.20 (3 H, s), 1.67 (3 H, s); MS, m/e 275 (M^+, 10), 276 (2); UV 216 nm (log ϵ 1.31).

Acetylation of 10j and 10k. Compound **10j** or **10k** (275 mg, 1 mmol) was dissolved in acetic anhydride (5 mL). 4-(Dimethylamino)pyridine (122 mg, 1 mmol) was added to the solution, and after standing overnight at room temperature, the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the solution was washed with 2 N Na_2CO_3. Then the organic phase was separated, dried over Na_2SO_4, and evaporated in vacuo. TLC (eluent: ethyl acetate) of the resulting residue afforded a pale yellow oil.

(5*RS*,1′*RS*)-Methyl 5-(1′-Acetoxy-1′-methylbenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10s). Compound **10j** was acetylated as described above to yield **10s** (165 mg, 52%) as a pale yellow oil: IR (film) 1735 (s), 1700 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (5 H, br s), 6.62 (1 H, br s), 3.73 (3 H, s), 3.33 (1 H, d, J_{gem} = 18 Hz), 3.00 (1 H, m), 2.82 (1 H, m), 2.40 (3 H, s), 2.03 (3 H, s), 1.87 (3 H, s).

(5*RS*,1′*SR*)-Methyl 5-(1′-Acetoxy-1′-methylbenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10t). Compound **10k** was acetylated as described above to yield **10t** (176 mg, 55%) as a pale yellow oil: IR (film) 1740 (s), 1715 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (5 H, br s), 7.25 (1 H, br s), 3.90 (3 H, s), 3.33 (1 H, d, J_{gem} = 16.5 Hz), 3.03 (1 H, m), 2.87 (1 H, d, J_{gem} = 16.5 Hz), 2.24 (3 H, s), 2.09 (3 H, s), 1.82 (3 H, s).

(5*RS*,1′*RS*)- and (5*RS*,1′*SR*)-Methyl 5-(1′-Cyclohexyl-1′-hydroxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10l and 10m). The solution of the enolate in 3 mL of THF was quenched with cyclohexyl phenyl ketone (960 mg, 5.1 mmol) in 5 mL of THF. RT: 5 h. *T*: room temperature. The diastereomeric mixture (1/1) was separated by TLC (eluents: ethyl acetate/CH_2Cl_2 = 1/1 (v/v)). Elution of the upper layer and recrystallization from ethyl acetate afforded **10l** (463 mg, 27%) as colorless crystals: mp 135–137 °C; IR (KBr) 1720 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42–7.21 (6 H, m), 7.05 (1 H, br s), 3.79 (3 H, s), 3.62 (1 H, d J_{AB} = 18 Hz), 3.10 (1 H, br s), 2.73 (1 H, d, J_{AB} = 18 Hz), 2.45 (1 H, d, J_{AB} = 12 Hz), 2.16 (3 H, s), 2.14–0.15 (12 H, m); MS, m/e 343 (M^+, 8), 344 (2); UV 216 nm (log ϵ 1.31). Anal. ($C_{21}H_{29}NO_3$) C, H, N. Elution of the lower layer and recrystallization from ethyl acetate afforded **10m** (515 mg, 30%) as colorless crystals: mp 134–135 °C; IR (KBr) 1710 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42–7.21 (5 H, m), 6.54 (1 H, m), 5.90 (1 H, br s), 3.60 (3 H, s), 3.52 (1 H, d, J_{AB} = 18 Hz), 3.19 (1 H, br s), 3.14 (1 H, d, J_{AB} = 12 Hz), 2.84 (1 H, d, J_{AB} = 18 Hz), 2.46 (3 H, s), 2.44–0.18 (12 H, m); MS, m/e 343 (M^+, 13), 344 (4); UV 214 nm (log ϵ 1.38). Anal. ($C_{21}H_{29}NO_3$) C, H, N.

(5*RS*,1′*RS*)- and (5*RS*,1′*SR*)-Methyl 5-(1′-Hydroxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10n and 10o). The solution of the enolate in 10 mL of THF was quenched with benzaldehyde (0.52 mL, 5.1 mmol). Fractionated crystallization of the diastereomeric mixture (**10n**/**10o** = 1/3) from ethyl acetate afforded **10o** (587 mg, 45%) as colorless crystals: mp 106–108 °C; IR (KBr) 1710 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.37 (6 H, br s), 6.62 (1 H, m), 5.05 (1 H, d, J = 3.5 Hz), 3.71 (3 H, s), 3.78–2.32 (5 H, m), 2.42 (3 H, s); MS, m/e 261 (M^+, 27), 262 (5); UV 216 nm (log ϵ 1.34). Anal. ($C_{15}H_{19}NO_3$) C, H, N. The diastereomer **10n** could not be separated and was characterized by the ^{1}H NMR spectrum of the remaining diastereomeric mixture (1/1). ^{1}H NMR ($CDCl_3$) δ 7.37 (5 H, br s), 7.12 (1 H, m), 4.95 (1 H, d, J = 3 Hz), 3.79 (3 H, s), 2.21 (3 H, s).

(5*RS*,1′*RS*)- and (5*RS*,1′*SR*)-Methyl 5-(3-Hydroxyoxindol-3-yl)-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (10p and 10q). The solution of the enolate in 10 mL of THF was quenched with isatin (750 mg, 5.1 mmol) in 10 mL of THF. RT: 2 h. *T*: room temperature. Crystallization of the diastereomeric mixture (1/1) from acetone afforded **10p** (610 mg, 40%) as colorless crystals: mp 184–190 °C; IR (KBr) 1735 (s), 1700 (s) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 10.43 (1 H, s), 7.33–6.70 (5 H, m), 6.27 (1 H, s), 3.70 (3 H, s), 3.47–2.00 (m), 2.07 (3 H, s); MS, m/e 302 (M^+, 4), 303 (1). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N. The mother liquor was evaporated and the resulting gum was treated with water to give a solid which was recrystallized to afford **10q** (120 mg, 8%) as colorless crystals: mp 152–160 °C; IR (KBr) 1715 (b) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 10.36 (1 H, s), 7.43–6.73 (5 H, m), 6.37 (1 H, s), 3.67 (3 H, s), 3.37–2.03 (m), 2.17 (3 H, s); MS, m/e 302 (M^+, 8), 303 (1). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N.

(3*RS*)-Methyl 3-(1-Acetylindol-3-yl)-1-methyl-1,2,3,6-tetrahydropyridine-3-carboxylate (12). The solution of the enolate in 10 mL of THF was quenched with chlorotrimethylsilane (0.76 mL, 6 mmol). The mixture was allowed to reach room temperature (30 min) before the solvent was removed in vacuo under exclusion of moisture. The residue was suspended in CH_2Cl_2 (5 mL) and the solution was filtered from the LiCl. Then the solution was added to a suspension, which was obtained by adding $TiCl_4$ (1.32 mL, 12 mmol) to a solution of *N*-acetylindoxyl[33] (1.05 g, 6 mmol) in CH_2Cl_2 (30 mL) at −78 °C and stirring for 30 min. The resulting mixture was heated to reflux for 60 min. After the mixture was cooled to room temperature, $NaHCO_3$ (4.2 g, 50 mmol) was added and the suspension was filtered through Celite. Washing of the filter cake with three 30-mL portions of CH_2Cl_2, workup as described above, and TLC (eluents: ethyl acetate/CH_2Cl_2 = 7/3 (v/v)) gave **12** (655 mg, 42%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 8.49 (1 H, m), 7.69 (1 H, m), 7.42–6.96 (3 H, m), 6.38–5.91 (2 H, m), 3.71 (3 H, s), 3.56–2.62 (4 H, m), 2.59 (3 H, s), 2.36 (3 H, s); MS, m/e 312 (M^+, 11), 313 (3). An analytical sample was prepared by recrystallization of **12**·$HClO_4$ from water/acetone: mp 196–207 °C; IR (KBr) 1735 (s), 1710 (s) cm^{-1}; UV 240 nm (log ϵ 1.58), 296 (log ϵ 0.62). Anal. ($C_{18}H_{21}N_2O_7Cl$) C, H, N.

Methyl 4-(Diisopropylamino)-1-methylpiperidine-3-carboxylate (13). The mother liquor of **10a** was subjected to TLC (eluent: ethyl acetate) to give after elution of the upper layer **13** (30 mg, 2%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.37 (3 H, s), 2.23 (3 H, s), 0.99 (12 H, d, J = 7.5 Hz); MS, m/e 256 (M^+, 10), 257 (2).

Dehydration of 10a–c. A 5-mmol sample of the appropriate compound was dissolved in acetic anhydride (20 mL). After the mixture was refluxed for 10 min, the solvent was removed in vacuo and the remaining oil was dissolved in CH_2Cl_2 (20 mL). Washing with 2 N Na_2CO_3 and evaporation of the organic layer in vacuo gave the crude products.

Methyl 5-Isopropylidene-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (14a). Dehydration of **10a** and distillation of the crude product in a Kugelrohr apparatus at 90 °C oven temperature (0.5 torr) gave **14a** (878 mg, 90%) as a colorless oil: IR (film) 1710 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.65 (1 H, m), 3.71 (3 H, s), 3.21 (2 H, br s), 3.11 (2 H, br s), 2.40 (3 H, s), 1.90 (3 H, br s), 1.78 (3 H, br s); MS, m/e 195 (M^+, 27), 196 (4); UV 212 nm (log ϵ 0.46), 286 nm (log ϵ 1.52).

Methyl 5-Cyclohexylidene-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (14b). Dehydration of **10b** yielded **14b** (1.01 g, 86%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.98 (1 H, m), 3.86 (3 H, s), 3.34 (2 H, br s), 3.25 (2 H, br s), 2.51 (3 H, s), 2.30 (4 H, m), 1.61 (6 H, br s); MS, m/e 235 (M^+, 22), 236 (3). An analytical sample was purified by recrystallization of **14b**·$HClO_4$ from methanol: mp 169–176 °C; IR (KBr) 1690 (s) cm^{-1}; UV 292 nm (log ϵ 2.22). Anal. ($C_{14}H_{22}NO_6Cl$) C, H, N.

Methyl 5-Benzhydrylidene-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate (14c). Dehydration of **10c** and recrystallization from acetone gave **14c** (1.40 g, 88%) as colorless crystals: mp 152 °C; IR (KBr) 1695 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50–6.91 (11 H, m), 3.70 (3 H, s), 3.36 (2 H, m), 3.19 (2 H, br s), 2.36 (3 H, s); MS, m/e 319 (M^+, 36), 320 (7); UV 208 nm (log ϵ 0.92), 2.46 (log ϵ 0.63), 320 (log ϵ 0.98). Anal. ($C_{21}H_{21}NO_2$) C, H, N.

Methyl 5-Benzhydrylidene-1-(ethoxycarbonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (15). Compound **14c** (3.2 g, 10 mmol) was dissolved in toluene (30 mL). After addition of K_2CO_3 (0.69 g, 5 mmol), the suspension was heated to reflux and ethyl chloroformate (1.2 mL, 12 mmol) was added over a period of 10 min. Refluxing was continued for a further 3 h. After cooling to room temperature the suspension was poured into water, and the organic layer was separated, dried, and evaporated in vacuo. Recrystallization of the residue from acetone gave **15** (3.4 g, 89%) as colorless crystals: mp 112–129 °C; IR (KBr) 1710 (s), 1690 (s)

cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.02 (11 H, m), 4.38–3.86 (6 H, m), 3.71 (3 H, s), 1.14 (3 H, t); MS, *m/e* 377 (M^+, 98), 378 (26). Anal. ($C_{23}H_{23}NO_4$) C, H, N.

Deprotection of the Esters 14a, 14c, and 15. A 10-mmol sample of the appropriate compound was dissolved in 48% HBr (12 mL) and CH_3COOH (6 mL). The solution was heated to reflux for 10 min. After removal of the solvents in vacuo, the residue was subjected to a Dowex 50 WX8 ion-exchange resin (Serva). The column was washed free from acid, and the products were obtained by eluting with 2 N NH_3 and evaporation of the solvent in vacuo.

5-Isopropylidene-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid (16a). Deprotection of **14a** as described above and recrystallization of the residue from acetone yielded **16a**·H_2O (1.6 g, 80%) as colorless crystals: mp 222–230 °C; IR (KBr) 1680 (s) cm^{-1}; ^1H NMR (NaOD) δ 6.63 (1 H, br s), 3.33 (1 H, d, J_{AB} = 13.5 Hz), 3.10 (1 H, d, J_{AB} = 13.5 Hz), 2.87 (2 H, m), 2.37 (3 H, s), 1.32 (6 H, br s); UV 210 nm (log ϵ 0.94), 276 (log ϵ 0.22). Anal. ($C_{10}H_{17}NO_3$) C, H, N.

5-Benzhydrylidene-1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid (16c). Deprotection of **14c** as described above and recrystallization of the residue from ethanol yielded **16c** (2.5 g, 82%) as colorless crystals: mp 232–241 °C; IR (KBr) 1640 (s) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.56–7.00 (11 H, m), 3.14 (4 H, m), 2.20 (3 H, s); UV 210 nm (log ϵ 1.39), 240 (log ϵ 1.34), 308 (log ϵ 1.94). Anal. ($C_{20}H_{19}NO_2$) C, H, N.

5-Benzhydrylidene-1,2,5,6-tetrahydropyridine-3-carboxylate (16d). Deprotection of **15** as described above and recrystallization of the residue from water yielded **16d** (1.9 g, 64%) as colorless crystals: mp 205–216 °C; IR (KBr) 1620 (s) cm^{-1}; ^1H NMR (NaOD) δ 7.47–6.87 (11 H, m), 3.60 (2 H, br s), 3.38 (2 H, br s); UV 210 nm (log ϵ 1.41), 240 (log ϵ 1.34), 308 (log ϵ 1.92). Anal. ($C_{19}H_{17}NO_2$) C, H, N.

5-Benzhydrylidene-3-(hydroxymethyl)-1-methyl-1,2,5,6-tetrahydropyridine (17). To **14c** (1.6 g, 5 mmol) in 20 mL of THF was added $LiAlH_4$ (145 mg, 3.8 mmol) and the resulting suspension was heated to reflux for 2 h. After cooling of the mixture to 0 °C, water was added and the suspension was filtered. Removal of the solvent in vacuo and recrystallization of the residue from acetone yielded **17** (1.35 g, 93%) as colorless crystals: mp 161–181 °C; IR (KBr); ^1H NMR ($CDCl_3$) δ 7.20 (10 H, m), 6.27 (1 H, br s), 4.10 (2 H, br s), 3.27 (2 H, s), 3.10 (2 H, br s), 2.33 (3 H, s), 1.93 (1 H, br s); MS, *m/e* 291 (M^+, 47), 292 (11); UV 214 nm (log ϵ 1.46), 288 (log ϵ 1.86). Anal. ($C_{20}H_{21}NO$) C, H, N.

Pharmacology. [^{3}H]GABA Uptake. For [^{3}H]GABA-uptake studies, a crude synaptosomal (P_2) fraction according to Whittaker[37] was prepared from whole brains (minus cerebellum) of male Sprague–Dawley rats (Forschungsanstalt für Versuchstierzucht, Himberg, Austria). The tissue was homogenized in 10 volumes (w/v) of ice-cold 0.32 M sucrose in a Thomas B 10001 glass homogenizer and centrifuged at 1000*g* at 4 °C (Sorvall RC-5B Superspeed centrifuge, SS 34 rotor). The pellet (P_2 pellet) was washed once with ice-cold sucrose, centrifuged again, and carefully resuspended in ice-cold incubation medium. The incubation medium contained (mmol/L): NaCl 100, KCl 5, NaH_2PO4 10, Na_2HPO_4 20, sucrose 40, *d*-glucose 40; pH 7.2. For estimation of the kinetic constants of [^{3}H]GABA uptake, portions of the resuspended P_2 pellet, equivalent to 1 mg of tissue wet weight, were incubated with increasing concentrations of [^{3}H]-GABA (specific activity 54 Ci/mmol; 1.3–40 μM) in the absence or presence of different concentrations of inhibitors. The protein suspension was always added last and the incubation was carried out for 4 min at 37 °C in a final volume of 1 mL. The incubations were terminated by filtration through Whatman GF/C glass fiber filters (2.5 cm) with a Millipore 1225 sampling manifold. The filters were then placed in scintillation vials containing 7 mL of "Atomlight" scintillation fluid (New England Nuclear) and desintegrated by shaking for 1 h on a Bühler SM 25 shaking apparatus (250 × min^{-1}), and the radioactivity was measured in a Packard Tri-Carb 460C liquid scintillation counter. All uptake values determined at 37 °C were corrected by subtracting a "blank value" obtained from parallel incubations at 4 °C. The results were plotted according to Lineweaver and Burk[34] and the kinetic and inhibition constants were calculated using a nonlinear curve fitting program.[38] All protein concentrations were determined by using the method of Lowry et al.[39]

Binding Assay. In the binding experiments crude membrane suspensions prepared from cerebellum of male Sprague–Dawley rats were used. The tissue was homogenized in 20 vol (w/v) of ice-cold Tris-HCl buffer (5 mM, pH 7.4, 4 °C) with use of an Ultra Turrax homogenizer. The homogenate was centrifuged at 48000*g* for 10 min at 4 °C. The pellet was rehomogenized in fresh cold Tris-HCl buffer and centrifuged again (see above). This step was repeated two more times, and the membranes were resuspended at 20 mL/g of tissue wet weight in Tris-HCl buffer (50 mM, pH 7.2, 4 °C) and frozen at −20 °C. On the day of the assay, aliquots of the membrane suspensions were thawed, washed twice in Tris-HCl buffer (50 mM), and resuspended at 20 mL/g of tissue wet weight (0.1–0.15 mg/mL of protein as determined by the method of Lowry et al.[39]). The binding assay was done according to the method of Enna and Snyder[40] with minor modifications. Briefly, routine [^{3}H]GABA binding assays were run by incubating 100 μL of crude membrane suspensions at 4 °C for 30 min with [^{3}H]GABA (specific activity 34.9 Ci/mmol; 5 nM) in a total volume of 0.4 mL of incubation buffer (50 mM Tris-HCl, pH 7.2). The inhibition of the specific binding of the radioligand was determined in the presence of various concentrations of unlabeled competing drugs. The highest concentration tested was 30 μM for all compounds. Incubations were terminated by centrifugation at 48000*g*. The resulting pellets were carefully rinsed two times with 1 mL of ice-cold Tris-HCl buffer, solubilized at 55 °C for 60 min in 150 μL of Protosol (New England Nuclear), and neutralized with acetic acid before liquid scintillation counting. Specific binding was defined as binding of radioactivity in the absence of unlabeled GABA (total binding) minus the binding in the presence of 100 μM unlabeled GABA (nonspecific binding). The affinity of drugs for the specific binding sites labeled by [^{3}H]GABA was expressed as the molar concentration inhibiting the specific binding by 50% (IC_{50}). These values were calculated from the displacement curves by log probit analysis.

Acknowledgment. We thank Dr. P. M. Müller (Hoffmann La Roche & Co. Inc., Basel) for providing [^{3}H]GABA. For assistance in experimental work we are indebted to H. Stöger.

Registry No. **6**, 63-75-2; (±)-**8a**, 98942-68-8; (±)-**8b**, 98942-69-9; (±)-**8c**, 98942-70-2; (±)-**8c**·HCl, 98942-71-3; (±)-**8d**, 98942-72-4; (tu)-**8d**·HCl, 98942-73-5; (±)-**8e**, 98942-74-6; (±)-**8e**·HCl, 98942-75-7; (±)-(*R*,St*)-**8f**, 98942-76-8; (±)-(*R*,S**)-**8f**·HCl, 98942-78-0; (±)-(***R****,*R**)-**8f**, 98942-77-9; (±)-(*R*,R**)-**8f**-HCl, 98976-54-6; (±)-**8g**, 98942-79-1; (±)-**8g**·HCl, 98942-80-4; (±)-**8h**, 98942-81-5; **9**, 98942-82-6; (±)-**10a**, 98942-83-7; (±)-**10b**, 98942-84-8; (±)-**10c**, 98942-85-9; (±)-(*R*,R**)-**10d**, 98942-86-0; (±)-(*R*,S**)-**10d**, 98942-87-1; (±)-(7*R*,S**)-**10f**, 98942-88-2; (±)-(*R*,R**)-**10f**, 98942-89-3; (±)-(*R*,S**)-**10h**, 98942-90-6; (±)-(*R*,R**)-**10h**, 98942-91-7; (±)-**10j**, 98942-92-8; (±)-**10k**, 98942-93-9; (±)-(*R*,-R**)-**10l**, 98942-94-0; (±)-(*R*,S**)-**10l**, 98942-95-1; (±)-(*R*,R**)-**10n**, 98942-96-2; (±)-(*R*,S**)-**10n**, 98942-97-3; (±)-(*R*,S**)-**10p**, 98942-98-4; (±)-(*R*,R**)-**10p**, 98942-99-5; (±)-(*R*,R**)-**10s**, 98943-00-1; (±)-(*R*,S**)-**10s**, 98943-01-2; **11**, 98943-02-3; (±)-**12**, 98943-03-4; (±)-**12**·$HClO_4$, 98943-04-5; **13**, 98943-05-6; **14a**, 98943-06-7; **14b**, 98943-07-8; **14b**·$HClO_4$, 98943-08-9; **14c**, 98943-09-0; **15**, 98943-10-3; **16a**, 98943-11-4; **16c**, 98943-12-5; **16d**, 98976-55-7; **17**, 98943-13-6; GABA, 56-12-2; CH_3I, 74-88-4; $C_6H_5CH_2Cl$, 100-44-7; $BrCH_2CH{=}CH_2$, 106-95-6; $C_6H_5CH_2CH_2Br$, 103-63-9; (±)-$H_3CCH(Br)C_6H_5$, 38661-81-3; H_3CCOCH_3, 67-64-1; $C_6H_5COC_6H_5$, 119-61-9; $C_6H_5COCH_3$, 98-86-2; C_6H_5CHO, 100-52-7; $(CH_3)_3SiCl$, 75-77-4; tricarbonylchromium fluorobenzene, 12082-05-2; phenyldiazonium tetrafluoroborate, 369-57-3; cyclohexanone, 108-94-1; 2-benzoylpyridine, 91-02-1; 3-benzoylpyridine, 5424-19-1; 4-benzoylpyridine, 14548-46-0; cyclohexyl phenyl ketone, 712-50-5; isatin, 91-56-5; *N*-acetylindoxyl, 33025-60-4.

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