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Synthesis of 2-substituted bamipine derivatives

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Abstract—2-Substituted derivatives of bamipine and its 1-phenyl analogue have been prepared in several steps from dihydropyridine-2(1*H*)-thiones. The configurations and the conformations of the formed diastereoisomers have been investigated by NMR spectroscopy. The antimycobacterial activities of the title compounds have been examined.

1. Introduction

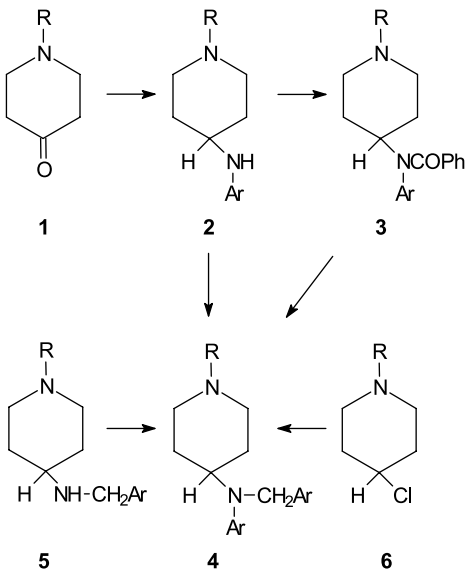
4-Aminopiperidines are substances of sustaining interest, because of their manifold pharmacological activities.[1] The 4-benzylanilinopiperidine bamipine (R=H) **4a** is used as antiallergic therapeutic agent. Besides it exhibits anticholine action[2] and a remarkable specific activity against *mycobacteria*.[3] Substances with both antihistaminic and antimycobacterial activity may be favorable for the therapy of leprosy because the incidence of cutaneous inflammations necessitates sometimes the use of an antihistaminic instead of the chemotherapeutic agent and thus the interruption of the therapy.[4]

Many derivatives of bamipine with different substitution of the aromatic rings[1,2,5–8] or replacement of one aromatic by a heteroaromatic ring[1,5,9–13] have been synthesized. Furthermore, the substitution of the piperidino nitrogen atom has been varied.[5,9–14] The derivatives possess antihistaminic,[9–14] antiserotonergic[15] or antiinflammatory properties.[5] However, analogues with substituents at ring positions 2 or 3 of the piperidine ring have not yet been reported, with the exception of a 2,5-dimethyl derivative.[6] The biologic activity of the latter substance has not been investigated. This paper deals with the synthesis of 2-substituted derivatives of bamipine and its 1-phenyl analogue which were prepared via new synthetic pathways. The antimycobacterial activities of those compounds have been examined.

2. Results and discussion

Bamipine **4a** and its analogues were usually synthesized from 1-substituted 4-piperidones **1**. Those were treated with anilines giving the corresponding Schiff's bases which were reduced to 4-anilinopiperidines **2**[2,5,7,13] and finally alkylated with benzylhalides[2,7,12] or a heteroaryl analogue[5] yielding compounds **4**. Besides the following methods have been applied: alkylation of **2** with benzaldehyde by the Wallach method,[6] benzoylation of **2** to anilides **3** which are converted to compounds **4** by reduction,[1] copper catalyzed coupling of 4-arylmethylaminopiperidines **5** with bromobenzene or 2-bromopyridine[11,13] and aminolysis of 4-chloropiperidines **6** with aryl-[8] or heteroaryl-methylanilines[16] have been reported for the preparation of compounds **4** (Scheme 1).

2-Substituted derivatives of bamipine might be prepared from 2-substituted 4-piperidones. Their synthesis has been accomplished by various methods. They were prepared by



Scheme 1. 4a: R=Me, Ar=Ph; **1**–**6**: Ar=aryl, heteroaryl.

Keywords: anilinopiperidines; antibacterials; bamipine; hydrogenation; piperidines; stereoisomerism.

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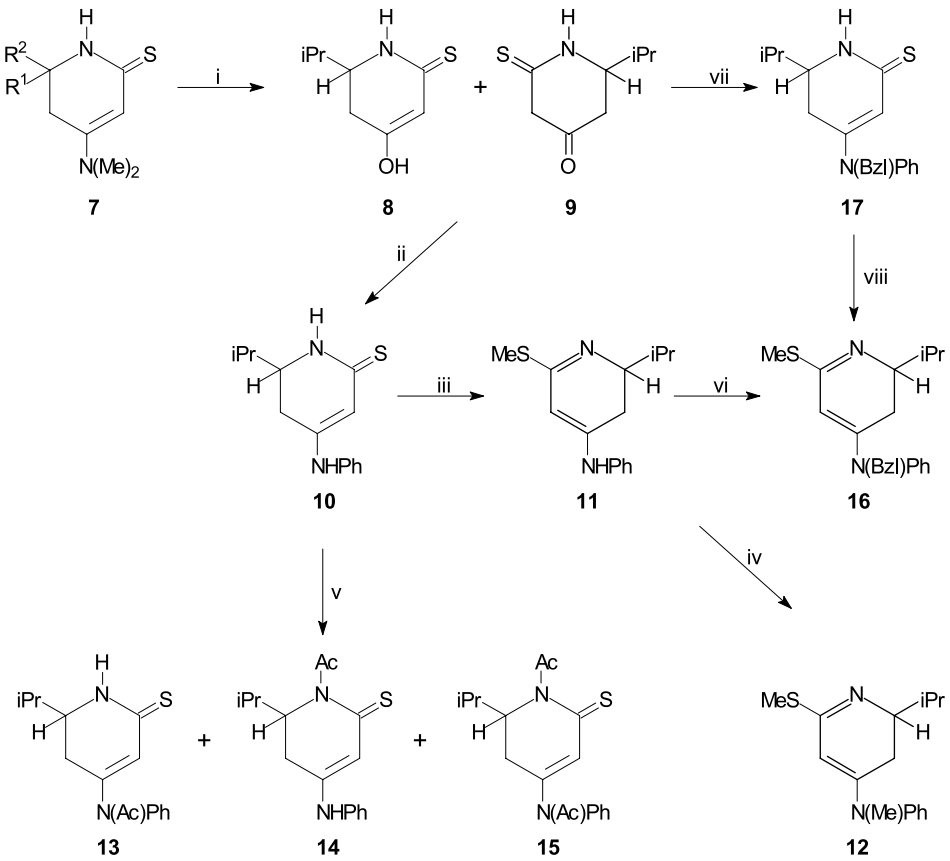
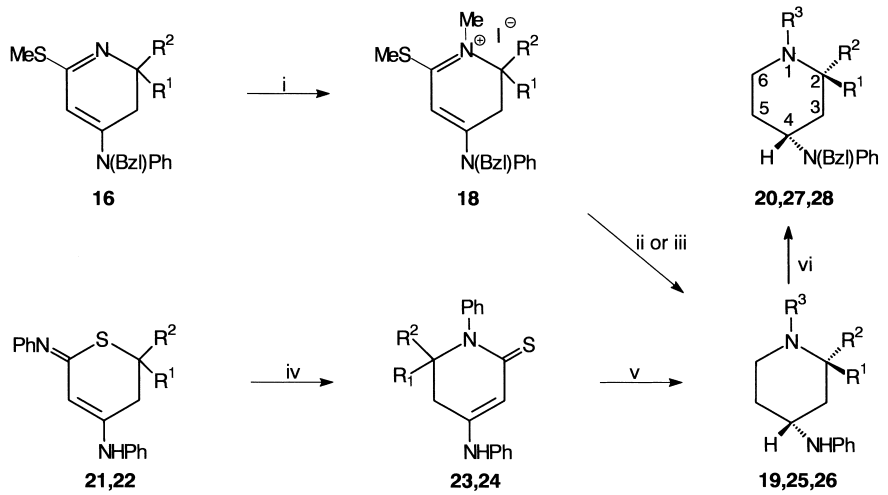


Scheme 2. **7**: R^1=H, alkyl; R^2=alkyl; **7a**: R^1=H; R^2=*i*Pr. *Reagents and reaction conditions*: (i) NaOH, 60°C, 72 h; (ii) aniline, 160°C, 16 h; (iii) (1) CH_3I, $CHCl_3$, room temperature, 6 h, (2) NaOH, room temperature, 30 min; (iv) (1) CH_3I, $CHCl_3$, room temperature, 16 h, (2) NaOH, room temperature, 1 h; (v) $(Ac)_2O$, pyridine, 155°C, 5 h; (vi) BzlBr, $NaNH_2$, PhMe, 120°C, 16 h; (vii) *N*-benzylaniline, 120°C, 8 h; (viii) (1) CH_3I, $CHCl_3$, room temperature, 16 h, (2) NaOH, room temperature, 1 h.

cyclization of α,β-unsaturated ketones in Mannich reactions[17–19] or by intermolecular double Michael reactions of α,β-unsaturated γ-ketosulfones with benzylamine.[20–22] Besides, cyclizations of imino acetales[23–25] and of pent-1,4-diene-3-ones with amines[26–29] have been reported. The flash vacuum thermolysis of 4-oxa-5-azaspiro[2.4]heptanes gave mixtures containing 1,2-disubstituted 4-piperidones.[30–32]

Although there were plenty of methods for the preparation of 4-piperidones we decided to synthesize the bamipine derivatives via a new pathway using 6-alkyl-4-dialkylamino-5,6-dihydropyridine-2(1*H*)-thiones **7** as synthons. Those are available in good yields from α,β-unsaturated ketones and ammonium thiocyanates in a one-pot reaction.[33] Exchange of the amino function has been accomplished by hydrolysis of **7a** yielding a mixture of the tautomeric compounds **8** and **9**. Those were treated with aniline giving the 4-anilino derivative **10**. Its methylthio derivative **11** has been prepared by a known procedure.[33,34] But further methylation of **11** afforded instead of the desired 1-methyl derivative the 4-(*N*-methylanilino)-dihydropyridine **12**, which was determined by NMR spectroscopy. Upon irradiation of the methylamino protons, we observed NOEs at the olefinic proton and at the aromatic ortho protons. Consequently, we tried to protect the anilino nitrogen by acetylation. However, both nitrogen atoms of **10** were readily acylated leading to a mixture containing compounds **13** and **14**, small quantities of the diacetyl product **15** and some starting material. After repeated chromatographic separations only less than 40% of the desired anilide **13** were afforded. The distinction of the isomers was accomplished by NMR spectroscopy: we observed a NOE from the aromatic *ortho* protons of **13** to the acetyl protons as well as a long-range coupling from the H at C-6 of **14** to the CO carbon. Attempts to protect the anilino nitrogen of **11** by benzylation failed, since **16** was obtained in unsatisfactory yields after troublesome workup (Scheme 2).

However, good overall yields were obtained by the following synthetic pathway: compounds **8**, **9** were fused with *N*-benzylaniline. The formed 4-(*N*-benzylanilino) derivative **17** was alkylated to the 2,3-dihydro-6-methylthiopyridine **16**. Further methylation of **16** with iodomethane yielded the dihydro-1-methylpyridinium salt **18** (Scheme 3). A possible alkylation of the anilino nitrogen was ruled out by a HMBC NMR experiment which was optimized for 5 Hz couplings. Long-range couplings from the 1-methyl protons to the C-2 and the C-6 of the dihydropyridine confirmed the formation of **18**. Our attempts to convert the latter selectively to the 2-isopropyl derivatives **20a**, **b** of bamipine were not successful. The use of Raney nickel that was inactivated with acetic acid yielded multicomponent mixtures containing **20a** as a by-product. Good yields of **19a** and small amounts of **20a** were obtained by treatment of **18** with Raney nickel W-2[35] at atmospheric pressure giving a mixture of both 4-aminopiperidines accompanied by low quantities of side products.



	16,18,21,23	22,24	19a,20a	19b,20b	25a,27a	25b,27b	26a,28a	26b,28b
R^1	iPr	Ph	iPr	H	iPr	H	Ph	H
R^2	H	H	H	iPr	H	iPr	H	Ph
R^3	----	----	Me	Me	Ph	Ph	Ph	Ph

Scheme 3. *Reagents and reaction conditions*: (i) CH_3I, $CHCl_3$, room temperature, 16 h; (ii) method A: Raney nickel W-2, ethanol, room temperature; (iii) Raney nickel W-7, ethanol, 30 psi (H_2), room temperature; (iv) DMF, 160°C, 16 h; (v) (1) CH_3I, $CHCl_3$, room temperature, 18 h, (2) Raney nickel W-2, ethanol, 30 psi (H_2), room temperature; (vi) BzlBr, $NaNH_2$, PhMe, 110°C, 16 h.

Compounds **19a** and **20a** were separated by CC. The formation of their isomers **19b** and **20b** was not observed in the ^{1}H NMR spectra of the collected fractions. To avoid chromatographic separations we tried to hydrogenize **18** selectively to **19a**. Since the prolongation of the reaction period or further addition of catalyst did not increase the yield of 4-anilinopiperidine **19a** we treated **18** with the more active Raney nickel W-7[36] varying pressure and amount of catalyst. Indeed, most of the obtained mixtures were free of compound **20a** but the afforded **19a** was always accompanied by *N*-benzylaniline and several other products. The chromatographic separations gave pure **19a** but the yields were far worse than by the above-mentioned method.

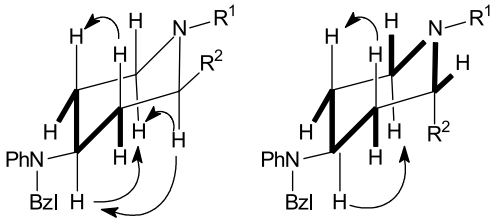
Alkylation of the 4-anilinopiperidine **19a** with benzyl bromide afforded **20a** in good yields. For the present this pathway seems to be limited to the preparation of 2-alkyl derivatives of bamipine because 6-aryl-5,6-dihydropyridine-2(1*H*)-thiones have so far been afforded in unsatisfactory yields.[37,38]

However, we were able to prepare 2-alkyl and 2-aryl derivatives of the corresponding 1-phenyl analogues of bamipine. Those were synthesized from the corresponding 1-phenyl analogues of compounds **7**. The 1-phenylpyridine-2(1*H*)-thiones **23** and **24** are accessible by a Dimroth rearrangement of the 6-phenylimino-2*H*-thiopyran-4-amines **21** and **22**.[39] The hydrogenation of the methoiodides of **23** and **24** gave the isomeric 4-anilino-1-phenylpiperidines **25a**,**b** and **26a**,**b** which were separated by CC.[39] Final alkylation with benzyl bromide afforded the 4-(*N*-benzylanilino)piperidines **27a**,**b** and **28a**,**b**.

The resonances in ^{1}H and ^{13}C NMR spectra of all new compounds were assigned with the aid of 2D NMR spectra (H,H-COSY and ge-HMQC). In the ^{13}C NMR spectra of compounds **20**, **27** and **28** we observed typical downfield shifts of ca. 5 ppm for the C-4s and upfield shifts of ca. 3 ppm for the C-3s and C-5s in comparison to compounds **19**, **25** and **26**. The relative configurations at C-2 and C-4 of compounds **20**, **27** and **28** were identified from the $^3J_{(2\text{-H, }3\text{-H})}$ and $^3J_{(3\text{-H, }4\text{-H})}$ coupling constants in their ^{1}H NMR spectra. The $^3J_{(3\text{-Hax, }4\text{-H})}$ couplings were ca. 12 Hz for all compounds indicating axial positions of the Hs at C-4. Furthermore, 12 Hz $^3J_{(2\text{-H,}3\text{-Hax})}$ couplings detected the axial positions of their Hs at C-2 in **20a**, **27a** and **28a**, whereas the equatorial Hs at C-2 in **27b** and **28b** caused typical 5 Hz $^3J_{(2\text{-H,}3\text{-Hax})}$ couplings.

The average conformations of compounds **20**, **27** and **28** were investigated by NOE and homodecoupling NMR experiments. An NOE from the axial protons in ring position 6 to the Hs at C-4 was observed for all prepared compounds **20**, **27** and **28**. The NOEs from the axial protons in ring position 3 to the axial Hs at C-5 were detectable with the exception of **20a** and **27b** where they were hidden due to the superposition of peaks. Upon irradiation of the axial Hs at C-2 in compounds **20a**, **27a** and **28a** we observed NOEs at the axial Hs at C-4 and C-6. Besides, w-couplings[40] were removed by homodecoupling experiments and detected in this way without measuring their exact values. We observed w-couplings between the equatorial protons in positions 3 and 5 with the exception of **20a** and **27a** where they were invisible due to the superposition of the signals of the involved protons. Furthermore, the w-couplings between the equatorial Hs at C-2 and C-6 of compounds **27b** and **28b** were revealed (Fig. 1). All above-mentioned observations indicate that the piperidine rings of compounds **20**, **27** and **28** prefer chair conformations.

The antimycobacterial activities of compounds **20**, **27** and



	20a	27a	27b	28a	28b
R^1	Me	Ph	Ph	Ph	Ph
R^2	iPr	iPr	iPr	Ph	Ph

Figure 1. NOEs (arrows) and w-couplings (bold) in ^{1}H NMR spectra of compounds **20**, **27**, **28**.

28 were preliminarily tested in liquid media by incubating 1:1000 diluted overnight cultures of *M. smegmatis* with increasing concentrations of compounds at 37°C under constant shaking. After 5 h incubation, the growth inhibitory activity was determined from the absorption of the compound-containing media at 600 nm using bamipine as reference compound. All compounds tested within this set-up showed antimycobacterial activity which will be further investigated against *M. tuberculosis* $H_{37}Rv$ by the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF, Southern Research Institute, America).

Isomeric 2-substituted 4-(*N*-benzylanilino)piperidines have been prepared via different pathways. Their configurations and their preferred conformations have been investigated by NMR spectroscopy. The title compounds have antimycobacterial activity.

3. Experimental

3.1. General

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin–Elmer). NMR spectra: Varian Inova 400 (298 K) 5 mm tubes, TMS as internal standard. ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba) at the Microanalytical Laboratory at the Institute of Physical Chemistry, University of Vienna; quite normally some of the crystals of the dihydrochlorides of **19**, **20**, **27** and **28** contained some C_2H_5OH and H_2O as has already been reported for the dihydrochloride of bamipine.[41,42] Hydrogenations were performed in a Parr hydrogenation apparatus shaker type 3911 at 30 psi or in an Erlenmeyer flask at atmospheric pressure. Chromatography: column chromatography (CC): LC: silica gel 60 (Merck), 0.063–0.200 mm, pore-diameter 60 Å, column diameter 40 mm, layer thickness 400 mm, rate of flow: 2 ml/min; MPLC: pump: Labomatic MD-80, silica gel 60 (Merck), 0.005–0.02 mm, pore-diameter 60 Å; column diameter 30 mm, layer thickness 340 mm, rate of flow: 9 ml/min, detection: Wellchrom K-2400 RI detector (Knauer); thin-layer chromatography (TLC): TLC plates (Merck) silica gel 60 F_{254}.

3.2. (*RS*)-(±)-4-Anilino-5,6-dihydro-6-isopropyl-pyridine-2(1*H*)-thione (10)

Compounds **8**, **9**[43] (0.05 mol) were dissolved in aniline (1 mol). A stream of argon was passed through the reaction mixture for 15 min and the reflux condenser was sealed with a balloon. The solution was heated on an oil-bath at 160°C for 16 h. Then the mixture was cooled and the solvent removed in vacuo. The residue was triturated with ethanol, filtered with suction and recrystallized. Yield: 8.70 g (70.6%); mp 169°C (ethanol); R_f=0.29 (toluene–methanol=4:1); IR (KBr): $\tilde{\nu}$=3171 (m), 3002 (m), 1582 (s), 1543 (s), 1513 (s), 1494 (s), 1445 (s), 1121 (s), 1055 (m), 690 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 0.97, 0.99 (2d, *J*=6.8 Hz, 6H, $CH(CH_3)_2$), 1.85 (dsept, *J*=6.6, 6.6 Hz, 1H, $CH(CH_3)_2$), 2.36 (dd, *J*=15.9, 5.1 Hz, 1H, 5-H), 2.48 (dd, *J*=15.9, 12.7 Hz, 1H, 5-H), 3.35–3.41 (m, 1H, 6-H), 5.97 (s, 1H, 3-H), 6.60 (s, 1H, NHPh), 6.87 (s, 1H, NHCS), 7.14–7.35 (m, 5H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 18.14, 18.42 ($CH(CH_3)_2$), 30.38 (C-5), 31.04 ($CH(CH_3)_2$), 57.83 (C-6), 99.07 (C-3), 123.47, 125.60, 129.42, 137.83 (aromatic C), 149.93 (C-4), 192.87 (C-2) ppm. Anal. calcd for $C_{14}H_{18}N_2S$ (246.37): C, 68.25; H, 7.36; N, 11.37; S, 13.01%. Found: C, 67.85; H, 7.41; N, 11.50; S, 12.76%.

3.3. 2,3-Dihydro-6-methylthiopyridines (11, 16)

General procedure. To an ice-cooled solution of the dihydropyridine-2-thiones **10**, **17** (0.03 mol) in 80 ml of chloroform, iodomethane (0.036 mol) was added through a dropping funnel within 1 h. The reaction mixture was stirred for 6 h at room temperature and the solvent was removed in vacuo. The residue was triturated with ethyl acetate, filtered with suction and dried. The crude yellow iminium salts were stirred in a 1 M solution of caustic soda (0.09 mol) in water for 30 min. The suspension was extracted with ether repeatedly. The combined organic layers were washed three times with water and dried with sodium sulphate. The solvent was removed and the residue recrystallized.

3.3.1. (*RS*)-(±)-4-Anilino-2,3-dihydro-2-isopropyl-6-methylthiopyridine (11). Yield: 7.57 g (96.9%); mp 97°C (ethanol–water); IR (KBr): $\tilde{\nu}$=3382 (m), 2951 (m), 2871 (m), 1629 (s), 1562 (s), 1517 (s), 1497 (m), 1443 (s), 1105 (m), 932 (m), 758 (m), 694 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 0.97, 1.01 (2d, *J*=6.6 Hz, 6H, $CH(CH_3)_2$), 1.77–1.88 (m, 1H, $CH(CH_3)_2$), 2.09–2.30 (m, 2H, 3-H), 2.25 (s, 3H, SCH_3), 3.01–3.09 (m, 1H, 2-H), 5.27 (s, 1H, 5-H), 7.00–7.35 (m, 5H, aromatic H), 8.40 (s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 11.20 (SCH_3), 19.24, 19.45 ($CH(CH_3)_2$), 30.08 (C-3), 33.13 ($CH(CH_3)_2$), 62.67 (C-2), 89.43 (C-5), 121.08, 122.89, 129.30, 140.53 (aromatic C), 149.52 (C-4), 161.93 (C-6) ppm. Anal. calcd for $C_{15}H_{20}N_2S$ (260.40): C, 69.19; H, 7.74; N, 10.76; S, 12.31%. Found: C, 68.80; H, 7.83; N, 11.09; S, 12.01%.

3.3.2. (*RS*)-(±)-4-(*N*-Benzylanilino)-2,3-dihydro-2-isopropyl-6-methylthiopyridine (16). Yield: 9.53 g (90.6%); mp 118°C (ethanol–water); IR (KBr): $\tilde{\nu}$=2962 (w), 2930

(w), 1619 (s), 1522 (s), 1396 (m), 1369 (m), 1329 (m), 1108 (s) cm^{-1}; ^1H NMR (DMSO-d_6, δ, 400 MHz): 0.84, 0.89 (2d, J=6.6 Hz, 6H, CH(CH_3)$_2$), 1.71 (dsept, J=6.6, 6.6 Hz, 1H, CH(CH$_3$)$_2$), 1.96–2.09 (m, 2H, 3-H), 2.22 (s, 3H, SCH$_3$), 2.99 (ddd, J=13.2, 6.6, 6.6 Hz, 1H, 2-H), 4.83, 4.88 (2d, J=17.7 Hz, 2H, NCH$_2$), 4.89 (s, 1H, 5-H), 7.19–7.39 (m, 10H, aromatic H) ppm; ^{13}C NMR (DMSO-d_6, δ, 100 MHz): 11.01 (SCH$_3$), 18.76, 19.43 (CH(CH_3)$_2$), 28.71 (C-3), 32.63 (CH(CH$_3$)$_2$), 55.38 (NCH$_2$), 62.91 (C-2), 92.66 (C-5), 126.14, 126.70, 126.92, 128.47, 129.30, 137.56, 144.35 (aromatic C), 153.07 (C-4), 161.86 (C-6) ppm. Anal. calcd for $C_{22}H_{26}N_2S$ (350.53): C, 75.38; H, 7.48; N, 7.99; S, 9.15%. Found: C, 75.10; H, 7.80; N, 8.20; S, 8.89%.

3.4. (*RS*)-(±)-2,3-Dihydro-2-isopropyl-4-(*N*-methylanilino)-6-methylthiopyridine (12)

A stream of argon was passed through an ice-cooled solution of **11** (0.005 mol) in 30 ml of chloroform. The reflux condenser was sealed with a balloon and iodomethane (0.015 mol) was added through a dropping funnel within 1 h. The reaction mixture was stirred for 16 h at room temperature and the solvent was removed in vacuo. The oily residue was treated with a 1 M solution of caustic soda (0.025 mol) in water for 1 h. The suspension was extracted with ether repeatedly. The combined organic layers were washed three times with water and dried with sodium sulphate. The solvent was removed. The residue was purified by MPLC eluting with toluene–methanol (4:1). The solvents were removed in vacuo. 0.39 g (0.0016 mol) of unchanged **11** were recovered. The fractions containing **12** were evaporated and the residue was triturated with heptane overnight. The mixture was sucked off giving **12** as an amorphous solid. Yield: 0.77 g (56.1%); R_f=0.12 (toluene–methanol=2:1); IR (KBr): $\tilde{\nu}$=2956 (m), 2923 (m), 2871 (m), 1609 (s), 1549 (s), 1495 (s), 1385 (s), 1108 (s), 924 (m), 767 (m), 701 (m) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.87, 0.95 (2d, J=6.8 Hz, 6H, CH(CH_3)$_2$), 1.73–1.85 (m, 1H, CH(CH$_3$)$_2$), 1.91–2.01 (m, 2H, 3-H), 2.39 (s, 3H, SCH$_3$), 3.05 (ddd, J=11.2, 8.3, 6.1 Hz, 1H, 2-H), 3.17 (s, 3H, NCH$_3$), 4.99 (s, 1H, 5-H), 7.04–7.37 (m, 5H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 11.74 (SCH$_3$), 19.07, 19.42 (CH(CH_3)$_2$), 28.75 (C-3), 32.93 (CH(CH$_3$)$_2$), 40.24 (NCH$_3$), 63.46 (C-2), 92.33 (C-5), 126.10, 126.62, 129.20, 145.56 (aromatic C), 153.36 (C-4), 162.87 (C-6) ppm. Anal. calcd for $C_{16}H_{22}N_2S$ (274.43): C, 70.03; H, 8.08; N, 10.21; S, 11.68%. Found: C, 69.86; H, 8.24; N, 10.23; S, 11.53%.

3.5. Acetylation of compound 10

The dihydropyridine-2(1*H*)-thione **10** (0.01 mol) was dissolved in 40 ml of dry pyridine. A stream of argon was passed through the solution and the reflux condenser was sealed with a balloon. After the mixture was heated on an oil-bath to 155°C acetic anhydride (0.01 mol) was added slowly through a dropping funnel and the mixture was heated for 5 h. The solution was cooled and the solvent was removed in vacuo. The residue was dissolved in dichloromethane and the solution was extracted three times with water. The organic layer was dried and the solvent evaporated. The residue was preliminary purified by LC eluting with toluene–methanol (19:1). The first fractions contained small amounts of the diacetylated compound **15** (R_f=0.55, toluene–methanol=4:1). Attempts to purify this product have failed so far due to its decomposability. Besides 0.37 g (0.0015 mol) of unchanged **10** (R_f=0.29, toluene–methanol=4:1) were recovered. The fractions containing mixtures of compounds **13** and **14** were collected and the isomers were separated by MPLC eluting with toluene–methanol (79:1). The solvent was evaporated and the residues recrystallized.

3.5.1. (*RS*)-(±)-*N*-(1,2,3,6-Tetrahydro-2-isopropyl-6-thioxo-4-pyridyl)acetanilide (13). Yield: 1.14 g (39.5%); mp 124°C (heptane); R_f=0.42 (toluene–methanol=4:1); IR (KBr): $\tilde{\nu}$=3194 (m), 2970 (m), 1698 (s), 1601 (s), 1581 (s), 1365 (s), 1236 (s), 1114 (s), 704 (m) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.02, 1.03 (2d, J=6.6 Hz, 6H, CH(CH_3)$_2$), 1.88–1.97 (m, 1H, CH(CH$_3$)$_2$), 1.93 (s, 3H, CH$_3$CO), 2.80–2.93 (m, 2H, 3-H), 3.36–3.43 (m, 1H, 2-H), 5.63 (s, 1H, 5-H), 7.18–7.51 (m, 6H, NH, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 18.34, 18.50 (CH(CH_3)$_2$), 25.22 (CH_3CO), 29.47 (C-3), 31.08 (CH(CH$_3$)$_2$), 58.80 (C-2), 118.28 (C-5), 128.51, 129.14, 130.36, 140.50 (aromatic C), 149.19 (C-4), 170.89 (CH$_3$CO), 192.78 (C-6) ppm. Anal. calcd for $C_{16}H_{20}N_2OS$ (288.41): C, 66.63; H, 6.99; N, 9.71; S, 11.12%. Found: C, 66.44; H, 7.33; N, 9.85; S, 10.64%.

3.5.2. (*RS*)-(±)-1-Acetyl-4-anilino-5,6-dihydro-6-isopropylpyridine-2(1*H*)-thione (14). Yield: 0.92 g (31.9%); mp 93°C (heptane); R_f=0.33 (toluene–methanol=4:1); IR (KBr): $\tilde{\nu}$=3231 (w), 2961 (m), 2927 (m), 1672 (m), 1569 (s), 1536 (s), 1222 (s), 1163 (m), 1028 (m), 693 (w) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.95, 0.97 (2d, J=6.8 Hz, 6H, CH(CH_3)$_2$), 2.03–2.15 (m, 1H, CH(CH$_3$)$_2$), 2.45 (br, d, J=17.4 Hz, 1H, 5-H), 2.64 (s, 3H, CH_3CO), 2.88 (ddd, J=17.4, 5.6, 1.5 Hz, 1H, 5-H), 4.80 (ddd, J=10.2, 5.6, 1.3 Hz, 1H, 6-H), 6.31 (s, 1H, NH), 6.40 (br, s, 1H, 3-H), 7.17–7.41 (m, 5H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 19.78, 20.21 (CH(CH_3)$_2$), 26.98 (CH_3CO), 28.59 (CH(CH$_3$)$_2$), 31.61 (C-5), 58.14 (C-6), 108.04 (C-3), 123.79, 126.39, 129.66, 137.26 (aromatic C), 150.13 (C-4), 173.83 (CH$_3$CO), 196.42 (C-2) ppm. Anal. calcd for $C_{16}H_{20}N_2OS$ (288.41): C, 66.63; H, 6.99; N, 9.71; S, 11.12%. Found: C, 66.45; H, 7.35; N, 9.87; S, 10.66%.

3.6. (*RS*)-(±)-4-(*N*-Benzylanilino)-6-isopropyl-5,6-dihydropyridine-2(1*H*)-thione (17)

Compounds **8**, **9**[43] (0.04 mol) were added to melted *N*-benzylaniline (0.05 mol) at 60°C on an oil-bath. Then a stream of argon was passed through the stirred reaction mixture for 5 min and the reflux condenser was sealed with a balloon. The temperature was increased to 120°C and heating was continued for 8 h. The mixture was cooled and the residue was triturated with ethanol and filtered with suction. The yellow precipitate was suspended in boiling chloroform, cooled and filtered. The filtrate was concentrated and the residue recrystallized. Yield: 9.16 g (68.1%); mp 154°C (ethanol); IR (KBr): $\tilde{\nu}$=3179 (m), 2966 (m), 1564 (s), 1501 (s), 1455 (m), 1394 (m), 1359 (m), 1116 (s) cm^{-1}; ^1H NMR (DMSO-d_6, δ, 400 MHz): 0.77, 0.79 (2d, J=6.8 Hz, 6H, CH(CH_3)$_2$), 1.83–1.96 (m, 1H, CH(CH$_3$)$_2$), 2.25 (dd, J= 16.4, 8.9 Hz, 1H, 5-H), 2.31 (dd,

J=16.4, 6.3 Hz, 1H, 5-H), 3.17–3.25 (m, 1H, 6-H), 4.90, 4.95 (2d, J=17.8 Hz, 2H, NCH_2), 5.33 (s, 1H, 3-H), 7.23–7.44 (m, 10H, aromatic H), 8.62 (s, 1H, NH) ppm; ^{1}H NMR (100 MHz, δ, DMSO-d_6): 18.00, 18.78 ($CH(CH_3)_2$), 27.27 (C-5), 29.86 ($CH(CH_3)_2$), 55.81 (NCH_2), 57.04 (C-6), 101.13 (C-3), 126.78, 127.16, 127.26, 127.58, 128.74, 129.70, 137.14, 143.86 (aromatic C), 152.01 (C-4), 190.44 (C-2) ppm. Anal. calcd for $C_{21}H_{24}N_2S$ (336.50): C, 74.96; H, 7.19; N, 8.32; S, 9.53%. Found: C, 74.66; H, 7.44; N, 8.61; S, 9.32%.

3.7. (*RS*)-(±)-4-(*N*-Benzylanilino)-2-isopropyl-1-methyl-6-methylthio-2,3-dihydropyridiniumiodide (18)

A stream of argon was passed through a solution of the dihydropyridine **16** (0.02 mol) in 40 ml of chloroform for 2 min. Then iodomethane (0.1 mol) diluted with 10 ml of chloroform was added and the apparatus sealed with a balloon. The reaction mixture was stirred for 16 h at room temperature, and the solvent was removed in vacuo. The oily residue was used for the synthesis of the 4-aminopiperidines **19a** and **20a** without further purification. Yield: 8.22 g (83.5%); yellow oil; IR (KBr): $\tilde{\nu}$=2963 (m), 2922 (m), 1644 (m), 1570 (s), 1513 (s), 1464 (s), 1418 (s), 1358 (m), 1327 (m), 1292 (m), 1242 (m), 1096 (m), 751 (s), 702 (m) cm^{-1}; ^{1}H NMR (DMSO-d_6, δ, 400 MHz): 0.70, 0.83 (2d, J=6.4 Hz, 6H, CH $(CH_3)_2$), 2.04–2.20 (m, 2H, $CH(CH_3)_2$, 3-H), 2.53 (s, 3H, SCH_3), 3.14 (dd, J=17.6, 6.4 Hz, 1H, 3-H), 3.36 (s, 3H, NCH_3), 3.59–3.67 (m, 1H, 2-H), 5.09, 5.33 (2d, J=16.1 Hz, 2H, NCH_2), 5.64 (s, 1H, 5-H), 7.28–7.56 (m, 10H, aromatic H) ppm; ^{13}C NMR (DMSO-d_6, δ, 100 MHz): 15.09 (SCH_3), 18.90, 19.54 $CH(CH_3)_2$, 27.99 (C-3, $CH(CH_3)_2$), 41.82 (NCH_3), 57.28 (NCH_2), 65.94 (C-2), 87.97 (C-5), 127.75, 127.98, 128.85, 129.07, 130.02, 135.09, 141.79 (aromatic C), 159.48 (C-4), 173.34 (C-6) ppm.

3.8. (2*RS*, 4*SR*)-(±)-4-Anilino-2-isopropyl-1-methylpiperidine (19a)

Method A. Raney nickel W-2[35] was added in portions to a solution of **18** (0.002 mol) in 50 ml of ethanol which was stirred in an Erlenmeyer flask at room temperature under a nitrogen atmosphere. The progress of reaction was monitored by TLC. The addition of the catalyst was stopped when compound **18** was no more detectable. The mixture was filtered, the solvent was removed in vacuo and the residue was purified by LC eluting with toluene–ethyl acetate–methanol (1:1:1). The fractions containing **19a** resp. **20a** were collected and the solvents were removed in vacuo. The oily residues were weighed out and treated with the double-molar amount of a 1 M solution of hydrogen chloride in diethylether. The solvents were evaporated and the residues recrystallized giving 0.56 g (85.3%) of **19a** and 0.036 g (4.4%) of **20a**.

Method B. 10 g of freshly prepared Raney nickel W-7[36] were added to a solution of compound **18** (0.002 mol) in 50 ml of ethanol. The mixture was shaken in a shaker apparatus at room temperature at 30 psi. The reaction was stopped when compound **20a** was no more detectable on TLC. The mixture was sucked off and the residue rewashed with 100 ml of ethanol. The solvent was removed in vacuo and the residue dissolved in dichloromethane and H_2O. The layers were separated and the aqueous phase was extracted once with dichloromethane. The combined organic layers were dried over sodium sulphate. The solvent was evaporated and the residue was purified by LC eluting with toluene–ethyl acetate–methanol (1:1:1). The fractions containing **19a** were collected and the solvents were removed in vacuo. The oily residue was treated with hydrogen chloride as mentioned under method A. Thus 0.23 g (35.0%) of the dihydrochloride of **19a** were yielded.

Mp (diHCl): 224°C (ethanol–ethyl acetate); R_f (base)=0.26 (toluene–ethyl acetate–methanol=1:1:1); IR (diHCl, KBr): $\tilde{\nu}$=3426 (m), 2967 (s), 2649 (s), 2479 (s), 1583 (m), 1460 (s), 1393 (m), 1042 (m), 756 (s), 696 (s) cm^{-1}; NMR (base): ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 0.86, 0.89 (2d, J=6.6 Hz, 6H, $CH(CH_3)_2$), 1.09 (ddd, J=11.8, 11.8, 11.8 Hz, 1H, 3-H_{ax}), 1.45 (dddd, J=12.7, 12.7, 12.2, 4.0 Hz, 1H, 5-H_{ax}), 1.87–1.92 (m, 1H, 3-H_{eq}), 1.95–2.13 (m, 3H, $CH(CH_3)_2$, 2-H_{ax}, 5-H_{eq}), 2.26 (ddd, J=12.2, 12.2, 2.4 Hz, 1H, 6-H_{ax}), 2.27 (s, 1H, NCH_3), 2.99 (ddd, J=12.2, 4.0, 2.9 Hz, 1H, 6-H_{eq}), 3.22–3.30 (m, 1H, 4-H_{ax}), 3.53 (br, s, 1H, NH), 6.53–7.17 (m, 5H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 14.74, 19.81 ($CH(CH_3)_2$), 27.46 ($CH(CH_3)_2$), 30.65 (C-3), 32.54 (C-5), 41.66 (NCH_3), 50.64 (C-4), 56.50 (C-6), 67.88 (C-2), 113.01, 117.01, 129.16, 146.90 (aromatic C) ppm. Anal. calcd for $C_{15}H_{26}Cl_2N_2$+0.3C_2H_5OH+0.5H_2O (328.12): C, 57.10; H, 8.85; Cl, 21.61; N, 8.54%. Found: C, 57.13; H, 8.83; Cl, 21.62; N, 8.53%.

3.9. 4-(*N*-Benzylanilino)-1-methylpiperidines 20, 27 and 28

General procedure. A solution of the 4-anilinopiperidines **19**, **25** or **26** (0.0005 mol) in 30 ml of dry toluene was kept in an inert-gas atmosphere. Sodium amide (0.003 mol) was added and the mixture was heated to 110°C on an oil-bath. When the evolution of ammonia ceased, benzyl bromide was added through a dropping funnel. After 16 h the mixture was cooled and poured into a separatory funnel where it was shaken twice with water. The organic layer was dried over potassium carbonate and the solvent removed in vacuo. The residue was purified by CC. The fractions containing compounds **19**, **25** or **26** were collected and concentrated. The oily residues were weighed out and treated with the double-molar amount of a 1 M solution of hydrogen chloride in diethylether. The solvent was evaporated and the residue recrystallized.

3.9.1. (2*RS*,4*SR*)-(±)-4-(*N*-Benzylanilino)-2-isopropyl-1-methylpiperidine (20a). Purification was accomplished by LC eluting with toluene–ethyl acetate–methanol (1:1:1). Yield: 0.176 g (85.5%); mp (diHCl): 195°C (ethanol–ethyl acetate); R_f (base)=0.39 (toluene–ethyl acetate–methanol=1:1:1); IR (diHCl, KBr): $\tilde{\nu}$=3456 (s), 2965 (m), 2933 (m), 2526 (s), 1599 (w), 1495 (m), 1461 (m), 1417 (m), 1053 (m), 750 (m), 698 (s) cm^{-1}; NMR (base): ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 0.81, 0.85 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.35 (ddd, J=11.9, 11.9, 11.9 Hz, 1H, 3-H_{ax}), 1.69–1.81 (m, 3H, 3-H_{eq}, 5-H), 1.82–1.88 (m, 1H, 2-H_{ax}), 2.03–2.12 (m, 1H, $CH(CH_3)_2$), 2.22 (s, 1H, NCH_3), 2.23 (ddd, J=11.6, 11.6, 3.9 Hz, 1H, 6-H_{ax}), 2.95 (ddd, J=11.6, 3.3, 3.3 Hz, 1H, 6-H_{eq}), 3.77–3.86 (m, 1H, 4-H_{ax}), 4.44, 4.52 (2d,

J=17.8 Hz, 2H, NCH_2), 6.65–7.31 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 14.90, 19.98 ($CH(CH_3)_2$), 27.04 (C-3), 27.86 ($CH(CH_3)_2$), 29.84 (C-5), 41.95 (NCH_3), 49.39 (NCH_2), 56.00 (C-4), 57.16 (C-6), 68.38 (C-2), 112.95, 116.49, 126.21, 126.40, 128.35, 129.20, 140.76, 149.16 (aromatic C) ppm. Anal. calcd for $C_{22}H_{32}Cl_2N_2$+0.2C_2H_5OH+0.4H_2O (411.84): C, 65.33; H, 8.32; Cl, 17.22; N, 6.80%. Found: C, 65.36; H, 8.31; Cl, 17.11; N, 6.77%.

3.9.2. (2*RS*,4*SR*)-(±)-4-(*N*-Benzylanilino)-2-isopropyl-1-phenylpiperidine (27a). Purification was accomplished by MPLC eluting with cyclohexane–ethyl acetate (39:1). Yield: 0.18 g (74.2%); mp (diHCl): 206°C (ethanol–ethyl acetate); R_f (base)=0.17 (cyclohexane–toluene=1:2); IR (diHCl, KBr): $\tilde{\nu}$=3397 (m), 2968 (m), 2919 (m), 2591 (m), 2551 (m), 1597 (m), 1490 (s), 1030 (m), 769 (m), 699 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.73, 0.78 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.55 (ddd, J=11.8, 11.8, 10.9 Hz, 1H, 3-H_{ax}), 1.72–1.79 (m, 1H, $CH(CH_3)_2$), 1.81 (dddd, J=11.6, 11.6, 10.7, 4.0 Hz, 1H, 5-H_{ax}), 1.88–1.96 (m, 2H, 3-H_{eq}, 5-H_{eq}), 2.91 (ddd, J=12.1, 10.7, 3.2 Hz, 1H, 6-H_{ax}), 2.99 (ddd, J=10.9, 3.2, 3.2 Hz, 1H, 2-H_{ax}), 3.17 (ddd, J=12.1, 4.0, 4.0 Hz, 1H, 6-H_{eq}), 3.96 (dddd, J=11.7, 11.7, 4.0, 4.0 Hz, 1H, 4-H_{ax}), 4.50, 4.60 (2d, J=17.8 Hz, 2H, NCH_2), 6.69–7.33 (m, 15H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 15.35, 19.62 ($CH(CH_3)_2$), 27.62 (C-3), 28.52 ($CH(CH_3)_2$), 30.27 (C-5), 49.49 (NCH_2), 55.41 (C-4), 55.60 (C-6), 63.84 (C-2), 113.02, 116.58, 123.81, 124.21, 126.20, 126.45, 128.39, 129.02, 129.22, 140.70, 149.14, 152.26 (aromatic C) ppm. Anal. calcd for $C_{27}H_{34}Cl_2N_2$+0.7C_2H_5OH (485.13): C, 69.65; H, 7.86; Cl, 14.48; N, 5.72%. Found: C, 69.77; H, 7.90; Cl, 14.13; N, 5.62%.

3.9.3. (2*RS*,4*RS*)-(±)-4-(*N*-Benzylanilino)-2-isopropyl-1-phenylpiperidine (27b). Purification was accomplished by MPLC eluting with cyclohexane–ethyl acetate (59:1). Yield: 0.184 g (80.4%); mp (diHCl): 185°C (ethanol–acetone); R_f (base)=0.50 (cyclohexane–toluene=1:2); IR (diHCl, KBr): $\tilde{\nu}$=3426 (w), 3043 (m), 2964 (m), 2427 (s), 1597 (w), 1494 (s), 758 (m), 697 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.93, 1.06 (2d, J=6.7 Hz, 6H, $CH(CH_3)_2$), 1.67 (ddd, J=12.8, 12.8, 5.1 Hz, 1H, 3-H_{ax}), 1.71 (dddd, J=12.1, 12.1, 12.1, 3.7 Hz, 1H, 5-H_{ax}), 1.77–1.84 (m, 1H, 5-H_{eq}), 1.97–2.03 (m, 1H, 3-H_{eq}), 2.33–2.45 (m, 1H, $CH(CH_3)_2$), 3.23 (ddd, J=14.6, 12.1, 2.8 Hz, 1H, 6-H_{ax}), 3.59 (ddd, J=10.5, 5.1, 1.7 Hz, 1H, 2-H_{eq}), 3.71–3.78 (m, 1H, 6-H_{eq}), 4.27–4.35 (m, 1H, 4-H_{ax}), 4.36, 4.41 (2d, J=17.9 Hz, 2H, NCH_2), 6.64–7.30 (m, 15H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 20.52, 20.85 ($CH(CH_3)_2$), 27.54 ($CH(CH_3)_2$), 28.12 (C-5), 28.86 (C-3), 41.21 (C-6), 49.04 (NCH_2), 51.23 (C-4), 62.59 (C-2), 112.86, 114.32, 116.69, 126.12, 126.45, 128.38, 129.25, 140.41, 149.00, 150.55 (aromatic C) ppm. Anal. calcd for $C_{27}H_{34}Cl_2N_2$ (457.49): C, 70.89; H, 7.49; Cl, 15.50; N, 6.12%. Found: C, 70.60; H, 7.56; Cl, 15.35; N, 5.91%.

3.9.4. (2*RS*,4*SR*)-(±)-4-(*N*-Benzylanilino)-1,2-diphenylpiperidine (28a). Purification was accomplished by MPLC eluting with cyclohexane–ethyl acetate (59:1). Yield: 0.225 g (86.7%); mp (diHCl): 225°C (ethanol–ethyl acetate); R_f (base)=0.10 (cyclohexane–toluene=1:1); IR (diHCl, KBr): $\tilde{\nu}$=3425 (w), 3043 (w), 2412 (m), 2364 (m), 1599 (m), 1494 (s), 753 (m), 696 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.86 (ddd, J=11.8, 11.8, 11.8 Hz, 1H, 3-H_{ax}), 1.98–2.08 (m, 2H, 5-H), 2.16–2.23 (m, 1H, 3-H_{equ}), 2.95–3.02 (m, 1H, 6-H_{ax}), 3.57 (ddd, J=12.3, 3.6, 3.6 Hz, 1H, 6-H_{equ}), 4.04–4.14 (m, 1H, 4-H_{ax}), 4.17 (dd, J=11.8, 2.9 Hz, 1H, 2-H_{ax}), 4.44, 4.52 (2d, J=17.7 Hz, 2H, NCH_2), 6.66–7.27 (m, 20H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 30.76 (C-5), 39.82 (C-3), 49.37 (NCH_2), 55.80 (C-4), 56.78 (C-6), 63.99 (C-2), 113.48, 116.95, 122.67, 123.65, 126.16, 126.45, 126.48, 127.06, 128.19, 128.39, 128.42, 129.15, 140.34, 143.80, 148.90, 152.00 (aromatic C) ppm. Anal. calcd for $C_{30}H_{32}Cl_2N_2$+0.6 C_2H_5OH (519.15): C, 72.18; H, 6.91; Cl, 13.66; N, 5.40%. Found: C, 72.16; H, 6.72; Cl, 13.27; N, 5.45%.

3.9.5. (2*RS*,4*RS*)-(±)-4-(*N*-Benzylanilino)-1,2-diphenylpiperidine (28b). Purification was accomplished by MPLC eluting with cyclohexane–ethyl acetate (59:1). Yield: 0.23 g (90.2%); mp (diHCl): 179°C (ethanol–ethyl acetate); R_f (base)=0.22 (cyclohexane–toluene=1:1); IR (diHCl, KBr): $\tilde{\nu}$=3432 (w), 3043 (w), 2419 (s), 1597 (m), 1493 (s), 1420 (m), 754 (m), 697 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.84 (dddd, J=11.6, 11.6, 11.6, 4.3 Hz, 1H, 5-H_{ax}), 1.85–1.94 (m, 1H, 5-H_{eq}), 2.13 (ddd, J=12.7, 12.7, 5.3 Hz, 1H, 3-H_{ax}), 2.45–2.53 (m, 1H, 3-H_{equ}), 3.41 (ddd, J=13.4, 11.4, 3.7 Hz, 1H, 6-H_{ax}), 3.90 (ddd, J=13.4, 3.2, 3.2 Hz, 1H, 6-H_{equ}), 3.96–4.06 (m, 1H, 4-H_{ax}), 4.44, 4.50 (2d, J=18.0 Hz, 2H, NCH_2), 5.26–5.28 (m, 1H, 2-H_{eq}), 6.54–7.38 (m, 20H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 29.19 (C-5), 32.71 (C-3), 42.73 (C-6), 49.23 (NCH_2), 50.80 (C-4), 57.36 (C-2), 112.96, 113.72, 116.77, 117.37, 126.15, 126.54, 126.69, 127.02, 128.45, 128.71, 129.14, 129.37, 140.43, 140.55, 148.83, 149.85 (aromatic C) ppm. Anal. calcd for $C_{30}H_{32}Cl_2N_2$+0.4 C_2H_5OH (509.93): C, 72.55; H, 6.80; Cl, 13.90; N, 5.49%. Found: C, 72.59; H, 6.79; Cl, 13.52; N, 5.28%.

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References

1. Aboul-Enein, M. N.; Khalifa, M.; El-Azouny, A. A. *Pharm. Acta Helv.* **1973**, *48*, 151–156.
2. Kallischnigg, R. (Knoll A.-G.). US 2683714, 1954; *Chem. Abstr.* **1955**, *49*, 10383e.
3. Meindl, W. *Arch. Pharm.* **1988**, *321*, 473–476.
4. Meindl, W. *Arch. Pharm.* **1989**, *322*, 493–497.
5. Kodama, T.; Tamura, M.; Oda, T.; Yamazaki, Y.; Nishikawa, M.; Takemura, S.; Doi, T.; Kyotani, Y.; Ohkuchi, M. (Kowa Co. Ltd.). US 6395753, 2002; *Chem. Abstr.* **2002**, *136*, 386028.
6. Prostakov, N. S.; Kuznetsov, V. V.; Gaivoronskaya, L. A.; Murugova, L. A.; Stashenko, E. E.; Zakharov, P. I. *Chem. Heterocycl. Compd.* **1988**, *24*, 887–891.

7. Knoll A.-G. Brit. 700097, 1953; *Chem. Abstr.* **1955**, *49*, 6318g.
8. Kallischnigg, R. (Knoll A.-G.). Ger. 891547, 1953; *Chem. Abstr.* **1958**, *52*, 13805h.
9. Janssens, F. E.; Diels, G. S. M.; Torremans, J. L. G.; Sommen, F. M. (Janssen Pharmaceutica N. V.). EP 282133, 1988; *Chem. Abstr.* **1989**, *110*, 75503q.
10. Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1925–1933.
11. Stoll, A.; Bourquin, J. P. (Sandoz Ltd.). US 2757175, 1956; *Chem. Abstr.* **1957**, *51*, 2055e.
12. Sandoz Ltd. Brit. 717227, 1954; *Chem. Abstr.* **1956**, *50*, 2684f.
13. Reitsema, R. H.; Hunter, J. H. *J. Am. Chem. Soc.* **1948**, *70*, 4009–4011.
14. Ito, Y.; Kato, H.; Yasuda, S.; Etsuchu, E.; Saito, K.; Kurata, S. (Hokuriku Pharmaceutical). JP 05148234, 1993; *Chem. Abstr.* **1993**, *119*, 203153a.
15. Malec, D.; Langwinski, R.; Pol, *J. Pharmacol. Pharm.* **1983**, *35*, 293–300.
16. Laskowska, W. (Krakowskie Zaklady Farmaceutyczne 'Polfa'). PL 65775, 1972; *Chem. Abstr.* **1972**, *77*, 151949g.
17. Bosch, J.; Rubiralta, M.; Domingo, A.; Sistaré, J. *J. Heterocycl. Chem.* **1981**, *18*, 47–54.
18. Bosch, J.; Rubiralta, M. *An. Quim., Ser. C* **1983**, *79*, 27–32.
19. Hohenlohe-Oehringen, K. *Monatsh. Chem.* **1963**, *94*, 1222–1224.
20. Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1998**, *39*, 1973–1976.
21. Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1998**, *39*, 7591–7594.
22. Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Eur. J. Org. Chem.* **2001**, 975–986.
23. Bosch, J.; Rubiralta, M.; Moral, M. *Heterocycles* **1982**, *19*, 473–476.
24. Bosch, J.; Rubiralta, M.; Moral, M.; Valls, M. *J. Heterocycl. Chem.* **1983**, *20*, 595–605.
25. Giralt, E.; Feliz, M.; Rubiralta, M.; Bosch, J. *J. Heterocycl. Chem.* **1984**, *21*, 715–720.
26. D'yakov, M. Y.; Peretokin, A. V.; Sokolova, T. D.; Moskovkin, A. S.; Unkovskii, B. V. SU 1490116, 1989; *Chem. Abstr.* **1989**, *111*, 214397.
27. Markaryan, R. E.; Airapetyan, G. K.; Noravyan, A. S. *Arm. Khim. Zh.* **1988**, *41*, 311–313.
28. Vartanyan, R. S.; Martirosyan, V. H.; Kolozyan, K. R. *Arm. Khim. Zh.* **1987**, *40*, 391–392.
29. Vartanyan, R. S.; Martirosyan, V. H.; Vartanyan, S. A. *Arm. Khim. Zh.* **1984**, *37*, 724–725.
30. Cordero, F. M.; Goti, A.; De Sarlo, F.; Gurana, A.; Brandi, A. *Tetrahedron* **1989**, *45*, 5917–5924.
31. Brandi, A.; Garro, S.; Gurana, A.; Goti, A.; Cordero, F. M.; De Sarlo, F. *J. Org. Chem.* **1988**, *53*, 2430–2434.
32. Brandi, A.; Gurana, A.; Goti, A.; De Sarlo, F. *Tetrahedron Lett.* **1986**, *27*, 1727–1730.
33. Zigeuner, G.; Schweiger, K.; Fuchsgruber, A. *Monatsh. Chem.* **1981**, *112*, 187–197.
34. Zigeuner, G.; Schweiger, K.; Baier, M. *Monatsh. Chem.* **1981**, *112*, 335–340.
35. Mozingo, R. *Organic Syntheses*; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. 3, pp 181–183.
36. Adkins, H.; Billica, H. R. *J. Am. Chem. Soc.* **1948**, *70*, 695–698.
37. Schweiger, K.; Zigeuner, G. *Monatsh. Chem.* **1978**, *109*, 543–550.
38. Weis, R.; Michl, G.; Belaj, F.; Brun, R.; Saf, R.; Seebacher, W. Submitted for publication.
39. Weis, R.; Schweiger, K.; Seebacher, W. *Tetrahedron* **2001**, *57*, 8305–8311.
40. Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; 2nd ed., Pergamon: Oxford, 1969; pp 334–341.
41. Birknes, B. *Acta Crystallogr.* **1977**, *B33*, 2301–2303.
42. Kuhnert-Brandstätter, M.; Linder, R. *Sci. Pharm.* **1977**, *45*, 40–47.
43. Weis, R.; Kungl, A. J.; Seebacher, W. *Tetrahedron* **2003**, *59*, 1403–1411.