Resolution, Absolute Stereochemistry, and Enantioselective Activity of Nomifensine and Hexahydro-1*H*-indeno[1,2-*b*]pyridines

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Nomifensine and three selected compounds from the series of H_{4a},H_5-*trans*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridines have been resolved into their enantiomers. All compounds exhibit pronounced enantioselective activity with respect to their inhibition of tetrabenazine-induced ptosis and potentiation of yohimbine toxicity. Nomifensine exhibits the same preference for one enantiomer with respect to dopamine and norepinephrine reuptake, whereas in the indeno[1,2-*b*]pyridine series in vitro experiments do not discriminate between the optical antipodes. The absolute stereochemistry of the pharmacologically active enantiomers in both series was determined by X-ray analyses and comparative CD spectra. For biological activity the diphenylmethane is an essential structure feature in both series. Its absolute configuration proved to be 4*S* for nomifensine and 5*S* for indenopyridines. The similar pharmacological profile of the two chemical entities is therefore reflected in an identical configuration of this pharmacologically important molecular part.

The enantioselective biological activity of psychotropic drugs is well-documented.[1] Reports on enantioselective activity with respect to biological experiments predictive for antidepressive activity in humans are available. For example, (1*S*,2*R*)-(+)-tranylcypromine is more active than its optical antipode in inhibiting rat liver MAO,[2] (*S*)-(+)-oxaprotiline is the more active form in inhibiting NE uptake,[3] (*S*)-(+)-mianserin is approximately 200–300 times more active than its antipode in the same test,[4] and (*S*)-viloxazine is about 10 times more active than its *R* isomer in the antagonism of reserpine-induced hypothermia in mice.[5] Recently a report on enantioselective inhibition of neuronal uptake of NE, DA, and 5-HT and of tetrabenazine-induced ptosis within the series of pyrrolo-[2,1-*a*]isoquinolines was published.[6]

In the course of our CNS research program we discovered a novel series of hexahydro-1*H*-indeno[1,2-*b*]pyridines that exhibits potent uptake inhibition for NE and DA.[7] The biological properties proved to be similar to the new antidepressant nomifensine.[8] In this study we report the biological activities of the enantiomers of hexahydro-1*H*-indeno[1,2-*b*]pyridines. Furthermore, these results are discussed in relation to the properties of the nomifensine enantiomers.

Chemistry

The synthesis of 2,3,4,4a,5,9b-hexahydro-1*H*-indeno-[1,2-*b*]pyridines has already been described.[7,9] Two diastereoisomeric series (**1**, **2**) are available. Biological activity was almost exclusively found in compounds **1**, bearing the relative configuration H_{4a},H_5-trans,H_{4a},H_{9b}-cis. Only compounds belonging to this series were resolved into their optical antipodes (**1a–c**) (Figure 1). Classical methodology furnished the pure enantiomers. L-(+)- and D-(−)-mandelic acids, respectively, were used to yield the diastereomeric salts of **1a** and **1b**. Recrystallization of the diastereomeric mandelates was performed in either a mixture of isopropyl alcohol, ethyl acetate, and diethyl ether (**1a**) or isopropyl alcohol (**1b**). Compound **1c** was resolved by crystallization of the diastereomeric di-*p*-toluoyl L-(+)- and D-(−)-tartrates in ethanol or a mixture of ethanol/water. The resolution was considered complete when the optical rotation did not change between two crystallization steps. The enantiomers were converted into their hydrochloride salts and all biological data refer to these derivatives. The physicochemical data of the compounds isolated during the resolution procedure are summarized in Table I.

The use of *N*-(phenylsulfonyl)-L-(+)-glutamic acid was most convenient in forming a diastereomeric salt with nomifensine (**3**). A maximum of optical purity was achieved by only two crystallization steps. The *N*-(phenylsulfonyl)-L-(+)-glutamic salt was purified and the free base, (+)-nomifensine, liberated in order to convert it to more suitable salts. The resulting mother liquors from the first crystallization steps were directly converted to their maleate salts, which were already optically pure [(−)-nomifensine]. Table II summarizes the physicochemical data of the compounds isolated.

A HPLC analysis was performed to further establish the enantiomeric purity of (+)- and (−)-nomifensine. Mosher's reagent [(*R*)-(+)- and (*S*)-(−)-2-methoxy-2-(trifluoromethyl)phenylacetic acid ((*R*)-(+)- and (*S*)-(−)-MPTA)] was used to convert the two enantiomers of nomifensine to their respective amides. Best separations were achieved with the amide made from (*R*)-(+)-MPTA and (+)-nomifensine and (*S*)-(−)-MPTA and (−)-nomifensine. With this method the optical purity of (−)-nomifensine was determined to be greater than 99.9% and (+)-nomifensine >98.7%. The same methodology failed when applied to the enantiomers of **1c**. Other methods for the determi-

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Table I. Physicochemical Parameters of 1*H*-Indeno[1,2-*b*]pyridine Enantiomers

compd	optical rotation	absolute confign	acid used for resolution	solvent used for resolution	specific rotation, deg (c 0.5, CH_3OH) free base	specific rotation, deg (c 0.5, CH_3OH) HCl	mp, °C (HCl)
1a	+	1*R*,4a*S*,5*R*,9b*S*[e]	D-(−)-mandelic acid	2-propanol, ethyl acetate, ether	−7.4[a]	+36.6	+42.4	266–267
	−	4a*R*,5*S*,9b*R*[f]	L-(+)-mandelic acid	ethyl acetate	+8.0[b]	−37.4	−44.0	266–267
1b	+	4a*R*,5*S*,9b*R*[f]	L-(+)-mandelic acid	2-propanol	+41.2[b]	+18.6	+8.2	232–234
	−	4a*S*,5*R*,9b*S*[f]	D-(−)-mandelic acid	2-propanol	−40.6[a]	−19.2	−7.8	230–232
1c	+	4a*S*,5*R*,9b*S*[f]	di-*p*-toluoyl L-(+)-tartaric acid	ethanol/H_2O (3:5)	−105.4[c]	+21.4	+8.6	328–330
	−	4a*R*,5*S*,9b*R*[f]	di-*p*-toluoyl D-(−)-tartaric acid	ethanol	+111.2[d]		−12.8	328–330

[a] D-(−)-mandelate. [b] L-(+)-mandelate. [c] Di-*p*-toluoyl L-(+)-tartrate. [d] Di-*p*-toluoyl D-(−)-tartrate. [e] Determined by X-ray analyses. [f] Determined by comparative CD spectra; identical spectra were recorded for (+)-**1a**, (−)-**1b**, (+)-**1c** and (−)-**1a**, (+)-**1b**, (−)-**1c**. In these cases an absolute configuration at position 1 cannot be assigned. One has to assume a nitrogen lone pair/hydrogen (methyl, *n*-propyl) inversion in solution. Therefore, it is likely to have an equilibrium between 1*R* and 1*S* configurated species.

Table II. Physicochemical Properties of Nomifensine Enantiomers

absolute confign	free base mp, °C	free base $[\alpha]^{20}_D$[a]	n-(phenylsulfonyl)-L-(+)-glutamic acid salt mp, °C	n-(phenylsulfonyl)-L-(+)-glutamic acid salt $[\alpha]^{20}_D$	hydrochloride mp, °C	hydrochloride $[\alpha]^{20}_D$[b]	maleate mp, °C	maleate $[\alpha]^{20}_D$[a]
4*S*	82–84	+78.1	201–204	*c*	233–236 dec	+54.9	183–185 dec	+34
4*R*	83–84	−77.8	*d*	*d*	232–235 dec	−54.8	184–186	−35.5

[a] In degrees (c 0.5, CH_3OH). [b] In degrees (c 0.5, H_2O). [c] Because of low solubility, no detection was possible. [d] No compound available.

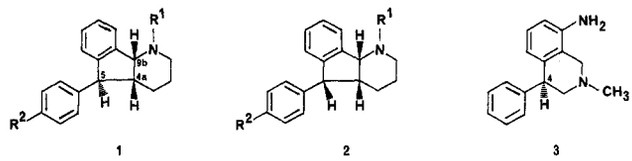

Figure 1. Illustration of the two diastereoisomeric hexahydro-1*H*-indeno[1,2-*b*]pyridines (**1**, **2**) in comparison to nomifensine (**3**).

nation of the enantiomeric purity of **1a–c** (for example, chiral stationary phases, NMR shift reagents) gave only poor results. Thus, in these cases a reliable enantiomeric excess could not be determined.

The absolute configuration was established in both chemical series by X-ray analyses. In the case of the indeno[1,2-*b*]pyridines, the most suitable crystals came from (+)-**1a** as D-(−)-mandelate. In the second series, (+)-nomifensine was examined as its *N*-4-bromobenzoyl derivative. The absolute configuration of (+)-**1a** was established as 1*R*,4a*S*,5*R*,9b*S*. The absolute configuration at position 1 is based on the lone electron pair of nitrogen as the fourth ligand. To what extent this configuration is retained in solution has not been determined.

The single cell unit of (+)-**1a** D-(−)-mandelate contains two conformationally different molecules (conformers A and B) (Figure 3). This difference is reflected in the torsion angle describing the tilting of the phenyl ring at position 5 (−133.2° and −125.0°). But, the overall conformation of the central tricyclic unit is practically identical in both conformers. The superposition (Figure 2) illustrates the small differences.

The absolute configuration of nomifensine was established as 4*S*. (+)-*N*-(4-Bromobenzoyl)nomifensine exists in two crystal modifications (needles and platelets). Both modifications were examined (Figure 5). The striking differences between these two are the position of the benzoyl side chain and a slight variation of the torsion angle describing the position of the free phenyl ring [129.8° (platelets) and 115.7° (needles)]. For illustration the two

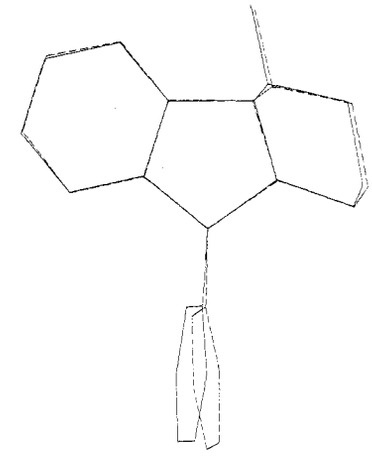

Figure 2. Superposition of the two conformers within the single-cell unit of (+)-**1a** (solid lines, conformer A; dashed line, conformer B). For clarification, the mandelic acid is not shown.

different conformers are superimposed in Figure 4.

The absolute configuration of (+)-**1a** determined by X-ray analysis was the basis of the correlation of the optical rotation of the enantiomers of **1b** and **1c** with the appropriate absolute configuration. For this reason CD spectra for all six enantiomers (+)- and (−)-**1a–c** were recorded. The reference compound (+)-**1a** exhibited a positive CD line at 271 nm (Figure 6). This line was attributed to the hydrindan system. The absolute configuration of the enantiomers of **1b,c** listed in Table I is based on the assumption that those compounds with a positive CD curve at 271 nm have the same absolute configurations as (+)-**1a**. It is interesting to note that, in compounds with identical configuration, the small change of the N-substituent from methyl in (+)-**1a** to *n*-propyl in (−)-**1b** causes a change in the direction of the optical rotation.

Biochemistry and Pharmacology

The antidepressant potential of the pure enantiomers was assessed by the prevention of tetrabenazine-induced ptosis in mice[10] and the potentiation of yohimbine-induced

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Table III. Pharmacological and Biochemical Data for (+)-, (−)-, 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 and (+)-, (−)-, and (±)-Nomifensine

					inhibn of monoamine uptake into rat brain synaptosomes			
		ED_{50},[a] mg/kg ip			in vitro IC_{50},[b] M			
compd	opt rotat	tetrabenazine-induced ptosis	yohimbine toxicity	LD_{50},[a] mg/kg ip	hypothalamus [^{14}C]NE	corpus striatum [^{3}H]DA	whole brain [^{3}H]-5-HT	ex vivo/in vivo IC_{50},[c] M
1a	±	0.4 (0.32–0.5)	1.3 (0.85–1.98)	46.7 (32.2–65.5)	1.2×10^{-7}	1×10^{-7}	$\sim 10^{-5}$	
	+	10 *inact*	5 *inact*	91 (74.8–110)	6×10^{-8}	1×10^{-7}	$>10^{-6}$	
	−	0.37 (0.31–0.45)	0.86 (0.75–1.29)	72 (57–91)	5×10^{-7}	3×10^{-7}	$>10^{-6}$	
1b	±	0.8 (0.3–2.3)	3.5 (2.4–5.0)	57 (38.7–82.6)	4.1×10^{-7}	1.1×10^{-7}	$>10^{-5}$	
	+	0.4 (0.31–0.53)	1.2 (0.8–1.84)	35 (27–45)	2×10^{-7}	2×10^{-7}	$>10^{-6}$	13 ± 2, 20 ± 2, 12 ± 3
	−	5 inact	5 inact	39 (30–51)	3.6×10^{-8}	4×10^{-8}	$>10^{-6}$	>90, 77 ± 9, 79 ± 7
1c	±	0.044 (0.026–0.073)	0.06 (0.04–0.1)	37 (28–50)	1.8×10^{-8}	4.4×10^{-8}	$>10^{-5}$	
	+	0.6 (0.47–0.8)	0.15 (0.13–0.23)	43 (31.5–58.3)	1.5×10^{-8}	5×10^{-8}	$>10^{-5}$	
	−	0.027 (0.019–0.036)	0.07 (0.04–0.13)	78 (60.2–100.3)	5×10^{-9}	2×10^{-8}	$>10^{-5}$	
nomifensine	±	0.72 (0.25–2.1)	1.1 (0.6–2.2)	141 (122–163)	3.2×10^{-8}	1.4×10^{-7}	1.2×10^{-5}	
	+	0.27 (0.16–0.41)	0.55 (0.22–1.4)	49.5 (34.7–70.7)	1.8×10^{-8}	5.3×10^{-8}	4.0×10^{-6}	
	−	>30	20.2 (12.1–33.7)	170 (estimate)	$\sim 10^{-5}$	$\sim 10^{-5}$	$>10^{-5}$	

[a] Values are calculated from five or six doses for each substance and $N = 5$. The 95% confidence limits are given in parentheses. [b] Values were determined graphically from the log concentration–response curves with four or five concentrations of each substance at least in triplicate. [c] Each value represents the mean ± SD of quadruplicate determinations of [^{14}C]NA uptake in a synaptosomal fraction of a pool of hypothalami from three rats, sacrificed after 1 h of treatment.

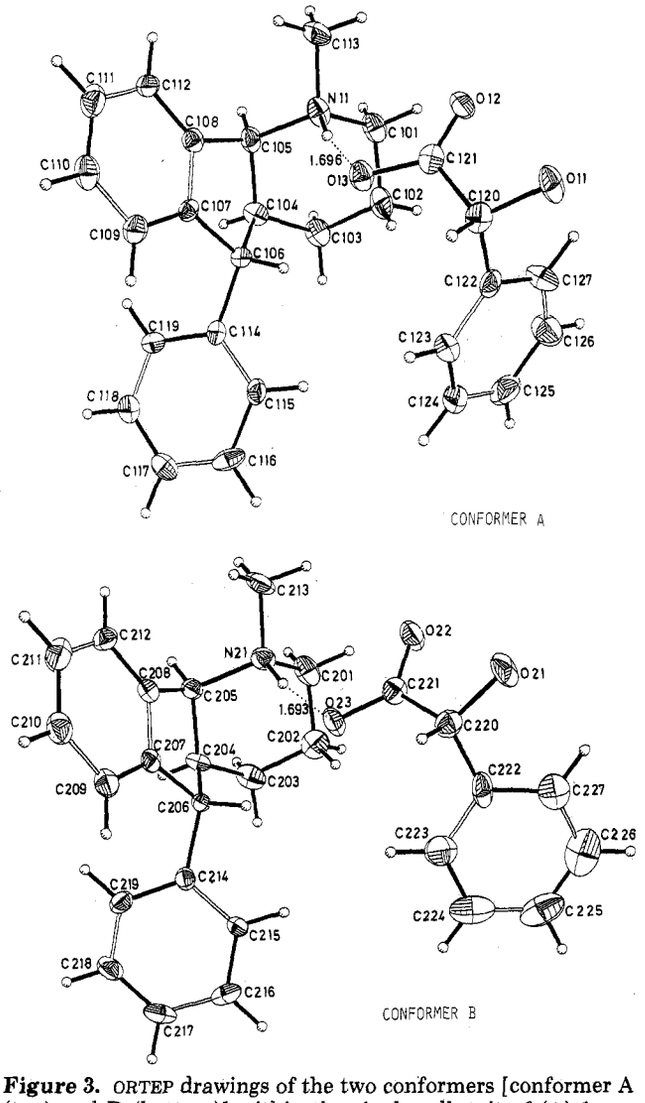

Figure 3. ORTEP drawings of the two conformers [conformer A (top) and B (bottom)] within the single-cell unit of (+)-**1a** as determined by X-ray analyses.

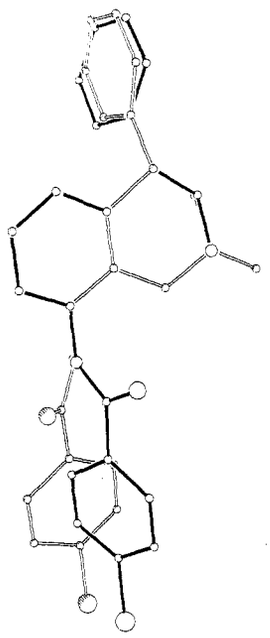

Figure 4. Superposition of the two modifications of (+)-8-[(4-bromobenzoyl)amino]-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (solid lines, platelets; open lines, needles).

toxicity[11] (ip routes). In addition to the pharmacological data, the reuptake inhibition of [^{14}C]NE, [^{3}H]DA, and [^{3}H]-5-HT into rat brain synaptosomes was determined.[12] For selected compounds [(+)-**1b** and (−)-**1b**] ex vivo/in vitro data on uptake inhibition of [^{14}C]NA (ip route) were established. The results are summarized in Table III.

Results and Discussion

The pharmacological data indicate for nomifensine and compounds **1a** and **1b** that only one enantiomer is responsible for the biological activity. The corresponding optical antipodes are devoid of any activity. Both enantiomers of **1c** are, however, still pharmacologically very potent. The less active (+)-enantiomer has an ED_{50} well below 1.0 mg ip in mice in the two pharmacological tests.

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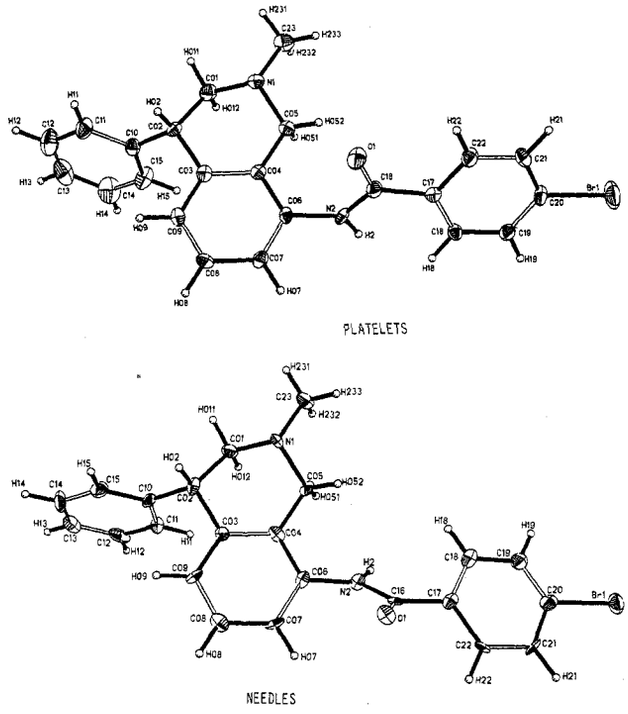


Figure 5. ORTEP drawing of the two modifications [platelets (top) and needles (bottom)] of (+)-8-[(4-bromobenzoyl)amino]-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline as determined by X-ray analyses.

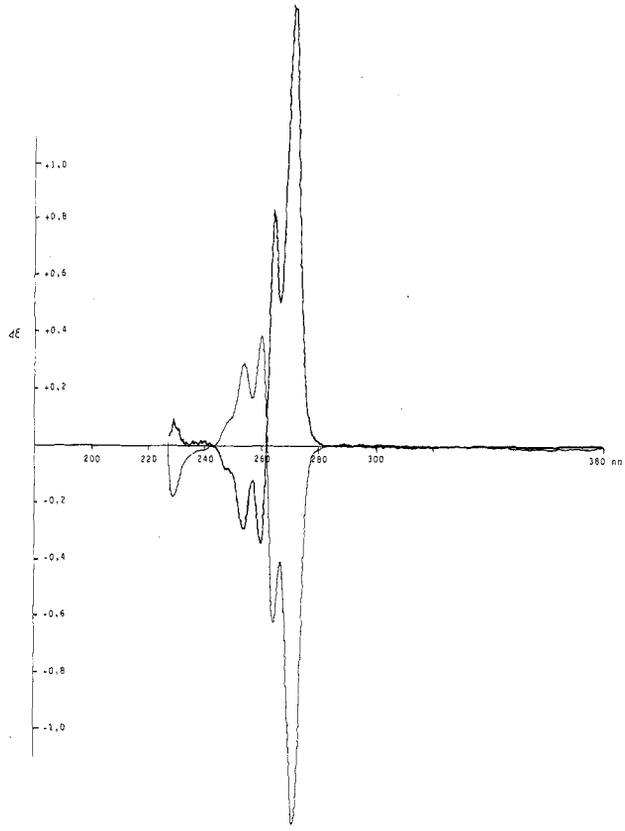
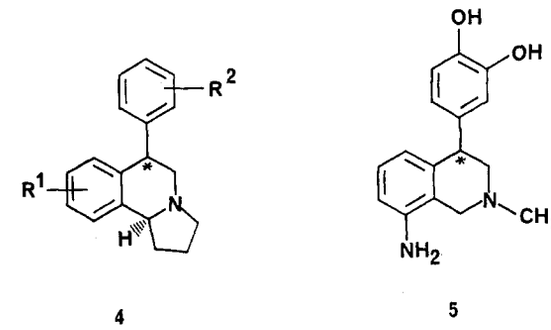


Figure 6. CD spectra of (+)-**1a** (*c* 0.326) (heavy line) and (−)-**1a** (*c* 0.379) (weak line) in ethanol. The CD spectra of (−)-**1b** and (+)-**1c** were identical with that of (+)-**1a**; those of (+)-**1b** and (−)-**1c** were identical with that of (−)-**1a**.

The more potent (−) enantiomer is approximately 30 times (tetrabenazine-induced ptosis) more active than the (+) antipode and about 3 times more active in the potentiation of yohimbine toxicity. It could be postulated that the less active enantiomer (+)-**1c** still contains some impurities of the very potent (−)-**1c** because it was not possible in this case to determine the enantiomeric excess in both enantiomers. However, in earlier studies we showed[7] that the introduction of the polar *p*-amino group probably overrules steric requirements that are necessary for activity. This explanation might hold true for (−)- and (+)-**1c**.



4 5

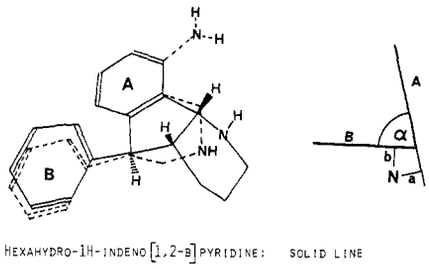
Figure 7. Examples for enantioselective active tetrahydroisoquinolines. Pyrrolo[2,1*a*]isoquinolines (**4**)[6] and dihydroxynomifensine[13] (**5**).

The results with nomifensine in the uptake-inhibition experiments are consistent with the pharmacological data. The (+) enantiomer is the active form, whereas the (−) enantiomer is almost completely devoid of any inhibitory activity. In contrast, hexahydro-1*H*-indeno[1,2-*b*]pyridines yield data more difficult to interpret.

Significant NE and DA uptake inhibition activity was found for all antipodes. These results are not reflections of the pharmacological data. Only in the case of **1c**, the (−) enantiomer is the more active antipode, both in vivo and in vitro. In contrast, the in vivo active enantiomers of **1a** and **1b** seem to exhibit less inhibitory activity in vitro. This is most pronounced with (+)-**1b** and (−)-**1b**. In this case the in vivo inactive (−)-**1b** is about 10 times more active in vitro than (+)-**1b**. With these results in mind, one might argue that in this series uptake inhibition is not a prerequisite to the in vivo activity. We attempted to clarify this by measuring the uptake inhibition of [^{14}C]NE ex vivo/in vitro after the treatment with (+)- and (−)-**1b** (10 mg/kg ip). In these experiments (−)-**1b** proved to be much less active than (+)-**1b**, in perfect agreement with the pharmacological data. We therefore have to assume that processes responsible for the kinetic and metabolic fate of the hexahydro-1*H*-indeno[1,2-*b*]pyridines discriminate between the two optical antipodes in vivo. These discriminative processes might not be optimal in selecting the most active compound for the target tissue. In the case of compound **1b**, only the in vitro less active enantiomer [(+)-**1b**] at the inhibition site reaches the pharmacologically relevant target, whereas the in vitro more active [(−)-**1b**] cannot reach it.

The X-ray data indicate that the biologically active enantiomer of nomifensine has a (+)-4*S* configuration. It is interesting to note that structurally related compounds with a slightly different biological profile exhibit the same preference for the absolute configuration. Pyrrolo[2,1-*a*]isoquinolines (**4**) contain the same structural fragment as nomifensine (Figure 7). The most interesting compound from this series (**4**, e.g., $R^{1,2}$ = H) exhibits in comparison to nomifensine, which is a selective NE and DA uptake inhibitor, an additional 5-HT-inhibitory activity. Yet, in the series of pyrrolo[2,1-*a*]isoquinolines[6] (**4**) and in nomifensine the absolute configuration of the asymmetric diphenylmethane fragment in the active isomer is identical. The enantiomers of the dihydroxy derivative of nomifensine (**5**) were tested for their dopaminergic ac-

Table IV. Geometrical Parameters Describing the Relative Position of the Nitrogen Atom



HEXAHYDRO-1H-INDENO[1,2-B]PYRIDINE: SOLID LINE
NOMIFENSINE: DASHED LINE

	nomifensine		indenopyridine	
	platelets[a]	needles[a]	conformer A[b]	conformer B[b]
α, deg	79.8	86.7	66.6	67.9
distance *a*, Å	0.53	0.53	1.23	1.40
distance *b*, Å	1.52	1.22	1.16	1.45

[a] Refers to the two different modifications. [b] Refers to the two different conformers within the single cell unit.

tivity.[13] An enantioselective activity is reported. The active enantiomer has a 4*S* configuration and is therefore in agreement with the active configuration of nomifensine and the interesting compounds within the pyrrolo[2,1*a*]-isoquinoline series.

The pharmacologically active enantiomers of **1a** and **1b** [(−)-**1a**, (+)-**1b**] possess identical absolute configuration. From the X-ray H_{4a},H_5-*trans*,H_{4a},H_{9b}-*cis*-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridines of (+)-**1a**, which is the inactive enantiomer of **1a**, it follows that the active enantiomers in the series of H_{4a},H_5-*trans*,H_{4a},H_{9b}-*cis*-2,3,4,5a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridines have a 4a*R*,5*S*,9b*R* configuration. Thus, the asymmetric diphenylmethane fragment of the in vivo active enantiomer in this series has the identical configuration (*S*) as in nomifensine. Additionally, in both series the nitrogen in the pharmacologically active enantiomers is located on top of the "roof", which is defined by the two aromatic planes. We have found this feature to be essential for activity.[14] Selected geometrical parameters are summarized in Table IV. They indicate the identical relative position of the basic nitrogen atom with respect to the aromatic planes (a = 0.53–1.40 Å, b = 1.16–1.52 Å) and the similarity of the angle formed by the two planes defined by the aromatic rings (66.6–86.7°). This is demonstrated by the superposition (Figure 8a,b) of the two X-ray structures. The aromatic planes of the diphenylmethane moiety can thus easily be matched by a least-squares fit. But a close comparison of the two X-ray structures reveals differences. The *N*-methyl bond in the two molecules points in different directions. The superposition indicates a difference of about 90°. Additionally, and probably more important, the position of the nitrogens differ substantially. This difference is characterized by the distance between the nitrogen and the center of the phenyl ring at positions 5 and 4, respectively. The values for the indeno[1,2-*b*]-pyridine and nomifensine are 5.95 (6.04) and 5.08 (5.14) Å, respectively.[15] This difference may account in part for

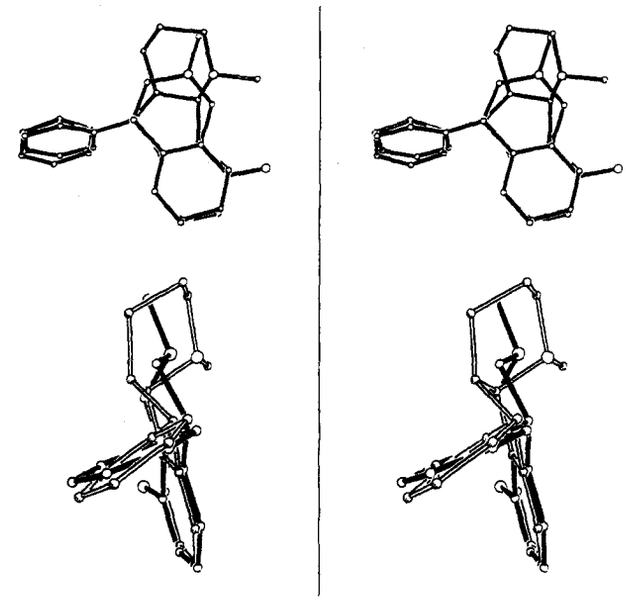


Figure 8. Superposition of the pharmacologically active enantiomers of **1a** and nomifensine [solid lines, (+)-nomifensine (4*S*), open lines, (−)-**1a** (5*S*)]. Steric view of two different positions. For clarification, the mandelic acid in (−)-**1a** and the 4-bromobenzoyl substituent in the (+)-nomifensine derivative are dismissed.

Table V. X-ray Data of Selected Phenylethylamines in Comparison to Nomifensine and Hexahydro-1*H*-indeno[1,2-*b*]pyridine

	τ_1	τ_2	distance between N and center of aromatic ring, Å
nomifensine, platelets	60.4	−173.7	5.14
nomifensine, needles	73.2	−167.8	5.08
phenethylamine[16] (hydrochloride)	72	171	5.16
dopamine (hydrochloride)[17]	79	174	5.14
amphetamine (sulfate)[18]	71–80	166–176	5.12–5.21
isoproterenol (sulfate)[19]	77	175	5.11
6-hydroxydopamine[20] (hydrochloride)	83	175	5.10
octopamine (hydrochloride)[21]	79	171	5.12
indenopyridine			5.95

the puzzling biological results with the hexahydro-1*H*-indeno[1,2-*b*]pyridine enantiomers compared to the nomifensine enantiomers.

The X-ray data of the phenylethylamine portion of nomifensine are in complete agreement with X-ray data reported for natural and synthetic phenylethylamines (Table V). The close relation of parts of the nomifensine molecule to natural substrates may therefore account for the high enantioselective action. Hexahydro-1*H*-indeno-

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(14) Kunstmann, R.; Fischer, G. *J. Med. Chem.* **1984**, *27*, 1312.
(15) The numbers in parentheses refer to the second molecule in the single cell unit of the 1*H*-indeno[1,2-*b*]pyridine and to the second modification of nomifensine; compare Table V.
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[1,2-*b*]pyridines differ from nomifensine in at least one important feature. They possess an incorporated propylamino instead of an ethylamino chain. This could be the reason for their lack of complete enantioselective action in vitro. The phenylpropylamino moiety does not fit the phenylethylamino receptor site. However, binding may be achieved at a closely related site (allosteric site), which is not capable of distinguishing clearly between two molecules of opposite configuration. In contrast, in vivo experiments exhibit an enantioselective action. Thus, kinetic and metabolic processes, which are not yet understood, discriminate between the two enantiomers. This leads to a correspondence in both series of in vivo activity and configuration (*S*). Whether this finding is only fortuitous or nature eliminates or deactivates selectively the "unnatural" configurated molecules more rapidly cannot be decided.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457 instrument), ^{1}H NMR (Varian A-60A instrument, tetramethylsilane), and MS (MS 902 S instrument, AEI) spectra. Optical rotation was detected with a polarimeter 141 (Perkin-Elmer instrument). CD spectra were recorded on a Mark III instrument (JSA), supported by a PDP-8 computer (DEC). For HPLC analyses a M 6000 A pump (Waters) was used in connection with a U 6 K high-pressure injection system and a spectral photometric detector (LC 55, Perkin-Elmer). Melting points were taken on a Tottoli apparatus (Büchi) and are uncorrected. Elemental analyses are within 0.4% of theoretical values.

(+)-8-Amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline [(+)-3]. At room temperature 142.8 g (0.6 mol) of (±)-8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline was treated with 172.2 g (0.6 mol) of *N*-(phenylsulfonyl)-L-(+)-glutamic acid in 5 L of ethanol. After the crystallization was finished, the crystals were isolated, and the free base was liberated by treatment with aqueous 2 N NaOH. Extraction with methylene chloride was followed by drying with magnesium sulfate and evaporation to dryness (yield of crude base, 73 g). The crude (+)-8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline was then converted to either one of the listed salts. Maleate: mp 183–185 °C dec; $[\alpha]^{20}_D$ +34.0° (*c* 0.5, CH_3OH). Anal. ($C_{16}H_{18}N_2 \cdot C_4H_4O_4$) C, H, N. Hydrochloride: mp 233–236 °C dec; $[\alpha]^{20}_D$ +54.9° (*c* 0.5, H_2O). Anal. ($C_{16}H_{18}N_2 \cdot HCl$) C, H, N.

(−)-8-Amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline [(−)-3]. The mother liquors from the crystallization of the *N*-(phenylsulfonyl)-L-(+)-glutamic acid with (±)-8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline were combined, and the crude free base was isolated by evaporation, treatment with aqueous 2 N NaOH, extraction with methylene chloride, and again evaporation and drying (yield, 61 g). The crude base was directly transferred to either one of the following salts in ethanol. Maleate: mp 184–186 °C dec; $[\alpha]^{20}_D$ −35.5° (*c* 0.5, CH_3OH) ($C_{16}H_{18}N_2 \cdot C_4H_4O_4$) C, H, N. Hydrochloride: mp 232–235 °C dec; $[\alpha]^{20}_D$ −54.8° (*c* 0.5, H_2O). Anal. ($C_{16}H_{18}N_2 \cdot HCl$) C, H, N.

Resolution of 1-Methyl-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (1a). In a mixture of 20 mL of 2-propanol, 20 mL of ethyl acetate, and 40 mL of diethyl ether, 5.26 g (0.02 mol) of (±)-1-methyl-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine was treated with 3.04 g (0.02 mol) of D-(−)-mandelic acid. A first crystalline crop was collected after the mixture was allowed to stand overnight at room temperature; 1.45 g; $[\alpha]^{20}_D$ −7.4° (*c* 0.5, CH_3OH). A second crop was isolated after evaporation of the mother liquor from the first crystallization step and recrystallization from 20 mL of ethyl acetate [1.3 g; $[\alpha]^{20}_D$ −7.8° (*c* 0.5, CH_3OH)]. The two combined fractions of the mandelic salts were converted to the free base. The hydrochloride was formed in a mixture of ethyl acetate and 2-propanolic HCl; yield 1.8 g (60%); mp 266–267 °C; $[\alpha]^{20}_D$ +42.4°.

The remaining mother liquors after isolation of the (+) enantiomer were combined, and the free base was isolated as a crude product (3.4 g, 0.012 mol). This was treated with 1.85 g (0.012 mol) of L-(+)-mandelic acid in 30 mL of ethyl acetate. The mandelic acid salt was formed (2.6 g, $[\alpha]^{20}_D$ +8°), which was converted in the above-mentioned manner to the hydrochloride: yield 1.6 g (53%); mp 266–267 °C; $[\alpha]^{20}_D$ −44.0° (*c* 0.5, CH_3OH).

Resolution of 1-*n*-Propyl-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (1b). In 15 mL of 2-propanol, 2.9 g (0.01 mol) of (±)-1-*n*-propyl-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine were combined with 1.5 g (0.01 mol) of D-(−)-mandelic acid at 50 °C. During the slow cooling process to room temperature (3–4 h) crystals of the mandelic acid salt were formed, which were collected (1.1 g; mp 136–137 °C; $[\alpha]^{20}_D$ −40.6° (*c* 0.5, CH_3OH). This salt was converted to the hydrochloride after liberation of the free base and treatment with 2-propanolic HCl in ethyl acetate; yield 0.95 g (58%); mp 230–232 °C; $[\alpha]^{20}_D$ −7.8°.

The mother liquor from the first crystallization step was evaporated to dryness and the free base isolated as crude material (1.5 g, 5.1 mmol). This material was dissolved in 10 mL of 2-propanol together with 0.76 g (5.1 mmol) of L-(+)-mandelic acid. A crystalline crop of the L-(+)-mandelic acid salt (1.1 g; $[\alpha]^{20}_D$ +41.2°) was collected and subsequently transformed to the hydrochloride (2-propanolic HCl/ethyl acetate); yield 0.4 g (54%); mp 232–234 °C; $[\alpha]^{20}_D$ +8.2°.

Resolution of 5-(4-Aminophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine (1c). To a mixture of 150 mL of ethanol and 250 mL of water, which was heated to 60 °C, was added 4.4 g (16 mmol) of (±)-5-(4-aminophenyl)-2,3,4,4a,5,9b-hexahydro-1*H*-indeno[1,2-*b*]pyridine together with 6.43 g (16 mmol) of di-*p*-toluoyl L-(+)-tartaric acid. After the mixture was slowly cooled and allowed to stand overnight, 2.9 g of a crude di-*p*-toluoyl L-(+)-tartrate was isolated. After six recrystallizations from ethanol the yield was 0.95 g; $[\alpha]^{20}_D$ −105.4°.

The base was liberated and converted to the hydrochloride in a mixture of ethyl acetate and 2-propanolic HCl; yield 0.52 g (21%); mp 328–330 °C; $[\alpha]^{20}_D$ +8.6°.

For the isolation of the (−) enantiomer, the same procedure was followed as described above except with di-*p*-toluoyl D-(−)-tartaric acid; yield 0.19 g (8%); mp 328–330 °C; $[\alpha]^{20}_D$ −12.8°.

HPLC Analysis. Derivatization of (+)- or (−)-Nomifensine. A solution of 45 mg (0.16 mmol) of (+)-nomifensine hydrochloride, 57 mg (0.23 mmol) of (−)-2-methoxy-2-(trifluoromethyl)phenylacetic acid chloride, 150 μL of ethyl diisopropylamine in 0.5 mL of 1,4-dioxane was kept at room temperature for 4–8 h. Water was added and the solution was extracted several times with dichloromethane. The organic layer was treated with aqueous 1 N HCl, 1 N NaOH, and saturated aqueous NaCl solution. After drying (Na_2SO_4) and evaporation, a suitable amount of the residue was dissolved and 5–10 μL was analyzed by HPLC. The following chromatographic conditions were used: column, LiChrosorb Si 60, 5 μm, 250 × 4 mm J. D. (Merck); mobile phase, *n*-hexane/ethyl acetate/methanol (4:1:0.1, v/v/v); flow, 1.5 mL/min; detection, UV at 254 nm. Result: content of (−)-nomifensine 99.9%, (+)-nomifensine 98.7%.

Pharmacology. Acute Toxicity in Mice after Intraperitoneal Administration.[7] Prevention of Tetrabenazine-Induced Ptosis in Mice.[7] Yohimbine-Induced Potentiation of Toxicity. Male mice (SPF-71, KF: NMRI) weighing 20–30 g were used and randomly assigned to test groups of 10 subjects. The compounds were dissolved in 1% methylcellulose (MH 300 medium viscosity, Fluka) and administered in volumes of 10 mL/kg of body weight. The test compounds were administered by ip route 30 min prior to the administration of yohimbine hydrochloride (20 mg/kg sc). After 18 h the number of dead animals was checked. An ED_{50} value was calculated at which 50% of the animals died.

Biochemistry. Uptake of Biogenic Amines by Synaptosomes.[7] Single-Crystal X-ray Analyses. The structures of (+)-**1a** D-(−)-mandelate and the two modifications (needles and platelets) of (+)-*N*-(4-bromobenzoyl)nomifensine were solved by X-ray analyses.

The X-ray intensities of the needles were measured on a Siemens diffractometer[22] and the intensities of the platelets and (+)-**1a** D-(−)-mandelate on a Nicolet diffractometer. The crystals

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Table VI. Cell Parameters and Other Characteristics of the X-ray Analyses of (+)-**1a** D-(−)-Mandelate and the Two Modifications of (+)-*N*-(4-Bromobenzoyl)nomifensine (Needles, Platelets)

	needles	platelets	(+)-**1a** D-(−)-mandelate
a, Å	24.68 (4)	12.224 (2)	14.319 (2)
b, Å	14.58 (2)	6.160 (1)	9.252 (2)
c, Å	5.53 (2)	13.086 (2)	17.967 (1)
β, deg		92.34 (1)	102.20 (1)
V, Å^3	1989.9	984.55	2326.5
space group	$P2_12_12_1$	$P2_1$	$P2_1$
M_r	421.35	421.35	415.53
Z	4	2	4
formula	$C_{23}H_{21}BrN_2O$	$C_{23}H_{21}BrN_2O$	$C_{27}H_{29}NO_3$
ρ_{calcd}, g/cm^3	1.406	1.421	1.186
ρ_{exptl} (in aqueous K_2HgI_4), g/cm^3	1.42	1.42	1.19
wavelength, Å	0.7107	0.7107	1.5418
unique reflections expected	1616	2617	2866
unique reflections measd	1616	2616	2866
measured reflections	1639	2732	3006
reflections $1\sigma(F)$	1544	1935	2438
reflections $2\sigma(F)$	1541	1651	2239
$R(1)$	10.66	10.01	8.0
$R(2)$, weighted according to the counting statistics	3.46	3.47	3.1

were sealed into a Mark tube to prevent atmospheric influences, to make handling easier, and to get unshadowed reflections. A $2\theta/\theta$ scan and a θ_{max} of 28° in the case of Mo radiation and a θ_{max} of 52.5° in the case of Cu radiation were used. The phase problem of the needles and (+)-**1a** D-(−)-mandelate could be solved by the direct method,[23,24] whereas in the case of the platelets the Patterson method had to be consulted. In all three cases the positions of the hydrogen atoms had to be calculated (C–H distance, 0.96 Å). In the least-squares refinement the cascade method[25] was applied. The refinement of the parameters was considered as finished when the largest change of a parameter was smaller than 10% of its standard deviation. The atomic scattering factors from ref 26 were used. All calculations and drawings were done with the SHELXTL program system.[25] The cell parameters and some characteristics are given in Table VI.

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Registry No. (±)-**1a**, 107035-04-1; (+)-**1a**, 107035-07-4; (+)-**1a**·D-(−)-mandelic acid, 107079-04-9; (+)-**1a**·HCl, 107079-05-0; (−)-**1a**, 107035-08-5; (−)-**1a**·L-(+)-mandelic acid, 107079-06-1; (−)-**1a**·HCl, 107079-07-2; (±)-**1b**, 107035-05-2; (+)-**1b**, 107035-10-9; (+)-**1b**·L-(+)-mandelic acid, 107079-10-7; (+)-**1b**·HCl, 107079-11-8; (−)-**1b**, 107035-09-6; (−)-**1b**·D-(−)-mandelic acid, 107079-08-3; (−)-**1b**·HCl, 107079-09-4; (±)-**1c**, 107035-06-3; (+)-**1c**, 107035-11-0; (+)-**1c**·di-*p*-toluoyl-L-(+)-tartaric acid, 107079-12-9; (+)-**1c**·HCl, 107079-13-0; (−)-**1c**, 107035-12-1; (−)-**1c**·di-*p*-toluoyl-D-(−)-tartaric acid, 107079-14-1; (−)-**1c**·HCl, 107079-15-2; (±)-**3**, 89664-19-7; (+)-**3**, 89664-18-6; (+)-**3**·maleic acid, 98461-27-9; (+)-**3**·HCl, 106976-98-1; (−)-**3**, 89664-20-0; (−)-3·maleic acid, 98461-26-8; (−)-**3**·HCl, 106976-99-2; L-(phenylsulfonyl)-glutamic acid, 20531-36-6; dopamine, 51-61-6; norepinephrine, 51-41-2; D-(−)-mandelic acid, 611-71-2; L-(+)-mandelic acid, 17199-29-0; di-*p*-toluoyl-L-(+)-tartaric acid, 32634-66-5; di-*p*-toluoyl-D-(−)-tartaric acid, 32634-68-7.

Supplementary Material Available: Atomic coordinates of (+)-**1a** D-(−)-mandelate (conformers A and B), atomic coordinates of (+)-8-[(4-bromobenzoyl)amino]-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (needles, platelets) as detected by X-ray analyses (4 pages). Ordering information is given on any current masthead page.

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