Laboratory, Department of Chemistry, University of California, Berkeley. Proton NMR spectra of the compounds were taken on a Varian FT-80 at 80 MHz in either D_2O or Me_2SO-d_6 and were consistent with assigned structures. All the chromatographic, spectral, and analytical data of inosine derivatives are in Table I, and all the data of IMP analogues are in Table II. Melting points were corrected and were done on a Fisher-Johns apparatus.

2-Alkyl- and 2-Arylinosines (II). Method A. In 50 mL of 1 N NaOEt (prepared from sodium metal and anhydrous ethanol) was added 1 g (3.99 mmol) of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (Sigma Chemical Co., St. Louis, MO). The solution was heated and stirred until clear before the addition of the appropriate ester. After refluxing for 4 h, when TLC in 4:1 chloroform–methanol indicated completion of reaction, the hot ethanolic solution was evaporated to dryness and redissolved in water. The pH was adjusted to 3.0 with concentrated HCl, and the solution was extracted four to six times with either ether or chloroform. The aqueous layer was neutralized with NaOH and concentrated in vacuo until the product precipitated. If the product did not precipitate, chilling or addition of ethanol caused it to do so. Recrystallization was from either water or water–ethanol. Compounds prepared in this manner are shown in Table I.

2-(Alkylthio)inosines (IV). Method B. One equivalent of 2-mercaptoinosine[3] was dissolved in 5 mL of dry dimethylformamide, and 1 equiv of anhydrous K_2CO_3 was added. To this stirred solution was added 1 equiv of the appropriate aryl halide. After stirring at room temperature for 2 h, the solution was poured into 30 mL of water, the pH was adjusted to 6 with dilute HCl, and the solution was concentrated in vacuo and cooled if necessary. Filtration and recrystallization of the product from H_2O/EtOH gave the products shown in Table I.

Synthesis of IMP Analogues (V and VI). Inosine analogues were phosphorylated by the method of Yoshikawa et al.[4] To 0.25 mmol of the appropriate nucleoside in 1.2 mL of freshly distilled trimethyl phosphate at 0 °C was added dropwise $POCl_3$ (1 mmol) in approximately 100 μL of trimethyl phosphate and 4.5 μL (0.25 mmol) of H_2O (precooled to 0 °C). After stirring at 0 °C for 5 h, the solution was allowed to stir at room temperature for another 2 h or longer, until reaction was complete as monitored by TLC in BuOH–AcOH–H_2O, 5:1:2. The solution was poured onto ice and neutralized with concentrated NH_4OH. This solution was stored overnight in the refrigerator, extracted with ether to remove trimethyl phosphate, evaporated in vacuo, and then redissolved in 5 mL water. Two methods then were used to purify the resulting diammonium salt of the nucleotide, which are shown in Table II.

Method C. The solution was filtered, and if necessary, the pH was adjusted to 7.0 with dilute HCl. Then, 500-μL aliquots of the mixture were injected into a reverse-phase column (Lichrosorb RP-18, particle size 10 μm, 1 × 30 cm) using as the eluant water containing 0.5% methanol. Evaporation of the appropriate fractions in vacuo, followed by lyophilization, yielded pure analytical product.

Method D. The solution was adjusted to pH 8.2 with NaOH and passed through a column of boric acid gel (5 mL, Sigma Chemical Co.). Compounds with cis diols will form a borate complex with the column, while salts and nucleosides phosphorylated at either the 2′- or 3′-position on the sugar will wash through. After the column was washed with 300 mL of 1 N $(NH_4)_2CO_3$, pH 9.5, the nucleotide was eluted with distilled, deionized water (measured pH, 6.2). The product emerged after approximately 20 mL of eluant. This solution was evaporated in vacuo, then redissolved in water, and either lyophilized or precipitated by the addition of acetone; it was then filtered, and the filtrate was dried.

Acknowledgment. We are indebted to Carla Robertson for expert technical assistance with enzyme isolation and assays. We also thank Dr. David Streeter, SRI International, Palo Alto, CA, for performing some enzyme assays. Additionally, some of the enzyme preparations were done by Dr. Edward B. Skibo. Some of the 2-substituted IMP analogues were graciously supplied to us by Dr. Akihiro Yamazaki, Ajinomoto Co., Kawasaki, Japan. We thank the National Cancer Institute, USPHS, for support for this work in the form of Grant CA 30157. C.G.W. was supproted by USPHS Training Grant GM 07175. We are indebted to Professor George Kenyon for many helpful discussions.

Registry No. 1, 131-99-7; 2, 26550-86-7; 3, 85-32-5; 4, 88868-94-4; 5, 15000-04-1; 6, 88868-95-5; 7·2NH_3, 88868-78-4; 8·2NH_3, 88868-79-5; 9·2NH_3, 88868-80-8; 10·2NH_3, 88868-81-9; 11·2NH_3, 88868-82-0; 12·2NH_3, 88868-83-1; 14·2NH_3, 88868-85-3; 15·2NH_3, 88868-86-4; 16·2NH_3, 88868-84-2; 17·2NH_3, 88868-88-6; 18·2NH_3, 88868-89-7; 19·NH_3, 88868-91-1; 20·NH_3, 88868-93-3; 21·2NH_3, 88868-92-2; 22·2NH_3, 88868-90-0; II (R = $CH_3(CH_2)_4$), 88868-61-5; II (R = $CH_3(CH_2)_5$), 88868-62-6; II (R = $CH_3(CH_2)_6$), 88868-63-7; II (R = $CH_3(CH_2)_7$), 88868-64-8; II (R = $CH_3(CH_2)_8$), 88868-65-9; II (R = $CH_3(CH_2)_9$), 88868-66-0; II (R = $PhCH_2$), 88868-67-1; II (R = 3-c-NC_5H_4), 88868-68-2; II (R = p-OCH_3Ph), 56489-60-2; II (R = PhCH=CH), 88868-69-3; II (p-OCH_3PhCH_2), 88868-70-6; II (R = 3-c-NC_5H_4-CH_2), 88868-71-7; IV (R = m-NO_2PhCH_2S), 88868-72-8; IV (R = 2-Cl-4-NO_2PhCH_2S), 88868-73-9; IV (R = p-NO_2PhCH_2S), 88868-74-0; IV (R = o-$ClPhCH_2S$), 88868-75-1; IV (R = 3,5-$(NO_2)_2PhCH_2S$), 88868-76-2; V (R = $CH_3(CH_2)_4$), 88868-77-3; V (R = p-OCH_3PhCH_2), 88868-87-5; 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide, 2627-69-2; 2-mercaptoinosine, 6544-32-7; IMP dehydrogenase, 9028-93-7.

2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines: Potential Antidepressants

Rudolf Kunstmann,* Ulrich Lerch, Hermann Gerhards, Margret Leven, and Ulrich Schacht

Hoechst Aktiengesellschaft, D-6230 Frankfurt 80, West Germany. *Received April 26, 1983*

The synthesis of various diastereoisomeric H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*- and H_{4a},H_5-*trans*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridines is described, as well as the evaluation of their antidepressant potency. Elucidation of structure–activity relationships revealed the H_{4a},H_5-trans compounds as being by far the more active of the two series of diastereoisomers. Pharmacological and biochemical data suggest that these compounds are potential antidepressants with central stimulating properties, which are characterized by strong norepinephrine and dopamine reuptake inhibition.

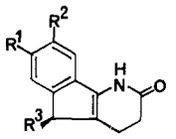
The antidepressant activity of the unsubstituted 5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridines has been reported, but no data on structure–activity relationships in this series have been available so far.[1] This structure was chosen as a lead in our effort to find new antidepressants with improved tolerability and potency and minimized side effects.

The lack of a suitable synthesis for 1*H*-indeno[1,2-*b*]-pyridines, allowing a broad variation of substituents, prompted us to look for a more versatile synthetic procedure. After the development of an appropriate method,[2]

(1) Augstein, J.; Ham, A. L.; Leeming, P. R. *J. Med. Chem.* **1972**, *15*, 466.

0022-2623/84/1827-0432$01.50/0 © 1984 American Chemical Society

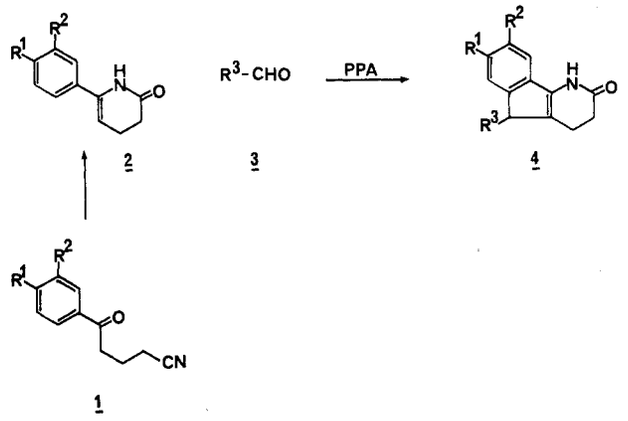
Table I. 1,2,3,4-Tetrahydro-5*H*-indeno[1,2-*b*]pyridin-2-ones (4)[a]



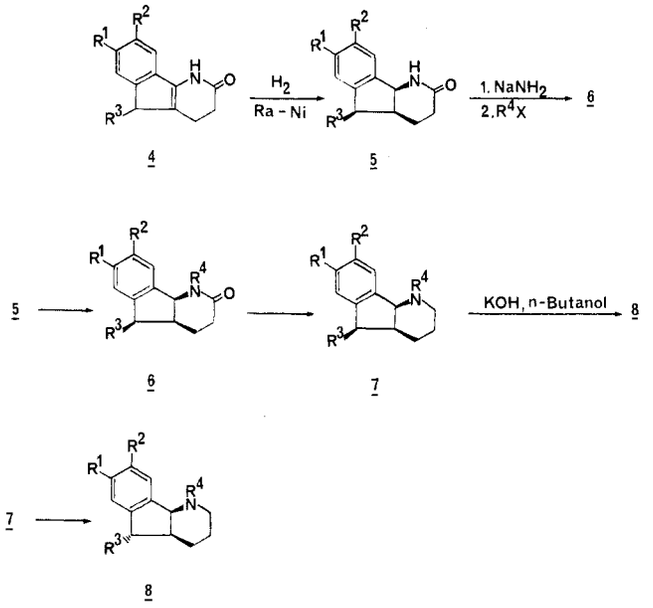
compd	R^1	R^2	R^3	mp, °C	recrystn solvent	yield, %	reaction time, h	formula	anal.
4a	H	H	3-NO_2-C_6H_4	226	DMF/methanol	58	2	$C_{18}H_{14}N_2O_3$	C, H, N
4b	H	H	4-CH_3-C_6H_4	195-198	ethanol	32	4	$C_{19}H_{17}NO$	C, H, N
4c	H	H	2-CH_3-C_6H_4	215	methanol	60	4	$C_{19}H_{17}NO$	C, H, N
4d	H	H	4-CH_3-3-NO_2-C_6H_3	226-230	methanol	58	4	$C_{19}H_{16}N_2O_3$	C, H, N
4e	OCH_3	H	4-*i*-C_3H_7-C_6H_4	191-195	methanol	47	4	$C_{22}H_{23}NO_2$	C, H, N
4f	OCH_3	H	4-CH_3-3-NO_2-C_6H_3	238-240	methanol	60	4	$C_{20}H_{18}N_2O_4$	C, H, N
4g	OCH_3	H	4-$N(CH_3)_2$-C_6H_4	234-236	methanol	53	4	$C_{21}H_{22}N_2O_2$	C, H, N
4h	OCH_3	OCH_3	C_6H_5	240-242	DMF/ethanol	62	2	$C_{20}H_{19}NO_3$	C, H, N
4i	H	H	2-F-C_6H_4	218-220	ethanol/chloroform	69	1	$C_{18}H_{14}FNO$	C, H, N

[a] Prepared according to method A.

Scheme I



Scheme II



the elaboration of structure–activity relationships revealed the antidepressant potency of this class of compounds.

Chemistry. The synthesis of the 2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridines is straightforward and follows Schemes I and II.

5-Oxo-5-phenylvaleronitriles (**1**) easily undergo cyclization to give 6-phenyl-3,4-dihydropyridin-2-ones (**2**), which are condensed readily with an appropriate aldehyde (**3**) in polyphosphoric acid to yield 1,2,3,4-tetrahydro-5*H*-indeno[1,2-*b*]pyridin-2-ones (**4**). If both substituents $R^{1,2}$ are not hydrogen, this condensation may yield two different products in which R^2 resides either at C_6 or C_8. The regiospecific condensation leading to the compounds (**4**) indicated has been proven by ^1H NMR spectra. The signals for the aromatic hydrogens in question are two singlets ($J_{H_6H_9} < 1$ Hz), suggesting a para position.

Catalytic hydrogenation of **4** leads to 2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridin-2-ones (**5**), which can be alkylated at the nitrogen to give the substituted lactams (**6**). The hydrogenation produces exclusively the all-cis configuration at the central five-membered ring. This configuration remains untouched during the subsequent alkylation. The epimerization at C_5 to yield **8** can be achieved by treating **7** with potassium hydroxide in 1-butanol at elevated temperature. For details of the synthetic procedure, see ref 2.

For the synthesis of the diastereoisomeric pair **5A,B** (R^3 = 4-NH_2-C_6H_4; R^4 = CH_3) in Table VI, one has to follow a different synthetic route for obvious reasons. Compound **4** (R = 4-NO_2-C_6H_4) can be hydrolyzed in acidic media. The resulting keto acid (**9**) is converted to the N-methylated lactam by treating **9** with methylamine to yield what we suppose to be the imino compound **10** which is not purified but subsequently hydrogenated in the presence of Raney nickel.

The saturated substituted lactam **11** thus obtained is converted into the corresponding amine in the usual manner (Scheme III).

Following the pathway described for the preparation of the indeno[1,2-*b*]pyridines, various substituents can be introduced at the positions 1, 5, 7, and 8 (R^1–R^4). Since the pure diastereoisomers **7** and **8** can be easily obtained, the influence of these structural variations on the biological activity could be examined in both series.

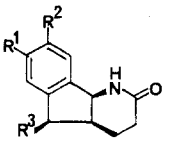
The new (see ref 2) compounds **4**–**8** are summarized in Tables I–V, respectively.

Pharmacology and Biochemistry. The potential antidepressant activity was assessed by the prevention of tetrabenazine (TBZ) induced ptosis in mice after intraperitoneal (ip) administration by the method of Bickel and Brodie.[3] A therapeutic index was calculated based on the

(2) Kunstmann, R.; Lerch, U.; Wagner, K. *J. Heterocycl. Chem.* **1981**, *18*, 1437.

(3) Bickel, M. H.; Brodie, B. B. *Int. J. Neuropharmacol.* **1964**, *3*, 611.

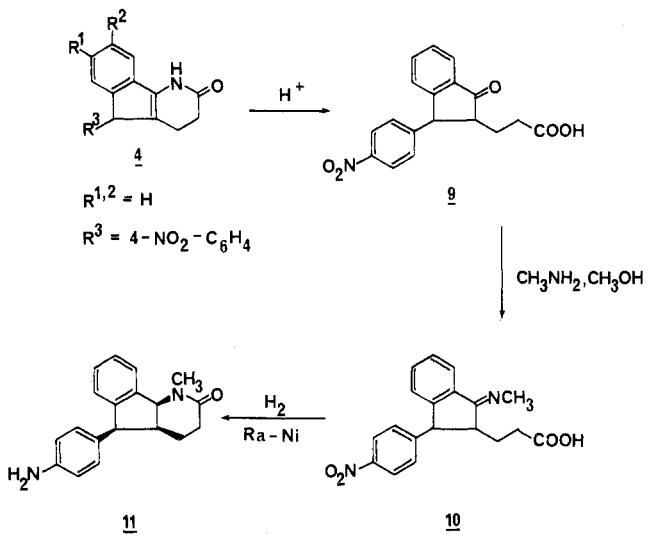
Table II. H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridin-2-ones (**5**)[a]



compd	R^1	R^2	R^3	mp, °C	recrystn solvent	yield, %	formula	anal.
5a	H	H	3-NH_2-C_6H_4	230-232	ethanol	63	$C_{18}H_{18}N_2O$	C, H, N
5b	H	H	4-CH_3-C_6H_4	231-233	ethanol	76	$C_{19}H_{19}NO$	C, H, N
5c	H	H	2-CH_3-C_6H_4	219-220	methanol	80	$C_{19}H_{19}NO$	C, H, N
5d	H	H	4-CH_3-3-NH_2-C_6H_3	267-270	methanol	64	$C_{19}H_{20}N_2O$	C, H, N
5e	OCH_3	H	4-CH_3-3-NH_2-C_6H_3	244-247	methanol	68	$C_{20}H_{22}N_2O_2$	C, H, N
5f	OCH_3	H	4-*i*-C_3H_7-C_6H_4	190-192	ethanol	60	$C_{22}H_{25}NO_2$	C, H, N
5g	OCH_3	H	4-$N(CH_3)_2$-C_6H_4	226-228	ethanol	73	$C_{21}H_{24}N_2O_2$	C, H, N
5h	OCH_3	OCH_3	C_6H_5	259-260	DMF	41	$C_{20}H_{21}NO_3$	C, H, N
5i	H	H	2-F-C_6H_4	203-204	ethanol/chloroform	83	$C_{18}H_{16}FNO$	C, H, F, N

[a] Prepared according to method B.

Scheme III



ratio of the acute toxicity in mice (LD_{50}, in milligrams per kilogram ip) and the ED_{50} (in milligrams per kilogram ip) for the prevention of TBZ-induced ptosis in mice. The pharmacological results and the values for acute toxicity are summarized in Table VI. Since stimulating properties were frequently observed in this series, the enhancement of locomotor activity in mice after oral administration has been measured with a selected compound (Table IX). In addition to the pharmacological data, the reuptake inhibition of [^{14}C]norepinephrine (NE), [^{3}H]dopamine (DA), and 5-hydroxy[^{14}C]tryptamine (5-HT) into rat brain synaptosomes was determined with selected compounds in vitro, following a published procedure[4a] (Table VII). In order to study the absorption mechanism and penetration of the blood–brain barrier, we carried out a few ex vivo/in vitro reuptake experiments. In these cases, the in vitro reuptake inhibition was measured 1 h after the administration of the drug either by the ip or oral route (Table VIII).

Results and Discussion[4b]

The most striking feature that governs the biological effects of these compounds is the relative configuration of the substituent in the 5-position. Thus, in the H_{4a},H_5-cis series, the acute toxicity will increase to LD_{50} values (ip in mice) even below 1 mg/kg when the R^4 hydrogen is replaced by a methyl substituent (**7B** and **8B**). In regards to the H_{4a},H_5-trans series, the acute toxicity decreases considerably when the NH is replaced by NCH_3 (**7A**, **8A**; **9A**, **10A**). However, the most important difference of the two diastereometric series is the almost complete loss of antitetrabenazine activity in the compounds with a H_{4a},H_5-cis configuration. Only very few compounds belonging to this series exhibit any activity, and in these cases they are less active than their corresponding H_{4a},H_5-trans compounds (**4B**, **5B**, **7B**, and **18B**). The potential of the trans compounds as antidepressants is also reflected in the therapeutic index. Whereas the few active compounds in the cis series only exhibit ratios up to 14 (**5B**), the maximum ratios in the trans series are well above several hundred (**4A** and **5A**) up to 1000 (**15A**). Enhancement of locomotor activity as a predictor for central stimulating activity was tested with the most promising compound (**4A**). Unfortunately, only a threefold increase of the ED_{50} for antitetrabenazine activity after oral administration enhances the locomotor activity by more than 100%, indicating an insufficient separation between antitetrabenazine and stimulating properties (Table IX).

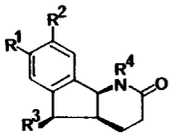
Biochemical data support the pharmacological findings. All trans compounds tested are strong inhibitors of norepinephrine (NE) and dopamine (DA) uptake, independent of the substituents introduced. Once again, the all-cis compounds (e.g., **4B**) are much less potent than the corresponding trans isomers (e.g., **4A**) (Table VII). A correlation test for tetrabenazine antagonism contra inhibition of norephinephrine uptake was carried out with the compounds listed in Table VII by the method by Spearman.[5] The rank correlation coefficient that was calculated missed only slightly the 95% confidence limit ($p \leq 0.05$ requires a ρ value of 0.564; ρ value calculated, 0.5394). An additional reuptake inhibition of 5-hydroxytryptamine (5-HT) could be found in compounds with R^1 = OH, especially in those lacking a substituent at the nitrogen (Table VII; **15A**, **17A**, and **18A**). Ex vivo/in vitro experiments suggest (Table VIII) a positive correlation between lipophilicity and resorption/penetration. Thus, the most polar compounds will not be resorbed and will not penetrate the blood–brain barrier significantly even if considerable activity has been detected in pharmacological tests after ip administration.

(4) (a) Schacht, U.; Leven, M.; Bäcker, G. *Br. J. Clin. Pharmacol.* **1977**, *4*(Suppl 2), 77 S. (b) The numbering of compounds in this and the following sections refers to the numbers of the diastereoisomeric pairs outlined in Table VI.

(5) Weber, E. "Grundriss der Biologischen Statistik"; Gustav Fischer Verlag: Stuttgart, 1972; p 538.

(6) Broto, P.; Moreau, G.; Vandycke, C. *Eur. J. Med. Chem.*, in press.

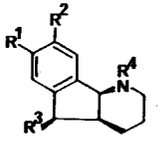
Table III. H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-1-Alkyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridin-2-ones (**6**)[a]



compd	R^1	R^2	R^3	R^4	mp, °C	recrystn solvent	yield, %	anal.
6a	H	H	C_6H_5	n-C_3H_7	112–114	diisopropyl ether	74	C, H, N
6b	H	H	4-CH_3-C_6H_4	CH_3	128–130	diisopropyl ether	84	C, H, N
6c	H	H	2-CH_3-C_6H_4	CH_3	149–150	diisopropyl ether	54	C, H, N
6d	OCH_3	H	4-CH_3-C_6H_4	CH_3	154–156	diisopropyl ether	85	C, H, N
6e	OCH_3	OCH_3	C_6H_5	CH_3	188–190	ethanol	72	C, H, N

[a] Prepared according to method C.

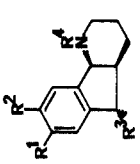
Table IV. H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines (**7**)



compd	R^1	R^2	R^3	R^4	salt	mp, °C	recrystn solvent	yield, %	method	formula	anal.
7a	H	H	C_6H_5	n-C_3H_7	HCl	225–226	acetone/ether	78	D	$C_{21}H_{26}ClN$	C, H, Cl, N
7b	H	H	3-NH_2-C_6H_4	H	2HCl	305–308	ethanol	50	D[b]	$C_{18}H_{22}Cl_2N_2$	C, H, Cl, N
7c	H	H	4-CH_3-C_6H_4	H	HCl	296–299	acetone/methanol	55	D	$C_{19}H_{22}ClN$	C, H, Cl, N
7d	H	H	4-CH_3-C_6H_4	CH_3	HCl	244–246	acetone	94	D	$C_{20}H_{24}ClN$	C, H, N
7e	H	H	3-CH_3-C_6H_4	H	HCl	135–138	acetone/methanol	79	D	$C_{19}H_{22}ClN$	C, H, N
7f	H	H	2-CH_3-C_6H_4	H	HCl	199–202	acetone/methanol	84	D	$C_{19}H_{22}ClN$	C, H, N
7g	H	H	2-CH_3-C_6H_4	CH_3	HCl	263–265	acetone/methanol	51	D	$C_{20}H_{24}ClN$	C, H, N
7h	H	H	4-CH_3-3-NH_2-C_6H_3	H	2HCl	240 dec	ethanol	54	D[a,b]	$C_{19}H_{24}Cl_2N_2$	C, H, Cl
7i	OCH_3	H	4-i-C_3H_7-C_6H_4	H	HCl	222–224	ether/ethanol	63	D	$C_{22}H_{28}ClNO$	C, H, N
7j	OH	H	4-i-C_3H_7-C_6H_4	H	HCl	245–246	acetone/ethanol	73	F	$C_{21}H_{26}ClNO$	C, H, Cl, N
7k	OCH_3	H	4-CH_3-3-NH_2-C_6H_3	H	HCl	220–225	ether/ethanol	88	D[b]	$C_{20}H_{25}ClN_2O$	C, H, N
7l	OH	H	4-CH_3-3-NH_2-C_6H_3	H	2HCl	291–293	ether/ethanol	58	G	$C_{19}H_{24}Cl_2N_2O$	C, H, Cl, N
7m	OCH_3	H	4-CH_3-C_6H_4	CH_3	HCl/H_2O	115–120	acetone/methanol	79	D[a]	$C_{21}H_{28}ClNO$	C, H, N
7n	OH	H	4-CH_3-C_6H_4	CH_3	HCl	240–242	ethanol	87	F	$C_{20}H_{24}ClNO$	C, H, Cl, N
7o	OCH_3	H	4-N(CH_3)$_2$-C_6H_4	H	HCl	222–224	ether/methanol	83	D	$C_{21}H_{27}ClN_2O$	C, H, Cl, N
7p	OH	H	4-N(CH_3)$_2$-C_6H_4	H	2HCl/1.5H_2O	248–252	ethanol/methanol	88	F	$C_{20}H_{26}Cl_2N_2O\cdot1.5H_2O$	C, H, Cl, N
7q	OCH_3	OCH_3	C_6H_5	H	HCl	234–236	acetone	48	D	$C_{20}H_{24}ClNO_2$	C, H, N
7r	OCH_3	OCH_3	C_6H_5	CH_3	HCl	268–270	acetone	85	D	$C_{21}H_{26}ClNO_2$	C, H, N
7s	H	H	2-CF_3-C_6H_4	H	HCl	226–230	acetone	84	D	$C_{19}H_{19}ClF_3N$	C, H, N
7t	H	H	2-F-C_6H_4	H	HCl	269–272	methanol/chloroform	90	D	$C_{18}H_{19}ClFN$	C, H, F, N
7u	H	H	2-F-C_6H_4	CH_3	HCl	252–253	acetone/methylene chloride	83	H	$C_{19}H_{21}ClFN$	C, H, Cl, N
7v	H	H	4-F-C_6H_4	H	HCl	274–277	ethanol	71	D	$C_{18}H_{19}ClFN$	C, H, Cl, N
7w	H	H	4-F-C_6H_4	CH_3	HCl	241–244	methanol	58	H	$C_{19}H_{21}ClFN$	C, H, Cl, N
7x	H	H	4-pyridyl	H	HCl	168–171	ethyl acetate/ether	78	D	$C_{17}H_{17}ClN_2$	C, H, N
7y	H	H	4-NH_2-C_6H_4	CH_3	2HCl	283–287	2-propanol	88	D	$C_{19}H_{23}Cl_2N_2$	C, H, N

[a] In THF. [b] Lactam/LAH, 1:4.

Table V. H_{4a},H_5-*trans*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines (8)



compd	R^1	R^2	R^3	R^4	salt	mp, °C	recrystn solvent	yield, %	method	formula	anal.
8a	H	H	C_6H_5	*n*-C_3H_7	HCl	195–198	ethanol	84	E	$C_{21}H_{26}ClN$	C, H, Cl, N
8b	H	H	3-NH_2-C_6H_4	H	HCl	262–265	ethanol	41	E		
					free base	123–125	diisopropyl ether			$C_{18}H_{20}N_2$	C, H, N
8c	H	H	4-CH_3-C_6H_4	H	HCl	247–253	acetone/methanol	85	E	$C_{19}H_{22}ClN$	C, H, Cl, N
8d	H	H	4-CH_3-C_6H_4	CH_3	HCl	250–252	acetone/ethanol	70	E		
					free base	99–100	petroleum ether			$C_{20}H_{23}N$	C, H, N
8e	H	H	3-CH_3-C_6H_4	H	HCl	228–230	acetone/methanol	62	E	$C_{19}H_{22}ClN$	C, H, Cl, N
8f	H	H	2-CH_3-C_6H_4	H	HCl	245–247	ethanol	80	E	$C_{19}H_{22}ClN$	C, H, Cl, N
8g	H	H	2-CH_3-C_6H_4	CH_3	HCl	248–249	acetone/methanol	76	E	$C_{20}H_{24}ClN$	C, H, Cl, N
8h	H	H	4-CH_3-3-NH_2-C_6H_3	H	HCl	241–244	acetone/ethanol	43	E	$C_{19}H_{23}ClN_2$	C, H, Cl, N
8i	OH	H	4-*i*-C_3H_7-C_6H_4	H	HCl	244–245	ether/ethanol	58	E	$C_{21}H_{26}ClNO$	C, H, Cl, N
8j	OH	H	4-CH_3-3-NH_2-C_6H_3	H	HCl	215–220	ether/ethanol	45	E	$C_{19}H_{23}ClN_2O$	C, H, Cl, N
8k	OH	H	4-CH_3-C_6H_4	CH_3	HCl	242–244	acetone/methanol	82	E	$C_{20}H_{24}ClNO$	C, H, Cl, N
8l	OCH_3	H	4-NH_2-C_6H_4	H	2HCl/H_2O	245–248	acetone/ethanol	38	E	$C_{19}H_{26}Cl_2N_2O_2$	C, H, N
8m	OCH_3	H	4-CH_3-C_6H_4	CH_3	HCl	183–185	acetone/ethanol	32	E	$C_{21}H_{26}ClNO_2$	C, H, N
8n	OH	H	4-$N(CH_3)_2$-C_6H_4	H	2HCl	225–227	ethanol	68	E	$C_{20}H_{26}Cl_2N_2O$	C, H, N
8o	H	H	4-pyridyl	H	1-maleate	179–180	ethanol	53	E	$C_{21}H_{22}N_2O_4$	C, H, N
8p	H	H	4-OH-C_6H_4	H	HBr	285	water	96	F	$C_{18}H_{20}BrNO$	C, H, Br, N
8q	H	H	4-NH_2-C_6H_4	CH_3	HCl	264–266	ethanol	43	E	$C_{19}H_{22}N_2$	C, H, N

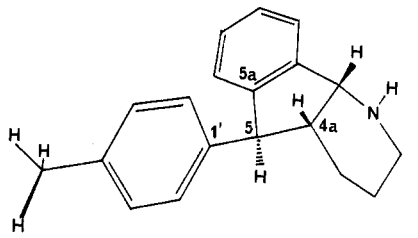
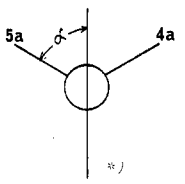


Figure 1. Dreiding-model view of **7A** after minimization procedure by SCRIPT.



*) plane of free rotating phenylring

Comp. Nr.	7A	9A	11A
α	49.8°	49.9°	50.3°

Figure 2. Newman projection of the axis (1′, 5) and calculated values for torsian angle α.

The substitution pattern within the H_{4a},H_5-trans,H_{4a},H_{9b}-cis series will additionally alter the activity considerably. Compounds with $R^{1,4} \neq H$ and R^3 representing a substituted phenyl ring do not show any tetrabenazine antagonism (**23A** and **24A**). This result suggests certain steric restrictions for these substituents. The loss of antidepressant activity in those cases in which the 4′-substituent of the phenyl ring in position 5 is changed to a more bulky one (**17A**, **20A**; **15A**, **22A**) and the decreased activity of the NCH_3 compounds in comparison to the NH compounds (**7A**, **8A**; **9A**, **10A**; **36A**, **37A**; **38A**, **39A**) underline the importance of the steric requirements for the interaction of the substrate with its binding site.

The biological activity seems to be related to the particular shape of the ring structure and, with one important exception, not to the electronically different phenyl substituents at the 5-position (**1A**, **7A**, **9A**, **13A**, **36A**, and **38A**). Because of synthetic problems, the interesting compounds (R^3 = 4-Cl- or 4-F-C_6H_4) could not be tested. The only exceptions so far are the compounds with R^3 = 4-NH_2-C_6H_5 (**4A**, **5A**, and **15A**). The amino group apparently introduces an additional property to the molecule that overrules the steric requirements. This is seen in the dramatic increase in activity in biological tests compared to the rest of the active molecules and the extreme potency of the H_{4a},H_5-cis,H_{4a},H_{9b}-cis compounds **4B** and **5B**.

The interesting finding that the compounds with R^3 = 2-CH_3-C_6H_4 (**11A** and **12A**) are devoid of any significant activity in contrast to the compounds **7A**, **8A**, **9A**, and **10A** with R^3 = 3- or 4-CH_3-C_6H_4 prompted us to carry out a conformational analysis on the compounds **7A**, **9A**, and **11A** using the program SCRIPT,[7] which is based on a force-field calculation. The results of this study indicate that relevant parameters describing the geometry of the three molecules in the conformation of lowest potential energy are not changed in the sequence R^3 = 4-, 3-, and 2-CH_3-C_6H_5 (see Figure 2). The expected change of the torsion angle between the two phenyl rings does not occur. The bulky environment at C_5 forces the phenyl ring even in **7A** (R^3 = 4-CH_3-C_6H_4) into a staggered conformation with respect to C_{4a} and C_{5a} (Figures 1 and 2). This obviously optimal orientation of the phenyl ring is not changed by the introduction of an additional bulky sub-

(7) Cohen, N. C.; Colin, P.; Lemoine, G. *Tetrahedron* **1981**, *37*, 1711.

Table VI. Comparison of H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis* (7) and H_{4a},H_5-*trans*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines (8) with Respect to Pharmacological Activity and Toxicity[d]

diastereomeric pair[a]	R^1	R^2	R^3	R^4	inhibn of TBZ-induced ptosis in mice: ED_{50}, mg/kg ip A	B	acute toxicity in mice: LD_{50}, mg/kg ip A	B	therapeutic index ratio of LD_{50} in mice ip and ED_{50}(TBP) in mice ip A	B
1A,B	H	H	C_6H_5	H	0.7	b	27	50	39	
2A,B	H	H	C_6H_5	CH_3	0.4	b	74	36	185	
3A,B	H	H	C_6H_5	n-C_3H_7	0.8	b	24	90	30	
4A,B	H	H	4-NH_2-C_6H_4	H	0.1	3	50	20	500	
5A,B	H	H	4-NH_2-C_6H_4	CH_3	0.1	0.5	50	7	500	14
6A,B	H	H	3-NH_2-C_6H_4	H	2	b	40	28	20	
7A,B	H	H	4-CH_3-C_6H_4	H	1	20	60	120	60	6
8A,B	H	H	4-CH_3-C_6H_4	CH_3	3	b	232	<1	77	
9A,B	H	H	3-CH_3-C_6H_4	H	0.3	b	21	34	70	
10A,B	H	H	3-CH_3-C_6H_4	CH_3	5	b	134	5	27	
11A,B	H	H	2-CH_3-C_6H_4	H	b	b	80	52		
12A,B	H	H	2-CH_3-C_6H_4	CH_3	>40	b	106	22		
13A,B	H	H	4-CH_3-3-NH_2-C_6H_3	H	2	b	40	45	20	
14A,B	OCH_3	H	4-NH_2-C_6H_4	H	1	b	60	50	60	
15A,B	OH	H	4-NH_2-C_6H_4	H	0.1	b	150	85	1500	
16A,B	OCH_3	H	4-CH_3-C_6H_4	H	nd[c]	b	nd[c]	54		
17A,B	OH	H	4-CH_3-C_6H_4	H	1	b	67	34	67	
18A,B	OH	H	4-CH_3-3-NH_2-C_6H_3	H	3	10	210	67	70	
19A,B	OCH_3	H	4-*i*-C_3H_7-C_6H_4	H	nd[c]	b	nd[c]	37		
20A,B	OH	H	4-*i*-C_3H_7-C_6H_4	H	b	b	50	90		
21A,B	OCH_3	H	4-$N(CH_3)_2C_6H_4$	H	nd[c]	b	nd[c]	48		
22A,B	OH	H	4-$N(CH_3)_2$-C_6H_4	H	b	b	159	67		
23A,B	OCH_3	H	4-CH_3-C_6H_4	CH_3	b	b	67	6		
24A,B	OH	H	4-CH_3-C_6H_4	CH_3	b	b	187	9		
25A,B	OCH_3	OCH_3	C_6H_5	H	nd[c]	b	nd[c]	70		
26A,B	OCH_3	OCH_3	4-NH_2-C_6H_4	H	nd[c]	b	nd[c]	94		
27A,B	OCH_3	OCH_3	C_6H_5	CH_3	nd[c]	b	nd[c]	70		
28A,B	H	H	2-CF_3-C_6H_4	H	nd[c]	b	nd[c]	24		
29A,B	H	H	2-F-C_6H_4	H	nd[c]	b	nd[c]	71		
30A,B	H	H	2-F-C_6H_4	CH_3	nd[c]	b	nd[c]	8		
31A,B	H	H	4-F-C_6H_4	H	nd[c]	b	nd[c]	61		
32A,B	H	H	4-F-C_6H_4	CH_3	nd[c]	b	nd[c]	22		
33A,B	H	H	4-pyridyl	H	2	nd[c]	20	nd[c]	10	
34A,B	OCH_3	OCH_3	3-pyridyl	H	nd[c]	b	nd[c]	30 (iv)		
35A,B	H	H	4-OCH_3-C_6H_4	CH_3	5	nd[c]	95	nd[c]	19	
36A,B	H	H	4-OC_4H_9-C_6H_4	H	1	nd[c]	46	nd[c]	46	
37A,B	H	H	4-OC_4H_9-C_6H_4	CH_3	10	nd[c]	134	nd[c]	14	
38A,B	H	H	4-OH-C_6H_4	H	2	nd[c]	30	nd[c]	15	
39A,B	H	H	4-OH-C_6H_4	CH_3	5	nd[c]	178	nd[c]	36	

[a] A refers to H_{4a},H_5-trans,H_{4a},H_{9b}-cis configuration; B refers to H_{4a},H_5-cis,H_{4a},H_{9b}-cis configuration, respectively, as in compounds 8 *and* 7. [b] No activity detected up to a dose of one-fifth of the LD_{50} ip in mice. [c] No compound for testing has been available. [d] See ref 2 for chemical data and synthesis for compounds that are included in this table and for precursors and end products not mentioned in Tables I–V.

Table VII. Inhibition of Monoamine Uptake into Rat Brain Synaptosomes in Vitro

compd[a]	IC_{50}, M hypothalamus [^{14}C]NE	corpus striatum [^{3}H]DA	whole brain [^{14}C]-5-HT
1A	1.8×10^{-8}	2×10^{-8}	$\sim 10^{-5}$
2A	1.2×10^{-8}	1×10^{-7}	$\sim 10^{-5}$
3A	4.1×10^{-7}	1.1×10^{-7}	$> 10^{-5}$
4A	7.4×10^{-9}	4.4×10^{-8}	$> 10^{-5}$
4B	1.8×10^{-7}	3.3×10^{-7}	2×10^{-5}
5A	1.1×10^{-7}	2.4×10^{-7}	$\sim 10^{-5}$
8A	6.5×10^{-8}	9×10^{-8}	$> 10^{-5}$
15A	1.5×10^{-8}	4.6×10^{-8}	1.6×10^{-6}
17A	3.1×10^{-8}	1.7×10^{-8}	2.8×10^{-7}
18A	4.0×10^{-8}	1.0×10^{-7}	4.3×10^{-7}
desipramine	2.5×10^{-8}		1.1×10^{-5}

[a] A refers to H_{4a},H_5-trans,H_{4a},H_{9b}-cis; B refers to H_{4a},H_5-cis,H_{4a},H_{9b}-cis (see Table VI).

stituent (e.g., R^3 = 2-CH_3-C_6H_5) into **11A**. (For details, see ref 8).

The lack of activity in **11A** and **12A** cannot be explained solely by geometrical factors. One might speculate that metabolic reactions or a transport mechanism involving the C_5 hydrogen atom might be responsible for activity, because only in **11A** and **12A** is this specific hydrogen extremely shielded from any attack by the *o*-methyl group of **11A** and **12A**, but this has to be proven by additional experiments.

Conclusion

2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines are potential antidepressants with central stimulating properties. The potential antidepressant activity has been indicated by tetrabenazine antagonism after ip administration and in vitro measurements of the inhibition of the reuptake of NE, DA, and 5-HT. Activity resides in only one (8) of the two diastereoisomeric series having the H_{4a},H_5-trans,H_{4a},H_{9b}-cis configuration. However, the most

(8) A paper on the conformational analyses of H_{4a},H_5-cis or -trans, H_{4a},H_{9b}-cis diastereoisomeric pairs is in preparation.

Table VIII. Effect of Drug Treatment on the Uptake of [^{14}C]NE and [^{14}C]-5-HT in Synaptosomes from Rat Whole Brain and Calculated Values for Log *P*

	80 mg po[b]		80 mg ip[b]		
compd[a]	[^{14}C]NE	[^{14}C]-5-HT	[^{14}C]NE	[^{14}C]-5-HT	log *P*[c]
8A	>90	>90	74.3 ± 0.2		
	>90	>90	24.5 ± 2.4	>90	3.83
	76.3 ± 3.1	88.1 ± 2.9	54.6 ± 3.6		
15A	>90	>90	>90	>90	1.91
		>90	37.6 ± 2.5	>90	
17A	>90	90.4 ± 2.6	68.2 ± 3.4	>90	3.13
		86.9 ± 8.9	62.0 ± 4.2	84.9 ± 6.4	
18A	>90		80.0 ± 8.8		
	83.5 ± 10.4	>90	>90	>90	2.33
	88.1 ± 5.0		87.7 ± 11.7		

[a] A refers to the H_{4a},H_5-trans,H_{4a},H_{9b}-cis diastereoisomer (see Table VI). [b] Each value represents the mean plus or minus standard deviation of quadruplicate determinations of [^{14}C]NE uptake in a whole brain fraction of a pool from $n = 3$ rats sacrificed after a 1-h treatment either by oral or ip administration and is calculated as a percentage of 100% uptake in control animals. [c] The values have been calculated for the system octanol/water by the program developed by P. Broto et al.[6]

Table IX. Enhancement of Spontaneous Motor Activity (SMA) in Mice after Oral Administration of Compound 4A

	total SMA counts[a]				enhancement of SMA, %	
	test compound		control			
dose,[d] mg/kg	exploration motility[b]	basis motility[c]	exploration motility	basis motility	exploration motility	basis motility
0.3	4809 ± 1999	5 501 ± 2332	5020 ± 1381	5931 ± 1097	−4	−7
1.0	7924 ± 1359	12 001 ± 3638	3662 ± 310	4465 ± 5	116	168
3.0	8827 ± 1376	17 510 ± 2958	3256 ± 464	3666 ± 730	171	377

[a] Each value represents the mean plus or minus standard deviation of the accumulated motility counts of three groups with five mice each. [b] Accumulated motility counts during 1st h of observation. [c] Accumulated motility counts during 2nd h of observation. [d] ED_{50} for inhibition of TBZ-induced ptosis in mice after Oral Administration of Compound 4A 0.3 mg/kg.

interesting compounds of the series exhibit either very strong central stimulating properties (e.g., **4A**) or will not be resorbed after oral administration (e.g., **17A**).

Experimental Section

Chemistry. The structure of all compounds are supported by their IR (Perkin-Elmer 457) ^{1}H NMR (Varian A-60 A, tetramethylsilane), and MS (MS 902 S, AEI) spectra. Melting points were taken on a Tottoli apparatus and are uncorrected. Elemental analyses are within 0.4% of theoretical values.

Method A (Table I). 5-Substituted 1,2,3,4-Tetrahydro-5*H*-indeno[1,2-*b*]pyridin-2-ones (4). The condensation of the aldehyde **3** and 5-oxo-5-phenylvaleronitrile to yield compounds **4** was performed as described in ref 2. The appropriate reaction time and the solvent for crystallization are listed in Table I.

Method B (Table II). H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridin-2-ones (5). The starting material (0.05 mol) was suspended in the appropriate solvent and hydrogenated over Raney nickel (half of the amount of substrate in grams). After the reaction was completed, the catalyst was removed by filtration and washed extensively with DMF. The combined organic layers were concentrated in vacuo, and the residue was recrystallized (see Table II). The following reaction conditions were applied (solvent; time; pressure; temperature). **5a**: DMF/MeOH, 2:1, 400 mL; 15 h, 50 atm, 80 °C. **5b**: DMF/MeOH, 1:1, 500 mL; 15 h; 60 atm; 60 °C. **5c**: DMF/MeOH, 250 mL, 20 h; 60 atm; 60 °C. **5d**: EtOH, 300 mL; 15 h; 100 atm; 80 °C. **5e**: EtOH, 600 mL; 15 h, 100 atm, 80 °C. **5f**: EtOH, 300 mL; 15 h; 100 atm; 100 °C. **5g**: EtOH, 600 mL; 15 h; 100 atm; 80 °C. **5h**: DMF, 800 mL; 20 h; 50 atm; 50 °C. **5i**: EtOH, 600 mL; 18 h; 80 atm; 90 °C.

Method C (Table III). H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-1-Alkyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridin-2-ones (6). The alkylation of compounds **5** to yield compounds **6** was accomplished according to ref 2.

Method D (Table IV). H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines (7). The reduction of compounds **5** and **6** with LAH was carried out as described in ref 2.

Method E (Table V). H_{4a},H_5-*trans*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines (8). The epimerization of compounds **7** in butanol in the presence of KOH follows the directions given in ref 2.

Method F (Tables IV and V). Phenol Ether Cleavage in Hydrogen Bromide/Acetic Acid. Directions for this reaction are given in ref 2.

Method G (Table IV). Phenol Ether Cleavage in Pyridinium Chloride. The reaction was carried out as described in ref 2.

Method H (Table IV). N-Methylation of 2,3,4,4a,5,9b-Hexahydro-1*H*-indeno[1,2-*b*]pyridines (7u,w). Methylation with formic acid was achieved according to ref 2.

H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-1-Methyl-5-(4-aminophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridin-2-one (11). Under vigorous stirring, 30.6 g (0.1 mol) of 5-(4-nitrophenyl)-1,2,3,4,-tetrahydro-5*H*-indeno[1,2-*b*]pyridin-2-one was refluxed in 500 mL of hydrochloric acid (aqueous HCl (35%)/H_2O, 1:1). The crude reaction product remains undissolved. After the aqueous layer was removed, the product was taken up in bicarbonate solution, cleared with Norite, and acidified (pH 2). The acid was taken up in methylene chloride, which was dried and evaporated. The crude keto acid **9** remained as a viscous, dark yellow oil [R_f 0.65 ($CHCl_3$/CH_3OH, 8:2)].

This crude acid was dissolved in 300 mL of 14% methylamine solution in methanol and kept at room temperature for 15 h. Then, Raney nickel was added, and hydrogenation was started (2 h, 50 °C, 50 atm, following 18 h, 90 °C, 100 atm). The catalyst was removed, and the solution was concentrated to 100 mL. After the solution was cooled the H_{4a},H_5-*cis*,H_{4a},H_{9b}-*cis*-1-methyl-5-(4-aminophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]-pyridin-2-one (11) precipitated and was collected on a Buchner funnel: yield 6.4 g (19%); mp 218–221 °C. Anal. ($C_{19}H_{20}N_2O$) C, H, N.

Pharmacology. Acute Toxicity in Mice after Intraperitoneal Administration. Male mice (SPF-71, KF: NMRI) weighing 20–30 g were used and randomly assigned to test groups of 10 subjects. The test compound was suspended in 1% methylcellulose (MH 300 medium viscosity, Fluka) and administered orally or intraperitoneally at the volume of 10 mL/kg of body weight.

After drug administration, groups of 10 mice were placed into a size B perspex cage with food and water ad libitum. They were

observed at hourly intervals up to 6 h after drug administration. Dead animals were removed, and the number of dead animals was recorded at 24 and 48 h after drug administration. The LD_{50} with 95% confidence limits was estimated by the method of Spearman Kaerber.[9]

Prevention of Tetrabenazine-Induced Ptosis in Mice. Male mice (SPF-71, KF: NMRI) weighing 20–30 g were used and randomly assigned to test groups of 10 subjects. All compounds were dissolved or suspended in 1% methylcellulose (MH 300 medium viscosity, Fluka) and administered in volumes of 10 mL/kg of body weight. The tetrabenazine solution was made from the methanesulfonate salt (76.8%), and the concentration was adjusted to allow administration, by ip injection, of 40 mg/kg of the tetrabenazine base.

The test compounds were administered ip, 30 min prior to TBZ. A control group was run with each test and received a solvent (1% MH) and TBZ by routes and at time intervals identical with the respective drug groups.

Thirty minutes after TBZ administration, the subjects were placed in individual plastic cages, and 1 min later, they were scored for ptosis on the following scale: eyes closed, 100% ptosis; eyes half closed, 50% ptosis; eyes wide open, 0% ptosis. Solvent control groups demonstrated 90 to 100% ptosis, and, therefore, the ptosis scores were not normalized. The ED_{50} values and 95% confidence intervals (CI) calculated by a computer program of linear regression analysis represent the dose at which 50% TBZ-induced ptosis was prevented.

Spontaneous Motor Activity (SMA) in Mice (2 h). Spontaneous motor activity was measured on electromagnetic sensors (LKB-ANIMEX): The sensor field measured 36 × 32 cm, and upon each was placed a 38 × 24 × 16 cm plastic cage. Groups of five male mice (20 to 30 g) were placed in each cage, and their combined activity provided an SMA count. The counts were recorded by an electronic printer at 5-min intervals. The counts were transformed into percent of controls to normalize the data, and control scores were compared with scores from compound-treated subjects by Student's *t* test.

A control group was included with every test sequence, and all subjects compared were taken from a single animal shipment. In order to maximize group homogeneity, all test animals were removed from their home cages and brought to the laboratory at least 45 min prior to the start of any testing. The mice were randomly assigned to various test groups, and the test compound was administered orally. Sixty minutes after dosing, the subjects were placed in the SMA chambers, and scores were recorded for 2 h in 5-min intervals.

Biochemistry. Uptake of Biogenic Amines by Synaptosomes.[10] [^{14}C]NA (55 mCi/mmol), [^{14}C]-5-HT (57 mCi/mmol), and [^{3}H]DA (2.3 Ci/mmol) were purchased from the Radiochemical Center (Amersham). All reagents used were of analytical grade.

Synaptosomal fractions from rat brain were obtained according to the method of Whittaker.[11] Synaptosomal uptake of [^{14}C]NA and [^{14}C]-5-HT was measured with Krebs–Henseleit bicarbonate buffer, pH 7.4, containing 11 mmol of glucose, whereas phosphate buffer was used for studying [^{3}H]DA uptake in synaptosomes from the corpus striatum.[12] Aliquots (2.5 mL) were taken from the synaptosome suspensions, and the samples were incubated with labeled monoamine (1×10^{-7} mol final concentration) at 37 °C in a shaking water bath in the presence or absence of drugs. Incubation time was 5 min with synaptosomes from whole brain, 10 min with synaptosomes from hypothalamus, and 3 min with striatal synaptosomes. The reaction was terminated by cooling the tubes in ice. To determine nonspecific adsorption, we incubated control samples at 0 °C in otherwise identical conditions.

The amount of accumulated monoamine was evaluated by the membrane filtration technique,[13] using a Millipore sampling manifold (Millipore GmbH, Neu-Isenburg) with cellulose nitrate filters, 25 mm in diameter and with 0.6-μm pore size (Sartorius GmbH, Göttingen). After the synaptosomes were collected under mild vacuum, the filters were transferred into counting vials and dissolved in 10 mL of scintillation fluid. Radioactivity of the samples was determined in a Packard Tricarb liquid scintillation counter, and the amount of monoamine accumulated by the synaptosomes was expressed as percentage radioactivity added to the incubation mixture.

IC_{50} values were evaluated as the concentration of drug inhibiting the uptake of either [^{14}C]NE, [^{14}C]-5-HT, or [^{3}H]DA by 50%. For each drug, three or four concentrations were used at least in triplicate.

Registry No. 1 ($R^1 = R^2 = H$), 10413-00-0; 1 ($R^1 = OCH_3$; $R^2 = H$), 26823-02-9; 1 ($R^1 = R^2 = OCH_3$), 54959-84-1; **1A**, 46955-93-5; **1B**, 38522-91-7; **2A**, 81202-76-8; **2B**, 88763-06-8; **3A**, 88823-34-1; **3B**, 88763-07-9; **4A**, 88763-08-0; **4B**, 81244-26-0; 4 ($R^1 = R^2 = H$; $R^3 = 4\text{-}NO_2C_6H_4$), 81152-87-6; **4a**, 88687-48-3; **4b**, 88687-17-6; **4c**, 88687-18-7; **4d**, 88687-19-8; **4e**, 88687-20-1; **4f**, 88687-21-2; **4g**, 88687-22-3; **4h**, 88687-23-4; **4i**, 88687-24-5; **5A**, 88823-35-2; **5B**, 88763-09-1; **5a**, 88762-95-2; **5b**, 88762-96-3; **5c**, 88687-25-6; **5d**, 88687-26-7; **5e**, 88687-27-8; **5f**, 88687-28-9; **5g**, 88687-29-0; **5h**, 88762-97-4; **5i**, 88687-30-3; **6A**, 88763-10-4; **6B**, 88763-11-5; **6a**, 88687-31-4; **6b**, 88762-98-5; **6c**, 88687-32-5; **6d**, 81153-15-3; **6e**, 81202-69-9; **7A**, 88823-36-3; **7B**, 88763-12-6; **7a**·HCl, 88687-33-6; **7b**·2HCl, 88823-25-0; **7c**·HCl, 88687-34-7; **7d**·HCl, 88823-49-8; **7e**·HCl, 88687-35-8; **7f**·HCl, 88762-99-6; **7g**·HCl, 88687-36-9; **7h**·2HCl, 88687-37-0; **7i**·HCl, 88687-38-1; **7j**·HCl, 88687-39-2; **7k**·HCl, 88687-40-5; **7l**·2HCl, 88687-41-6; **7m**·HCl, 88687-42-7; **7n**·HCl, 88763-99-9; **7o**·HCl, 88687-43-8; **7p**·2HCl, 88687-44-9; **7q**·HCl, 88823-26-1; **7r**·HCl, 88823-27-2; **7s**·HCl, 81202-72-4; **7t**·HCl, 81153-16-4; **7u**·HCl, 88687-45-0; **7v**·HCl, 88687-46-1; **7w**·HCl, 81153-17-5; **7x**·HCl, 88687-47-2; **7y**·2HCl, 88687-16-5; **8A**, 88763-13-7; **8B**, 88763-14-8; **8a**·HCl, 88763-96-6; **8b**·HCl, 88823-28-3; **8c**·HCl, 88763-00-2; **8d**·HCl, 88823-50-1; **8e**·HCl, 88763-01-3; **8f**·HCl, 88823-29-4; **8g**·HCl, 88763-97-7; **8h**·HCl, 88763-02-4; **8i**·HCl, 88823-30-7; **8j**·HCl, 88763-03-5; **8k**·HCl, 88687-49-4; **8l**·2HCl, 88763-04-6; **8m**·HCl, 88823-31-8; **8n**·2HCl, 88823-32-9; **8o** maleate, 88823-33-0; **8p**·HBr, 88687-50-7; **8q**·HCl, 88763-05-7; **9**, 88687-53-0; **9A**, 88823-37-4; **9B**, 88763-15-9; **10A**, 88763-16-0; **10B**, 88763-98-8; 11, 88687-52-9; **11A**, 88763-17-1; **11B**, 88687-15-4; **12A**, 88823-38-5; **12B**, 88763-18-2; **13A**, 88823-39-6; **13B**, 88763-19-3; **14A**, 88823-40-9; **14B**, 88763-20-6; **15A**, 88763-21-7; **15B**, 88763-22-8; **16A**, 88763-23-9; **16B**, 88763-24-0; **17A**, 88763-25-1; **17B**, 88763-26-2; **18A**, 88823-41-0; **18B**, 88763-27-3; **19A**, 88763-28-4; **19B**, 88763-29-5; **20A**, 88763-30-8; **20B**, 88763-31-9; **21A**, 88763-32-0; **21B**, 88763-33-1; **22A**, 88763-34-2; **22B**, 88763-35-3; **23A**, 88763-36-4; **23B**, 88763-37-5; **24A**, 88763-38-6; **24B**, 88823-42-1; **25A**, 88763-39-7; **25B**, 88763-40-0; **26A**, 88763-41-1; **26B**, 88763-42-2; **27A**, 88763-43-3; **27B**, 88763-44-4; **28A**, 88763-45-5; **28B**, 88763-46-6; **29A**, 88763-47-7; **29B**, 88763-48-8; **30A**, 88763-49-9; **30B**, 88763-50-2; **31A**, 88763-51-3; **31B**, 88763-52-4; **32A**, 88763-53-5; **32B**, 88763-54-6; **33A**, 88763-55-7; **33B**, 88763-56-8; **34A**, 88763-57-9; **34B**, 88763-58-0; **35A**, 81202-81-5; **35B**, 88763-59-1; **36A**, 88763-60-4; **36B**, 88763-61-5; **37A**, 88763-62-6; **37B**, 88763-63-7; **38A**, 88763-64-8; **38B**, 88763-65-9; **39A**, 88763-66-0; **39B**, 88763-67-1; $3\text{-}NO_2C_6H_4CHO$, 99-61-6; $4\text{-}CH_3C_6H_4CHO$, 104-87-0; $2\text{-}CH_3C_6H_4CHO$, 529-20-4; $4\text{-}CH_3\text{-}3\text{-}NO_2C_6H_3CHO$, 31680-07-6; $4\text{-}i\text{-}C_3H_7C_6H_4CHO$, 122-03-2; $4\text{-}(CH_3)_2NC_6H_4CHO$, 100-10-7; C_6H_5CHO, 100-52-7; $2\text{-}F\text{-}C_6H_4CHO$, 446-52-6.

(9) Cavalli-Sforza, L.; Lorenz, R. J. "Biometrie-Grundzüge Biologischmedizinischer Statistik"; Gustav Fischer Verlag: Stuttgart, 1969; p 171–173.
(10) Schacht, U.; Heptner, W. *Biochem. Pharmacol.* **1974**, *23*, 3143.
(11) Whittaker, V. P. *Handb. Neurochem.* **1969**, *2*, 327.
(12) Kuczenski, R. *Neuropharmacology* **1975**, *14*, 1.
(13) Hendley, E. D.; Snyder, S. H.; Fanley, J. J.; Lapidus, J. B. *J. Pharmacol. Exp. Ther.* **1972**, *183*, 103.