First Preparative Enantiomer Resolution of Pirlindole, a Potent Antidepressant Drug

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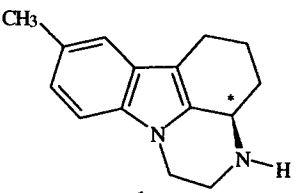
Pirlindole is an antidepressant drug. It acts principally as reversible inhibitor of monoamine oxidase-A (RIMA) and appears relatively potent in comparison with reference drugs. Pirlindole possesses stereogenic center but is generally used as racemate. In this work, the first preparative resolution of its enantiomeric couple is described. Whereas selective crystallization of salts of chiral acid failed, two asymmetric synthetic pathways were also examined; however, without success. Finally separation and isolation of enantiomers of pirlindole was completed by using the derivatization method coupled with preparative HPLC. Optical purity of each isomer was determined by chiral HPLC. The specific rotation of each antipode was also determined.

Introduction. – Pirlindole (= 8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j*,*k*]-carbazole hydrochloride) was characterized as a potential antidepressant drug [1–3]. A recent review has been entirely devoted to the preclinical properties of pirlindole [4]. Its activity is related to a selective reversible inhibition of monoamine oxidase-A (RIMA) [5]. In clinical trials, the efficacy and safety of pirlindole have been demonstrated in comparison with placebo [6] and reference standard drugs such as maprotiline [7], imipramine [8], amitriptyline [9], mianserin [10], and, very recently, moclobemide [11].



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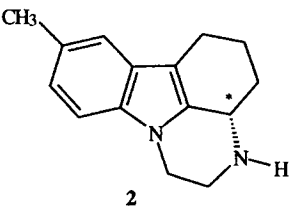

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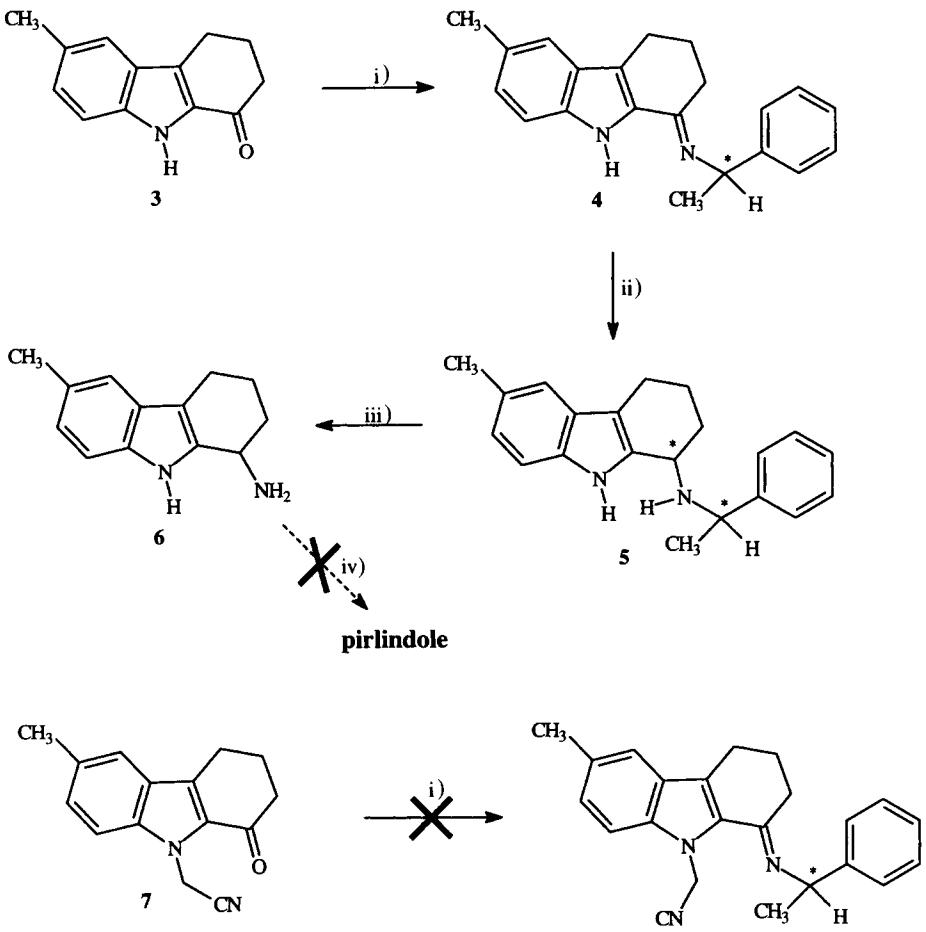
Pirlindole possesses one stereogenic center. Since resolution of the two enantiomers, **1** and **2**, has never been attempted, pharmacological tests have been so far performed on the racemate. Therefore, the resolution of the enantiomers appeared to be very interesting in order to study the influence of configuration on the pharmacological properties of this drug. Herein, we present the first optical separation of the two isomers of pirlindole at a preparative scale.

We first attempted at the conventional selective crystallization of pirlindole salts with optically active acids. However, the racemate appeared to resist resolution with different acids such as L-tartaric acid, L-mandelic acid, (+)-camphor-10-sulfonic acid, (−)-dibenzoyltartaric acid, and L-naproxen.

As a classical preparative approach to optical resolution, two different asymmetric synthetic pathways were examined. Because of the failure of the synthetic approach, resolution was eventually accomplished by an indirect separation method based on the reaction of the secondary amine function of pirlindole with different chiral derivative agents (CDA). The optical rotation of the two enantiomers was also determined.

Results and Discussion. – *Schemes 1* and *2* present the two attempted stereoselective synthetic routes to the enantiomers of pirlindole. The first pathway (*Scheme 1*) was based

Scheme 1



i) (*R*)- or (*S*)- *α*-Methylbenzylamine. *ii*) $BH_3 \cdot THF$. *iii*) Pd/C 10%, H_2. *iv*) Ring closure agents such as 1,1-dibromoethane, 2-bromoethanol, or cyanomethylbenzenesulfonate.

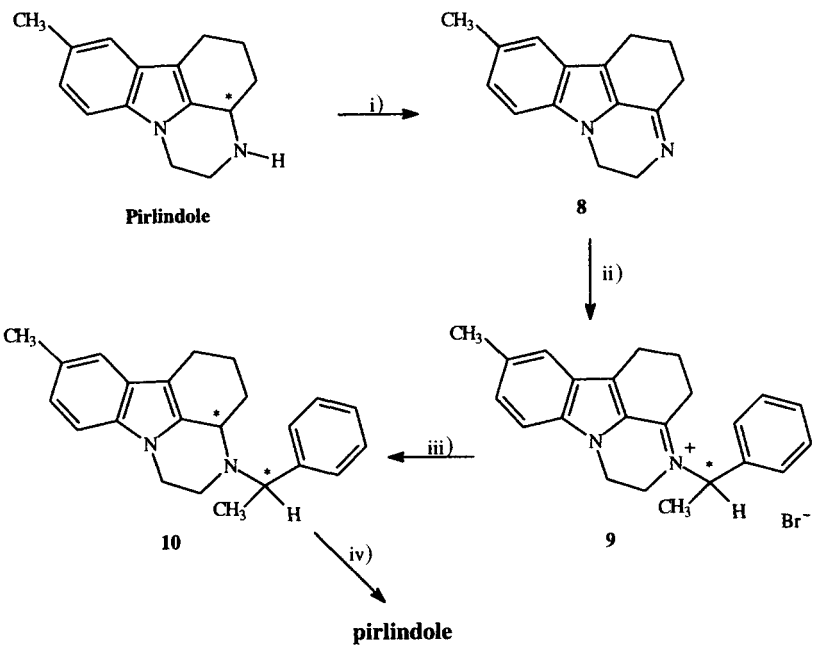
on the classical synthesis of pirlindole [12][13]. 1-Phenylethylamine was used as a chiral auxiliary [14]. Thus, reaction of the 1,2,3,4-tetrahydro-6-methylcarbazol-1-one intermediate (**3**) with (*R*)- or (*S*)-1-phenylethylamine gave the corresponding chiral imines **4**. Reduction of the imine function with $BH_3 \cdot THF$ should result in the addition of hydrogen to the less bulky face. This reaction led, after classical debenzylation, to the expected optically pure amino intermediates **6**. As all our attempts at ring closure failed, we did not verify the stereoselectivity of the reduction step.

To resolve this ring closure, another intermediate was used: 1,2,3,4-tetrahydro-6-methyl-1-oxo-9*H*-carbazole-9-acetonitrile (**7**). Unfortunately, this condensation was also unsuccessful.

The second asymmetric synthetic route to pirlindole (*Scheme 2*) was also based on the principle of stereospecific reduction, and again 1-phenylethyl synthon was used as chiral auxiliary.

Racemic 1-phenylethyl bromide was used to introduce the second asymmetric center. The reaction of the starting material, the dehydropirlindole (**8**), with the chiral reagent led, by alkylation of the imine function of **8**, to the iminium salt **9**, as a mixture of enantiomers (*Scheme 2*). Reduction with $NaBH_4$ yielded the corresponding amine **10**. The ^1H- and ^{13}C-NMR spectra of **10** indicated that a mixture of enantiomers was formed. According to these data and to the fact that the auxiliary used was a racemate, preferred addition of the hydride ion on the less bulky face appeared to be confirmed. Indeed, a non-stereospecific reduction of the mixture **9** would furnish a mixture of diastereoisomers, easily distinguishable by NMR. However, the decisive difficulty of this

Scheme 2

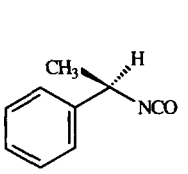


i) $K_2Cr_2O_7$, AcOH. *ii*) 1-Phenethyl bromide, $MeNO_2$. *iii*) $NaBH_4$. *iv*) Pd/C 10%, H_2.

route lay in the availability of the optically pure 1-phenylethyl electrophilic synthon. Indeed, it was reported in the literature that, depending on the reagent used, halogenation of commercially available (*R*)- or (*S*)-1-phenylethyl alcohol gave generally rise to partial or total racemization [15–17]. Moreover, because of stability problems, it was also impossible to isolate optically active 1-phenylethyl tosylate or mesylate [18][19]. Therefore, some other indirect resolution methods and, particularly, derivatization strategies were taken into consideration. A promising approach was the one using chiral derivative agents (CDAs) in order to obtain separable diastereoisomers with the enantiomers.

To accomplish preparative-scale resolution of pirlindole, the CDA to be used should satisfy certain requirements. Indeed, CDA for this application should preferentially be commercially available, of low cost, or easily accessible. Hydrolysis of the separated diastereoisomers, allowing the isolation of the optically active enantiomers, represented, compared to an analytical approach, the restrictive step of this strategy. Recoverability of the CDA after the final hydrolytic step would also represent a great advantage. Moreover, a suitable analytical method was required to determine the final chiral purity.

Considering these different parameters and the data from the literature, we chose the following CDAs: (*R*)-1-phenylethyl isocyanate (**11**) [20], (*R*)-1-(naphthalen-1-yl)ethyl isocyanate (**12**) [21], (−)-menthyl chloroformate (**13**) [22], L-naproxen chloride, (**14**) [23],



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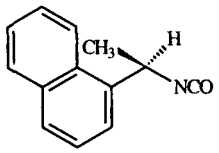

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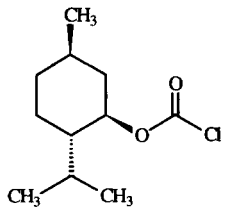

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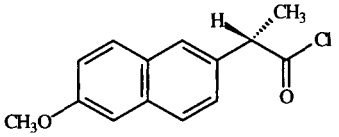

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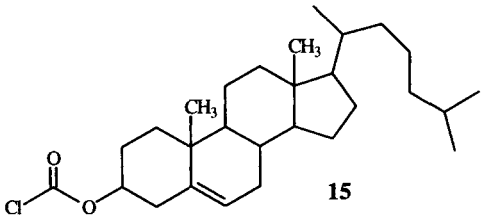

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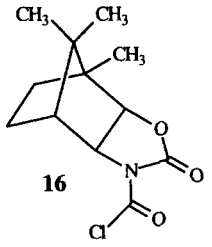

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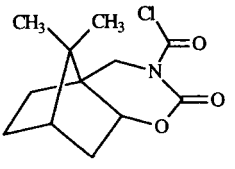

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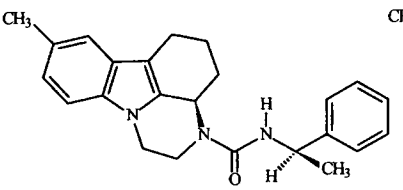
cholesteryl chloroformate (**15**), and two *endo*-borneol derivatives [24], namely [(2*R*,6*S*)-*endo*]-5-(chloroformyl)-1,10,10-trimethyl-3-oxa-5-azatricyclo[5.2.1.$0^{2,6}$]decan-4-one (**16**) and [(6*S*)-*endo*]-3-(chloroformyl)-11,11-dimethyl-5-oxa-3-azatricyclo[6.2.1.$0^{1,6}$]undecan-4-one (**17**), which were described as very effective CDAs for racemic amines but were obtained from a difficult five-steps synthetic route [25]. All other agents were commercially available. Pirlindole hydrochloride was converted into the corresponding base and then derivatized with the different CDAs. Except for the (−)-menthyl derivative, all diastereoisomers formed were isolated as white solids and characterized by different classical analytical techniques. First, TLC was used to check the resolution potency of the CDA and to evaluate the feasibility of a liquid chromatography separation. *Table 1* shows the highest R_f differences (ΔR_f) between the diastereoisomers obtained and the selected agent of derivatization, using several mobile phases.

Table 1. *Yields of Derivatization Step of Pirlindole, Highest* ΔR_f *Obtained, and the Mobile Phase Used*

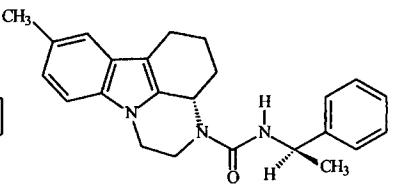
CDA	Product No. Yield [%]	ΔR_f	Mobile phase
11	**18** (95)	0.05	cyclohexane/$CHCl_3$/Et_3N 15:5:2
12	**19** (85)	0.02	petroleum ether (40–60°)/AcOEt 9:11
13	no pure product	no separation	
14	**20** (65)	0.15	petroleum ether (40–60°)/AcOEt 15:5
15	**21** (75)	no separation	
16	**22** (70)	0.15	hexane/AcOEt 16:4
17	**23** (55)	0.05	cyclohexane/$CHCl_3$/Et_3N 15:5:2

Among those CDA, reagents **14** and **16** gave two isomers, **20** and **22** (see *Exper. Part*), respectively, clearly separable on TLC. Classical flash chromatography (silica gel *60*, *Merck*-Darmstadt; 230–400 mesh ASTM) allowed preparative isolation of the pure diastereoisomers **20** and **22**. Subsequent hydrolysis was required to recover the optically pure enantiomers of pirlindole. Compound **14** formed an amide linkage with the secondary amine function of pirlindole. Unfortunately, all attempts to cleave this amide bond failed even under strongly basic (10–30% NaOH or KOH in EtOH, N_2, reflux; MeLi, Et_2O) or acidic conditions (70% H_2SO_4, Δ; 12N HCl, Δ, MeOH; or 70% $HClO_4$, Δ; or CF_3COOH, Δ). Basic hydrolysis (10% NaOH or KOH, in EtOH N_2, reflux) of the diastereoisomers obtained with **16** led to the final release of pirlindole. However, these conditions led to complete destruction of the CDA. This fact is quite important considering the aimed preparative scale of the resolution and the difficulties in obtaining the chiral reagent. Regarding these different problems, CDA **11**, though its resolution potency appeared to be comparatively lower on racemic pirlindole, turned out to be an interesting alternative. Indeed, this commercially available reagent, reacted very rapidly with pirlindole to give, in good yield, the corresponding urea derivatives **18a** and **18b**.

Isolation and purification of **18a** and **18b** turned out to be very easy. Separation of the diastereoisomers appeared to be difficult by flash chromatography but was attained by preparative HPLC. Finally, basic hydrolysis furnished, in very good yields, optically pure enantiomers **1** and **2**. This route, in spite of the relative slowness of the HPLC



18a



18b

procedure, appears to be the most favorable in order to isolate small amounts ($\pm$ 2 g) of each enantiomer of pirlindole. Optical and chemical purity of each enantiomer were determined by chiral HPLC [26], classical HPLC, elemental analysis, and spectroscopical methods. The optical rotation measurements were conducted in methanolic solutions of the pure isomers. *Table 2* presents the capacity factor (k'), the selectivity (α), and the resolution factor (R_s) of the diastereoisomers obtained by reaction of **11** with pirlindole under the conditions of the preparative HPLC, and of the two enantiomers under the conditions of the chiral HPLC, the specific rotations ($[\alpha]_D$), and the ee values. The melting points of the two pure isomers of pirlindole are almost identical and lower than the melting point of the racemic mixture. This fact seems to indicate that pirlindole is indeed a racemate.

Table 2. *Chromatographic Data of the Diastereoisomers and Enantiomers of Pirlindole, Specific Rotation, and ee Values*

Enantiomer	k'(diastereoisomer)[a])	k' (chiral HPLC)[b])	$[\alpha]_D$ (c)[c])	ee
1	18.9 (α = 1.13, R_s = 1.72)	1.82 (α = 1.75, R_s = 5.2)	−105.26° (0.00475)	>99.5
2	16.7 (α = 1.13, R_s = 1.72)	1.05 (α = 1.75, R_s = 5.2)	+105.16° (0.00485)	>99.5

[a]) HPLC Data of **18a** and **18b** under the conditions described in the *Exper. Part.* [b]) HPLC Data of **1** and **2** the conditions described in the *Exper. Part.* [c]) Specific rotation with c = concentration in g/ml

Resolution of pirlindole and isolation of sufficient amounts of the two enantiomers should permit the study of the stereochemical influence at the pharmacological level [27][28].

Experimental Part

General. Elemental analyses (C, H, N, S): *Carlo-Erba EA 1108* elemental analyzer, within $\pm$ 0.4% of theoretical values. M.p.: *Büchi-Tottoli* cap. apparatus, uncorrected. IR Spectra: as KBr pellets on a *Perkin-Elmer 1750 FT* spectrophotometer. ^{1}H-NMR Spectra: *Bruker AW-80* (80 MHz) instrument, in (D_6)DMSO or $CDCl_3$ with HMDS as internal standard. ^{13}C-NMR Spectra: *Bruker AM-400* (400 MHz) instrument, in (D_6)DMSO; chemical shifts δ [ppm] relative to internal HMDS. TLC: silica gel, *Merck 60F 254*. Chiral LC: *L-6200 A* pump, *AS-2000 A* autosampler equipped with a 100-µl loop, *L-5025* programmable column oven, and *L-4250* UV-VIS detector, all from *Merck-Hitachi*. Prep. HPLC *L-6210* pump, *AS-4000 A* autosampler equipped with a 500-µl loop, fraction collector *L-5200*, all from *Merck-Hitachi*, and a *SpectraSystem UV2000* detector from *Spectraphysics*. Optical rotation: solutions of enantiomers in MeOH (5 mg/ml), *Jasco ORD/UV-5* ORD recorder at 589 nm and 25°. MS: Electrospray MS (*VG* platform *Fission*), following the FAB procedure.

6-Methyl-1,2,3,4-tetrahydrocarbazol-1-one (**3**). The title compound was obtained according to the literature [12][13].

6-Methyl-1-{[(R)-1-phenylethyl]imino}-1,2,3,4,-tetrahydrocarbazole Hydrochloride (**4**). Compound **3** (4.0 g) and (*R*)-1-phenylethylamine (6 ml) were dissolved in dry toluene (50 ml). A catalytic amount of TsOH was added to the soln. The mixture was heated under reflux in a *Dean-Stark* apparatus for 5 h. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$. The org. layer was washed with 1N HCl, and the solvent was removed under reduced pressure. To the oily residue, a minimal volume of AcOEt was added and the mixture saturated with HCl (g). Et_2O was added until complete precipitation. The yellow precipitate was collected by filtration, washed with Et_2O, and dried: 55%. M.p. 186–189°. IR (KBr): 3104, 3060 (arom. C–H); 2976, 2923 (aliph. C–H); 1614 (C=N); 1532, 1496 (C=C). ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.4 (*d*, MeC–N); 1.9 (*m*, 2 H–C(3)); 2.4 (*s*, Me–C(6)); 2.5–2.9 (br. *m*, 2 H–C(3), 2 H–C(4)); 4.8 (*m*, NC*H*Me); 6.9–7.5 (br. *m*, 8 H, carbazol, Ph). MS: 303 ($MH^{+\cdot}$).

6-Methyl-1-{[(R)-1-phenylethyl]amino}-1,2,3,4-tetrahydrocarbazole Hydrochloride (**5**). Compound **4** (0.5 g) was dissolved in dry THF (12.5 ml) under N_2. The soln. was cooled on ice-water, and 1M soln. of BH_3 in THF (3.3 ml) was added. The mixture was allowed to warm up r.t. for 5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in abs. EtOH (50 ml), and the mixture stirred for 30 min at r.t. EtOH was evaporated under reduced pressure, and the residue was triturated with a soln. of AcOEt, saturated with HCl (g), and Et_2O was added until complete precipitation. The white precipitate was collected by filtration, washed with Et_2O, and dried: 92%. M.p. 160–162°. IR (KBr): 3263 (NH); 1614 (C=N); 1572 (C=C). ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.7 (*d*, MeC–N); 2.2 (*s*, Me–C(6)); 1.2–2.5 (br. *m*, 2 H–C(2), 2 H–C(3), 2 H–C(4)); 4.7 (br. *s*, H–C(1)); 5.1 (br. *m*, N–C*H*Me); 6.9–8 (br. *m*, carbazol, Ph, NH); 8.6 (br. *s*, NH). MS: 305 ($MH^{+\cdot}$).

1-Amino-6-methyl-1,2,3,4-tetrahydrocarbazole Hydrochloride (**6**). Compound **5** (0.1 g) was dissolved in MeOH (10 ml). To the soln. ammonium formate (0.1 g) and 10% Pd/C (0.04 g) were added, and the soln. was heated under reflux for 10 min. The charcoal was eliminated by filtration, and the filtrate was concentrated under reduced pressure. H_2O was added, and the pH was adjusted 12 with dil. NaOH (5%). The aq. soln. was extracted with $CHCl_3$. The org. layer was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was triturated with a soln. of AcOEt saturated with HCl (g), and Et_2O was added. The precipitate was collected by filtration, washed with Et_2O, and dried: 80%. M.p. 178–180°. ^{1}H-NMR ((D_6)DMSO, 80 MHz): 1.6–2.6 (br. *m*, 2 H–C(2), 2 H–C(3), 2 H–C(4)); 2.35 (*s*, Me–C(6)); 4.4 (br. *m*, H–C(1)); 6.8 (*d*, H–C(7)); 7.05 (*s*, H–C(5)); 7.2 (*d*, H–C(8)); 8.6 (br. *s*, NH_3^+); 10.8 (br. *s*, NH). MS: 200 ($M^{+\cdot}$).

Dehydropirlindole Hydrochloride (= *8-Methyl-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole Hydrochloride*; **8**). Pirlindole (1.3 g) was dissolved in glacial AcOH (30 ml). $K_2Cr_2O_7$ (3.0 g) was added to the soln. After 2½ h, 5% NaOH aq. soln. was added, and the soln. was extracted with CH_2Cl_2 (3 × 50 ml). The org. layer was dried ($MgSO_4$) and treated with charcoal. The solvent was evaporated, and the residue was dissolved in a minimum volume of MeOH. Et_2O saturated with HCl (g) was added: 70%. M.p. 280–285°. ^{1}H-NMR ((D_6)DMSO, 400 MHz): 2.17 (*m*, 2 H–C(5)); 2.4 (*s*, Me); 3.0 (*m*, 2 H–C(4), 2 H–C(6)); 4.1 (*t*, 2H–C(1)); 4.35 (*t*, 2 H–C(2)); 7.4–7.6 (br. *m*, arom. H).

*8-Methyl-3-(1-phenylethyl)-2,4,5,6-tetrahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazol-3-ium Bromide* (**9**). Compound **8** (1 g) was dissolved in $EtNO_2$ (10 ml), and (±)-1-phenylethyl bromide (0.5 g) was added. The mixture was heated under reflux for several hours. After cooling, Et_2O (3 volumes) was added, and the yellow precipitate formed was collected by filtration and suspended in Me_2CO. Subsequent filtration furnished the expected crude product. This compound was used without further purification.

*8-Methyl-3-(1-phenylethyl)-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole* (**10**). Compound **9** (0.5 g) was dissolved in MeOH/H_2O (30 ml; 2:1 (*v*/*v*)). To the yellow soln., an excess of $NaBH_4$ (0.3 g) was added. The precipitate appeared immediately and was collected by filtration, washed with H_2O, dried and was crystallized in MeOH: 75%. M.p. 180–186°. ^{1}H-NMR ($CDCl_3$, 400 MHz): 1.45 (*d*, MeC–N); 2.40 (*d*, Me–C(8)); 3.48 (*t*, 2 H–C(2)); 3.95 (*m*, H–C(1), H–C(3a)); 4.5 (*m*, MeC*H*); 6.9–7.48 (br. *m*, 8 arom. H). ^{13}C-NMR ($CDCl_3$, 400 MHz): 8.4 (*Me*C–N); 21.5 (Me–C(8)); 20.6 (C(4)); 22.3 (C(5)); 28.0 (C(6)); 43.1–43.4 (C(1), C(2)); 53.7 (C(3a)); 55.6 (Me*C*–N).

*8-Methyl-*N*-[(R)-1-phenylethyl]-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole-3-carboxamide* (**18**). Pirlindole base (0.4 g) was dissolved in a minimum volume of dry toluene. (*R*)-1-phenylethyl isocyanate (0.25 ml) was rapidly added to this soln. After 10 min at r.t., the precipitate was collected by filtration, washed with petroleum ether (40–60°), and dried. Crystallization in hexane: 90%. M.p. 90–95°. ^{1}H-NMR ((D_6)DMSO, 80 MHz): 1.7 (*d*, MeC–N); 2.3 (*s*, Me–C(8)); 1.7–3.0 (br. *m*, 3 CH_2); 3.8–4.6 (br. *m*, 2 CH_2); 4.8 (br. *m*, H–C(3a)); 5.9 (br. *m*, MeC*H*); 6.8–8 (br. *m*, 8 arom. H); 8.2 (br. *s*, NH). MS: 374 ($MH^{+\cdot}$). Anal. calc. for $C_{24}H_{27}N_3O$: C 77.18, H 7.3, N 11.24; found: C 76.87, H 7.55, N 10.75.

*8-Methyl-*N*-[(R)-1-(naphthalen-1-yl)ethyl]-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole-3-carboxamide* (**19**) was obtained as described for **18**: 85%. M.p. 127–131°. MS: 424 ($MH^{+\cdot}$). Anal. calc. for $C_{28}H_{29}N_3O$: C 79.41, H 6.9, N 9.92; found: C 79.80, H 7.2, N 9.62.

*3-[(S)-2-(6-Methoxynaphthalen-2-yl)propanoyl]-8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole-3-carboxamide* (**20**). *(S)-2-(6-Methoxynaphtalen-2-yl)propanoyl chloride* (**14**) was prepared as described in [23]. The acid chloride (1 g) and dry pyridine (1.8 ml) were dissolved in CH_2Cl_2 (50 ml). Pirlindole base (2 g) was added to this mixture under stirring. The soln. was heated under reflux during 90 min. The formed precipitate was eliminated by filtration. The filtrate was washed with dil. HCl (0.5N) and a 5% aq. soln. of $NaHCO_3$. The org. layer was dried ($MgSO_4$), and petroleum ether (40–60°) was added until complete precipitation. The precipitate was collected by filtration, washed with petroleum ether, and dried: 65%. M.p. 130–132°. ^{1}H-NMR ((D_6)DMSO, 80 MHz): 1.55 (*d*, α–Me); 2.35 (*s*, Me–C(8)); 3.4–4.4 (br. *m*, 2 CH_2, MeO, H–C(3a)); 5.3 (*m*, CHCO); 6.7–8.0 (br. *m*, 9 arom. H). MS: 439 (MH^+). Anal. calc. for $C_{29}H_{30}N_2O_2$: C 79.42, H 6.89, N 6.39; found: C 79.02, H 7.04, N 6.45.

*3-Cholesteryl-8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole-3-carboxylate* (**21**). Pirlindole base (0.2 g) and Et_3N (3 drops) were dissolved in toluene (3 ml). *3-Cholesteryl chloroformate* (**15**, 0.4 g) was added to this soln. After stirring 1 h at r.t., the mixture was washed with H_2O (3 × 10 ml) and with a dil. soln. of HCl (0.5N). The org. layer was then dried ($MgSO_4$), and petroleum ether (40–60°) was added. The precipitate formed was collected by filtration, washed with petroleum ether (40–60°), and dried: 75%. M.p.: 104–106°. MS: 640 (MH^+). Anal. calc. for $C_{43}H_{62}N_2O_2$: C 80.84, H 9.8, N 4.4; found: C 80.50, H 10.2, N 4.40.

*8-Methyl-3-{[(2*R*,6*S*)-*endo*]-1,10,10-trimethyl-4-oxo-3-oxa-5-azatricyclo[5.2.1.0^{2,6}]decane-5-carbomyl}-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole* (**22**). *[(2*R*,6*S*)-*endo*]-1,10,10-trimethyl-3-oxa-5-azatricyclo[5.2.1.0^{2,6}]decan-4-one* (**16**, 1.0 g) was dissolved in dry Et_2O (40 ml). A 20% soln. of MeLi in Et_2O was added under stirring to the mixture. After formation of a white precipitate, a cool 20% toluene soln. of phosgene (7.5 ml) was added. The precipitate was eliminated by filtration, and the filtrate was evaporated under reduced pressure. The formed chloroformate was then dissolved in CH_2Cl_2 (20 ml) and added dropwise to pirlindole base (0.7 g) in CH_2Cl_2 (20 ml). After 2 h, the solvent was removed under reduced pressure, and the residue was triturated with H_2O (60 ml). The pH of the soln. was adjusted to 4 with HCOOH. The resulting precipitate was collected by filtration, washed with H_2O, and dried: 70%. M.p. 223–226°. MS: 449 (MH^+). Anal. calc. for $C_{27}H_{33}N_3O_3$: C 72.46, H 7.43, N 9.39; found: C 72.53, H 7.47, N 9.22.

*3-{[(6*S*)-*endo*]-11,11-Dimethyl-4-oxo-5-oxa-3-azatricyclo[5.2.1.0^{1,6}]undecane-3-carbonyl}-8-methyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrazino[3,2,1-*j,k*]carbazole* (**23**) was obtained as described for **22**: 55%. MS: 449 (MH^+). Anal. calc. for $C_{27}H_{33}N_3O_3$: C 72.46, H 7.43, N 9.39; found: C 72.80, H 7.21, N 9.41.

Hydrolysis of **18a** *and* **18b**. Diastereoisomer **18a** or **18b** (1.5 g) was dissolved in a 10% soln. of NaOH in EtOH (100 ml). Sodium hypophosphite (1.5 g) was added to the mixture, and the suspension was heated under reflux and under N_2 for 5 h. The solvent was eliminated under reduced pressure, and the residue was triturated with a 3N aq. HCl soln. To this layer, an identical volume of $CHCl_3$ was added. The hydrochloride formed precipitated and was collected by filtration, washed with a minimum volume of cold H_2O, and dried at 70° under reduced pressure. Starting from pure **18a** or **18b** (after separation by prep. HPLC), optically pure enantiomers **1** and **2** were obtained as hydrochlorides (70%). The spectral data of these enantiomers were identical to those of the racemic mixture. The optical purity of these isomers was checked by chiral HPLC. M.p. of the (–)- and of the (+)-isomers of pirlindole were 171–173° and 172–173°, resp. (m.p. of the racemate 180–182°).

Conditions for Prep. HPLC. All experiments were conducted in isocratic and in normal phase mode. The mobile phase used for prep. resolution of **18a** and **18b** consisted in a mixture of 0.7% of i-PrOH in toluene (*v*/*v*). The stationary phase used was a *Macherey-Nagel ET 250-1/2''-10 Nucleosil 100-5* column. The flow rate was 3 ml/min, and the detection was performed at 220 nm. The injected soln. was prepared by dissolving 6 g of the isomeric mixture in 1 l of the mobile phase.

Conditions for Chiral HPLC. The exper. conditions used for the determination of the optical purity of the enantiomers of pirlindole are identical to those described by *Ceccato et al.* [26]. The mobile phase used consisted of a mixture of a 50 mM phosphate buffer containing $NaClO_4$ (0.05M), adjusted to pH 5.0 with a 10% soln. of NaOH and MeCN (65:35 (*v*/*v*)). The column used was a *Chiralcel OD-R* (250 × 4.0 mm i.d.). The flow rate was 0.5 ml/min, and the detection was performed at 220 nm.

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REFERENCES

[1] P. A. Martorana, R. E. Nitz, *Arzneim.-Forsch. Drug Res.* **1979**, *29*, 946.
[2] M. D. Mashkovsky, N. I. Andrejeva, *Arzneim.-Forsch. Drug Res.* **1981**, *31*, 75.

[3] J. Maj, J. Michaluk, A. Rawlow, Z. Rogoz, G. Skuza, *Arzneim.-Forsch. Drug Res.* **1986**, *36*, 1198–1201.
[4] J. Bruhwyler, J.-F. Liégeois, J. Géczy, *Pharmacol. Res.* **1997**, *36*, 23.
[5] V. E. Schraven, R. Reibert, *Arzneim.-Forsch. Drug Res.* **1984**, *34*, 1258.
[6] J. De Wilde, S. Geerts, J. Van Dorpe, J. Bruhwyler, J. Géczy, *Acta Psychiatr. Scand.* **1996**, *94*, 404.
[7] W. Pöldinger, in 'Psychiatry. The state of the art. Vol. 3, Pharmacopsychiatry', Eds. P. Pichot, P. Berner, R. Wolf, and K. Thau, Plenum Press, New York, 1983, pp. 283–289.
[8] O. Schäpperle, F. Eckmann, H. Immich, in 'Psychiatry. The state of the Art. Vol. 3, Pharmacopsychiatry', Eds. P. Pichot, P. Berner, R. Wolf, and K. Thau, Plenum Press, New York, 1983, pp. 297–302.
[9] L. Blaha, in 'Psychiatry. The state of the Art. Vol. 3, Pharmacopsychiatry', Eds. P. Pichot, P. Berner, R. Wolf, and K. Thau, Plenum Press, New York, 1983, pp. 303–309.
[10] J. De Wilde, C. Mertens, J. Van Dorpe, J. Bruhwyler, J. Géczy, *Human Psychopharmacol.* **1997**, *12*, 41.
[11] A. Tanghe, S. Geerts, J. van Dorpe, B. Brichard, J. Bruhwyler, J. Géczy, *Acta Psychiatr. Scand.*, in press.
[12] V. I. Shvedov, L. B. Altukhova, N. I. Andreeva, M. D. Mashkovskii, A. N. Grinev, translated from *Khim. Farm. Zh.* **1972**, *10*, 14.
[13] P. Y. Ivanov, M. L. Alekseeva, A. I. Bokanov, V. I. Shvedov, Y. N. Sheinker, translated from *Khim. Farm. Zh.* **1987**, *1*, 71.
[14] P. W. Manley, U. Quast, *J. Med. Chem.* **1992**, *35*, 2327.
[15] H. M. Hoffmann, E. D. Hughes, *J. Chem. Soc.* **1964**, 1244.
[16] R. O. Hutchins, D. Masilamani, C. A. Maryanoff, *J. Org. Chem.* **1976**, *41*, 1071.
[17] A. R. Stein, R. D. Dawe, J. R. Sweet, *Can. J. Chem.* **1985**, *63*, 3442.
[18] H. M. Hoffmann, *J. Chem. Soc.* **1965**, 6753.
[19] H. M. Hoffmann, *J. Chem. Soc.* **1965**, 6748.
[20] J. A. Thompson, J. L. Holtzman, M. Tsuru, C. L. Lerman, *J. Chromatogr.* **1982**, *238*, 470.
[21] R. A. Carr, R. T. Foster, D. Freilag, F. M. Pasutto, *J. Chromatogr.* **1991**, *566*, 155.
[22] J. I. Seeman, C. G. Chavdarian, H. V. Secor, *J. Org. Chem.* **1985**, *50*, 5419.
[23] H. Spahn, *Arch. Pharm.* **1988**, *321*, 847.
[24] M. R. Banks, J. I. Cadogan, M. I. Dawson, I. Gosney, K. J. Grant, S. Gaur, P. K. Hodgson, D. E. Stevenson, *Chromatographia* **1992**, *34*, 48.
[25] M. R. Banks, A. J. Blake, J. I. Cadogan, I. M. Dawson, I. Gosney, K. J. Grant, S. Gaur, P. K. Hodgson, K. S. Knight, G. W. Smith, D. E. Stevenson, *Tetrahedron* **1992**, *48*, 7979.
[26] A. Ceccato, P. Hubert, P. de Tullio, J.-F. Liégeois, A. Felekidis, J. Géczy, J. Crommen, submitted to *J. Pharm. Biomed. Anal.*
[27] J. Bruhwyler, J.-F. Liégeois, E. Chleide, C. Lejeune, P. de Tullio, J. Géczy, submitted to *Behav. Pharmacol.*
[28] J. Gérardy, J.-F. Liégeois, J. Bruhwyler, P. de Tullio, J. Delarge, J. Géczy, A. Dresse, submitted to *Naunyn-Schmiedeberg's Arch. Pharmacol.*

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