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2-Substituted 4-anilinopiperidines from 2*H*-thiopyran-2-thiones

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Abstract—4-Dimethylamino-5,6-dihydro-2*H*-thiopyran-2-thiones were converted to 4-anilinodihydropyridine-2(1*H*)-thiones in several steps. The latter were alkylated giving a mixture of isomeric methylthioderivatives which were hydrogenated with Raney nickel yielding 2-alkyl- and 2-aryl-substituted 4-anilinopiperidines. The configurations as well as the conformations of the formed diastereoisomers are investigated by means of NMR.

1. Introduction

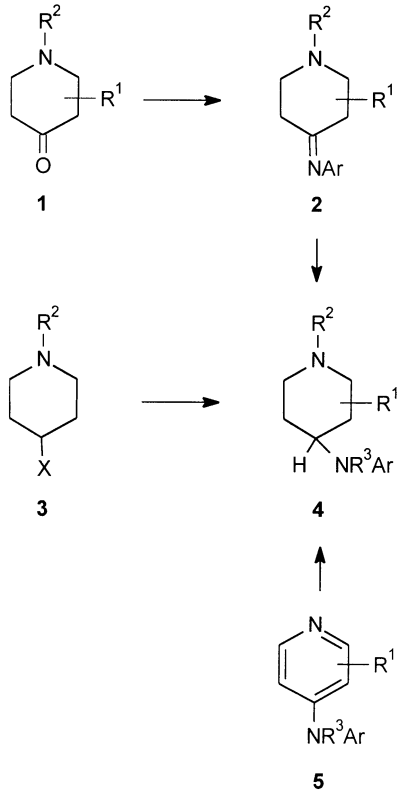
1-Substituted 4-anilinopiperidines **4** are used as precursors for the synthesis of narcotic analgesics and antihistamines which are used in medical therapy.[1–3] A number of analogues has already been prepared,[4–18] some of them showing enhanced activity. Furthermore the 4-anilinopiperidine unit was inserted as linker group in antibacterial[19] and antiarrhythmic agents,[20] in adrenoceptor[21] and platelet-activating factor antagonists[22] and in orally active, nonpeptide oxytocin[23,24] and vasopressin antagonists.[25] Quite recently, 1-substituted 4-anilinopiperidines had been reported as serotonin antagonists[26], neurokinin receptor antagonists[27] and N-type calcium channel blockers.[28–30]

Usually they are prepared by the reaction of aniline with 1-substituted 4-piperidones **1** and the subsequent reduction of the resulting Schiff bases **2**.[5–14,20–30] Moreover they were synthesized by the reaction of the corresponding 4-chloropiperidines **3** with aniline derivatives[1] or by the nucleophilic aromatic substitution of electron-deficient halobenzenes with 1-substituted 4-aminopiperidines.[19] Another convenient method is the hydrogenation of the respective 4-anilinopyridines **5**.[15] (Scheme 1).

4-Anilino-1-arylpiperidines **4** with no further substitution of the piperidine ring have already been prepared from 4-bromo-1-arylpiperidines **3**,[31,32] but ring-substituted 4-anilino-1-phenylpiperidines have not yet been reported. This paper deals with the synthesis of 2-alkyl- and 2-aryl-substituted 4-anilino-1-phenylpiperidines by an alternative pathway.

2. Results and discussion

Our method is based on the conversion of 6-iminodihydro-2*H*-thiopyrans to dihydropyridine-2-thiones by a Dimroth-type[33] rearrangement. The 6-phenylimino-3,6-dihydro-2*H*-thiopyran-4-anilines **13** were synthesized from 5,6-dihydro-2*H*-thiopyran-2-thiones **8**, which are available from α,β-unsaturated methylketones **6** and dimethylammonium



Scheme 1. R^1: alkyl; R^2: H, acyl, alkyl, aryl; R^3: H, acyl, alkyl; Ar: aryl; X: halogen.

Keywords: piperidines; rearrangement; hydrogenation; stereoisomerism.

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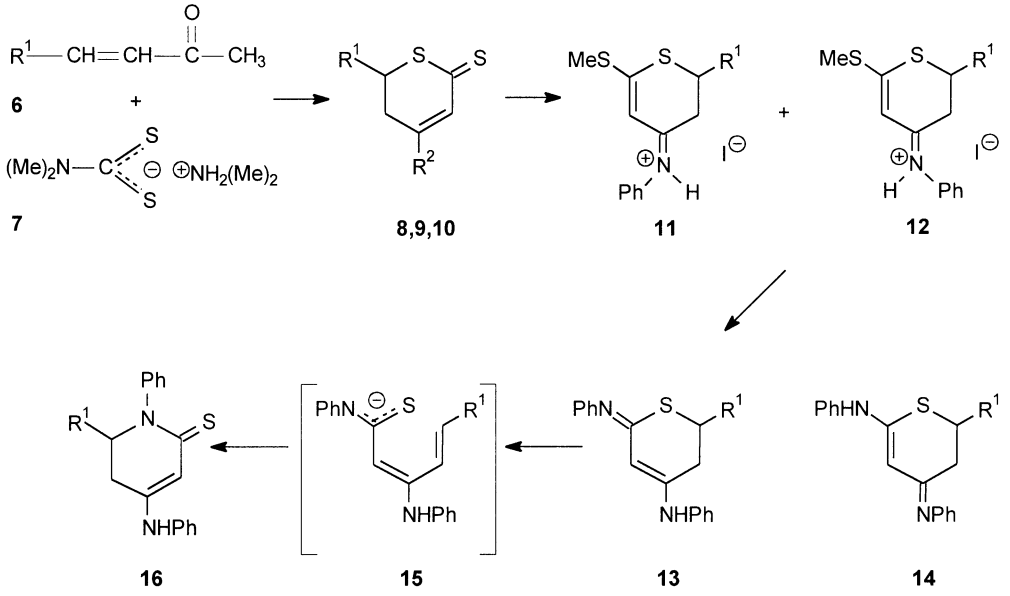
Table 1. Ratio of isomeric methoiodides determined by ^{1}H NMR integration

Isomer	**11a**, **12a**	**11b**, **12b**	**17a**, **18a**	**17b**, **18b**
syn-Isomer	73	60	86	67
anti-Isomer	27	40	14	33

N,*N*-dimethyldithiocarbamate **7** in a one-pot reaction.[34] The 4-dimethylamino group of the latter was removed by alkaline hydrolysis yielding the 4-hydroxy derivatives **9**, which gave upon treatment with aniline the 4-phenylamino-2*H*-thiopyran-2-thiones **10**. The thiones **10** were quantitatively alkylated to a mixture of the isomeric methylthioderivatives **11**, **12** with the *syn*-isomers **11a**, **b** as main components (Table 1). The relative configurations of compounds **11** and **12** were deduced from their ^{1}H- and ^{13}C NMR spectra: the shielding of the 4-anilino ring causes upfield shifts of the signals for neighbouring protons and carbons in *syn* position. Furthermore, NOE measurements proved the 3-Hs in **11a**, **b** and the 5-Hs in **12a**, **b** to be *cis* relative to the corresponding NHs. The reactions of **11** and **12** with aniline gave their 6-phenyliminoderivatives **13**. In ^{1}H NMR spectra we observed signals for ca. 16% of a second isomeric form, however we did not investigate if there is an equilibrium with tautomer **14** or if it is a rotational isomer of **13**. In ge-HMQC spectra which were optimized for 10 Hz we observed long-range couplings from the NHs to C-3 and C-5 of the thiopyran ring establishing the 4-amino compounds **13** against the 4-imino tautomers **14** as main components. Compounds **13** were converted to 1-phenyl-5,6-dihydropyridine-2(1*H*)-thiones **16** by a Dimroth rearrangement, which was obvious from the signal of the thioxo carbon at 192 ppm in their ^{13}C NMR spectra. The transposition starts with the removal of a proton in position 3 of the thiopyran ring, whereupon ring cleavage between S-1 and C-2 occurs. The formed α,β,γ,δ-unsaturated anions **15** undergo protonation and ring closure to the dihydropyridinethiones **16** (Scheme 2).

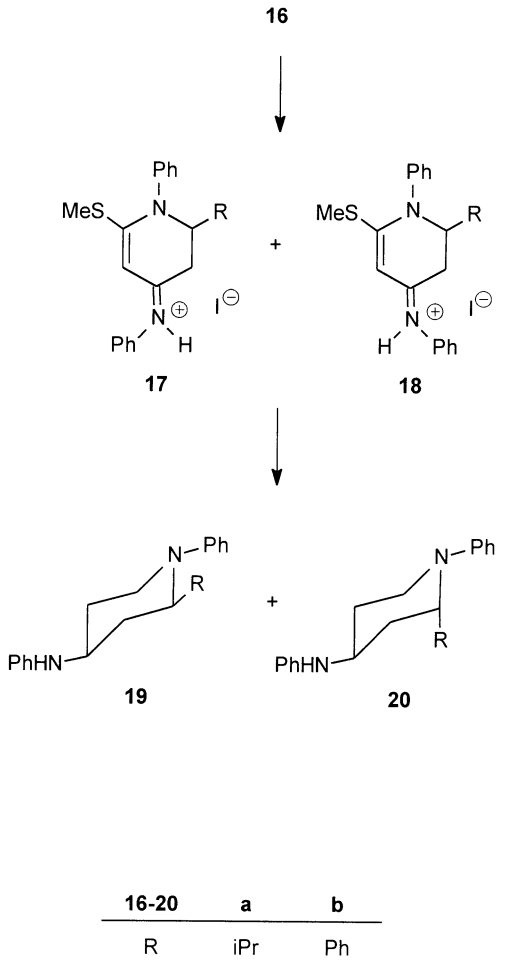
Their methoiodides **17** and **18** were a mixture of *syn*- and *anti*-isomers. In ^{1}H NMR spectra the *syn*-isomers **17a**, **b** were revealed as main components by characteristic upfield shifts of the signals for the protons in *syn* position to the 4-anilino ring (Table 1).

These results were confirmed by NOE measurements. Upon irradiation of the NHs we observed NOEs at the 3-Hs in **17a**, **b** and at the 5-Hs in **18a**, **b**. The hydrogenation of the dihydropyridine-2(1*H*)-thiones **16** to 4-anilinopiperidines **19** and **20** with Raney nickel failed under mild reaction conditions, whereas an increase of the pressure, the temperature or the activity of the catalyst always caused the cleavage of the heterocyclic ring. The hydrogenations of the methoiodides **17** and **18** with Raney nickel W-7[35] gave even at ambient temperature and atmospheric pressure



	6a	**6b**	**8a**	**8b**	**9a**	**9b**	**10a**	**10b**	**11a-16a**	**11b-16b**
R^1	iPr	Ph	iPr	Ph	iPr	Ph	iPr	Ph	iPr	Ph
R^2	----	----	$N(Me)_2$	$N(Me)_2$	OH	OH	NHPh	NHPh	----	----

Scheme 2.



Scheme 3.

mixtures of 4-anilinopiperidines with large amounts of non-cyclized compounds. Therefore **17** and **18** were treated with Raney nickel W-2[36] at room temperature affording mixtures of **19** and **20** in good yields. The isomers were separated by LC yielding larger amounts of compounds **19**, which are energetically favoured due to the equatorial substituent in ring position 2 (Scheme 3).

The resonances in ^{1}H- and ^{13}C NMR spectra were assigned with the aid of 2D NMR spectra (H,H-COSY and ge-HMQC). The relative configurations at C-2 and C-4 of compounds **19** and **20** were deduced from the $^{3}J_{(2\text{-H, }3\text{-H})}$ and $^{3}J_{(3\text{-H, }4\text{-H})}$ coupling constants in ^{1}H NMR spectra. The $^{3}J_{(3\text{-H, }4\text{-H})}$ couplings were ca. 11 Hz for all compounds indicating axial positions of 3-Hs and 4-Hs. Furthermore, 11 Hz $^{3}J_{(2\text{-H, }3\text{-H})}$ couplings revealed the axial positions of the 2-Hs in **19a**, **b**, whereas the equatorial 2-Hs in **20a**, **b** caused typical 5 Hz $^{3}J_{(2\text{-H, }3\text{-H})}$ couplings.

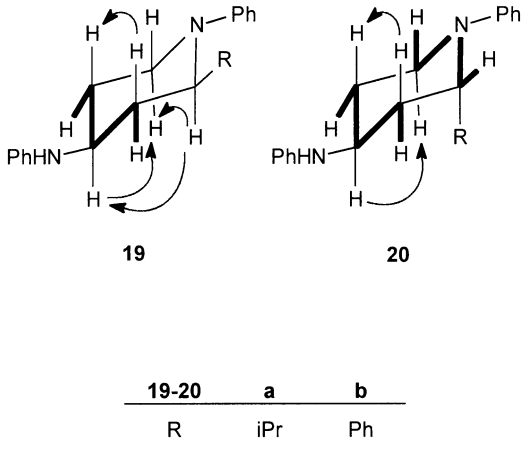


Figure 1. NOEs (arrows) and w-couplings (bold) in ^{1}H NMR spectra of **19** and **20**.

The conformations of compounds **19** and **20** were investigated by NOE and homodecoupling NMR experiments. NOEs from the axial protons in ring position 3 to the axial 5-Hs as well as from the axial protons in ring position 6 to the 4-Hs were detected. Upon irradiation of the axial 2-Hs in compounds **19** we observed NOEs at the axial 6-Hs and 4-Hs. Besides, w-couplings[37] between the equatorial protons in positions 3 and 5 of **19** and **20** were detected by homodecoupling experiments. Additional w-couplings were established between the equatorial 2-Hs and 6-Hs of compounds **20** (Fig. 1). Their values were estimated from the reduction of the signal half-width during homodecoupling.

All above-mentioned observations indicate that the piperidine rings of compounds **19** and **20** prefer chair conformations.

The present method provides an access to 2-alkyl and 2-aryl substituted 4-anilino-1-arylpiperidines from easily available α,β-unsaturated methylketones.

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. Assignments marked with an asterisk are interchangeable between *syn*- and *anti*-isomers. Isomeric ratios were determined by ^{1}H NMR integration. Microanalyses: Microanalytical Laboratory at the Institute of Physical Chemistry, University of Vienna. Hydrogenations were performed in a Parr hydrogenation apparatus shaker type 3911. Chromatography: column chromatography (CC): pump: Labomatic MD-80, silica gel 60 (Merck), 0.015–0.025 mm, pore-diameter 60 Å; column diameter 40 mm, layer thickness 410 mm, rate of flow: 15 ml min^{-1}, detection: Wellchrom K-2400 RI detector (Knauer), thin-layer chromatography (TLC): TLC plates (Merck) silica gel 60 F_{254}.

3.1.1. (*RS*)-(±)-4-Dimethylamino-6-(1-methylethyl)-5,6-dihydro-2*H*-thiopyran-2-thione (8a). 5-Methylhex-3-en-2-one **6a** (1.0 mol) and dimethylammonium *N*,*N*-dimethyldithiocarbamate **7** (0.5 mol) were suspended in 350 ml of bromobenzene. The mixture was refluxed at a water separator for 6 h and the solvent removed in vacuo. The residue

was triturated with ethanol, filtered and recrystallized. Yield: 62.5 g (58.0%); mp 161°C (ethanol); IR (KBr): $\tilde{\nu}$=2962 (m), 2865 (w), 1548 (s), 1486 (s), 1262 (s), 989 (s) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.05, 1.06 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.91–2.02 (m, 1H, $CH(CH_3)_2$), 2.53 (dd, J=16.4, 12.2 Hz, 1H, 5-H), 2.86 (dd, J=16.4, 3.5 Hz, 1H, 5-H), 3.14 (s, 6H, $N(CH_3)_2$), 3.26 (ddd, J= 12.2, 6.2, 3.5 Hz, 1H, 6-H), 6.52 (s, 1H, 3-H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 19.44, 19.99 ($CH(CH_3)_2$), 30.43 (C-5), 31.24 ($CH(CH_3)_2$), 40.72 ($N(CH_3)_2$), 50.08 (C-6), 112.74 (C-3), 159.15 (C-4), 208.05 (C-2); Anal. Calcd for $C_{10}H_{17}NS_2$ (215.38): C, 55.77; H, 7.96; N, 6.50; S, 29.77%. Found: C, 55.77; H, 8.04; N, 6.53; S, 29.52%.

3.1.2. (*RS*)-(±)-4-Dimethylamino-6-phenyl-5,6-dihydro-2*H*-thiopyran-2-thione (8b). 8b was obtained from methylstyrylketone **6b** and dimethylammonium-*N*,*N*-dimethyldithiocarbamate **7** according to a reported procedure.[34] Mp 192°C (mp[34] 194°C); IR (KBr): $\tilde{\nu}$=2870 (w), 1536 (s), 1469 (s), 1432 (s), 1411 (s), 1250 (s), 979 (s) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 400 MHz): 2.94 (dd, J=17.1, 13.0 Hz, 1H, 5-H), 3.08 (dd, J=17.1, 3.4 Hz, 1H, 5-H), 3.12 (s, 6H, $N(CH_3)_2$), 4.57 (dd, J=13.0, 3.4 Hz, 1H, 6-H), 6.61 (s, 1H, 3-H), 7.31–7.39 (m, 5H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 34.00 (C-5), 40.88 ($N(CH_3)_2$), 47.70 (C-6), 112.65 (C-3), 127.60, 128.34, 128.97, 137.86 (aromatic C), 158.69 (C-4), 207.67 (C-2) ppm.

3.2. 4-Anilino-5,6-dihydro-2*H*-thiopyran-2-thiones (10)

General procedure. The 4-dimethylamino-2*H*-thiopyran-2-thiones (0.2 mol) were suspended in a 2 M solution of sodium hydroxide (0.5 mol) and stirred at 60°C for 24 h. The mixture was cooled and filtered. The ice-cooled solution was acidified with HCl_{conc} and repeatedly extracted with toluene (300 ml). The organic layers were carefully washed with H_2O and brine. After drying over Na_2SO_4, ca. 50 ml of the solvent were removed in vacuo. Without further purification of the formed 4-hydroxy compounds **9**, aniline (0.2 mol) and acetic acid (0.12 mol) were added to the solution and the mixture was heated at a water separator for 8 h. The mixture was cooled and the solvents removed in vacuo. The residue was triturated with 2-propanol, filtered with suction and recrystallized.

3.2.1. (*RS*)-(±)-4-Anilino-6-(1-methylethyl)-5,6-dihydro-2*H*-thiopyran-2-thione (10a). Yield: 37.2 g (70.6%); mp 205°C (2-propanol); IR (KBr): $\tilde{\nu}$=2958 (w), 1518 (s), 1494 (m), 1449 (m), 1395 (m), 1236 (m), 980 (m) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.02, 1.03 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.88–1.97 (m, 1H, $CH(CH_3)_2$), 2.73 (dd, J=16.2, 11.9 Hz, 1H, 5-H), 2.82 (dd, J=16.2, 3.7 Hz, 1H, 5-H), 3.28 (ddd, J=11.9, 6.4, 3.7 Hz, 1H, 6-H), 6.66 (s, 1H, 3-H), 7.17–7.37 (m, 5H, aromatic H), 7.49 (br, s, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 19.66, 19.86 ($CH(CH_3)_2$), 31.22 ($CH(CH_3)_2$), 33.63 (C-5), 50.48 (C-6), 112.23 (C-3), 124.73, 127.00, 129.59, 136.61 (aromatic C), 155.91 (C-4), 212.22 (C-2); Anal. Calcd for $C_{14}H_{17}NS_2$ (263.42): C, 63.83; H, 6.50; N, 5.32; S, 24.34%. Found: C, 63.64; H, 6.71; N, 5.30; S, 24.21%.

3.2.2. (*RS*)-(±)-4-Anilino-6-phenyl-5,6-dihydro-2*H*-thiopyran-2-thione (10b). Yield: 40.3 g (67.7%); mp 234°C (2-propanol); IR (KBr): $\tilde{\nu}$=3005 (w), 1519 (s), 1507 (s), 1448 (m), 1391 (m), 1237 (m), 966 (m) cm^{-1}; ^1H NMR (DMSO-d_6, δ, 400 MHz): 3.02 (dd, J=16.6, 3.1 Hz, 1H, 5-H), 3.39 (dd, J=16.6, 12.4 Hz, 1H, 5-H), 4.84 (dd, J= 12.4, 3.1 Hz, 1H, 6-H), 6.50 (s, 1H, 3-H), 7.28–7.51 (m, 10H, aromatic H), 9.98 (br, s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, δ, 100 MHz): 34.92 (C-5), 46.57 (C-6), 111.01 (C-3), 124.70, 126.55, 127.69, 128.10, 128.87, 129.60, 137.33, 138.54 (aromatic C), 156.80 (C-4), 208.28 (C-2); Anal. Calcd for $C_{17}H_{15}NS_2$ (297.44): C, 68.65; H, 5.08; N, 4.71; S, 21.56%. Found: C, 68.53; H, 5.16; N, 4.69; S, 21.63%.

3.3. 6-Methylthio-*N*-phenyl-2*H*-thiopyran-4(3*H*)-iminiumiodides (11, 12)

General procedure. A solution of iodomethane (0.12 mol) in 50 ml of $CHCl_3$ was added through a dropping funnel to a suspension of **10** (0.1 mol) in $CHCl_3$ (200 ml) within 1 h. The reaction mixture was stirred for 16 h at room temperature. The solvent was removed in vacuo. The residue was triturated with ethyl acetate, filtered with suction and recrystallized.

3.3.1. (*RS*)-(±)-2-(1-Methylethyl)-6-methylthio-*N*-phenyl-2*H*-thiopyran-4(3*H*)-iminiumiodide (11a, 12a). Yield: 38.4 g (94.7%); mp 145°C (chloroform/ethyl acetate); IR (KBr): $\tilde{\nu}$=2769 (m), 1601 (m), 1570 (m), 1514 (s), 1491 (m), 1452 (m), 1282 (m), 1269 (m) cm^{-1}; **11a** (main component): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.15, 1.18 (2d, J= 6.9 Hz, 6H, $CH(CH_3)_2$), 2.09–2.23 (m, 1H, $CH(CH_3)_2$), 2.59 (s, 3H, SCH_3), 3.19 (dd, J=17.2, 13.3 Hz, 1H, 3-H), 3.55 (ddd, J=13.3, 6.1, 3.0 Hz, 1H, 2-H), 4.36 (dd, J=17.2, 3.0 Hz, 1H, 3-H), 6.53 (s, 1H, 5-H), 7.41–7.51 (m, 5H, aromatic H), 12.95 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 16.18 (SCH_3), 19.59, 20.01 ($CH(CH_3)_2$), 31.37 ($CH(CH_3)_2$), 32.76 (C-3), 50.41 (C-2), 105.49 (C-5), 125.07, 129.35, 129.86, 134.37 (aromatic C), 167.14 (C-4), 183.71 (C-6) ppm. **12a** (minor constituent): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.97, 1.04 (2d, J=6.9 Hz, 6H, $CH(CH_3)_2$), 1.96–2.10 (m, 1H, $CH(CH_3)_2$), 2.79 (s, 3H, SCH_3), 2.92 (dd, J=17.3, 12.2 Hz, 1H, 3-H), 3.11 (dd, J= 17.3, 3.2 Hz, 1H, 3-H), 3.36 (ddd, J=12.2, 6.1, 3.1 Hz, 1H, 2-H), 7.41–7.51 (m, 5H, aromatic H), 8.11 (s, 1H, 5-H), 12.95 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 17.83 (SCH_3), 19.45, 19.87 $CH(CH_3)_2$, 30.73 (C-3), 31.07 ($CH(CH_3)_2$), 49.88 (C-2), 109.33 (C-5), 125.04, 129.40, 129.78, 133.95 (aromatic C), 168.32 (C-4), 179.53 (C-6); Anal. Calcd for $C_{15}H_{20}INS_2$ (405.36): C, 44.45; H, 4.97; I, 31.31; N, 3.46; S, 15.82%. Found: C, 44.53; H, 4.92; I, 31.29; N, 3.44; S, 15.77%.

3.3.2. (*RS*)-(±)-6-Methylthio-*N*,2-diphenyl-2*H*-thiopyran-4(3*H*)-iminiumiodide (11b, 12b). Yield: 42.7 g (97.2%); mp 168°C (chloroform/ethyl acetate); IR (KBr): $\tilde{\nu}$=2812 (m), 1601 (m), 1569 (m), 1508 (s), 1490 (s), 1454 (s), 1281 (m), 1265 (m) cm^{-1}; **11b** (main component): ^1H NMR ($CDCl_3$, δ, 400 MHz): 2.56 (s, 3H, SCH_3), 3.73 (dd, J=17.4, 13.7 Hz, 1H, 3-H), 4.40 (dd, J=17.4, 3.1 Hz, 1H, 3-H), 5.01 (dd, J=13.7, 3.1 Hz, 1H, 2-H), 6.55 (s, 1H, 5-H), 7.29–7.56 (m, 10H, aromatic H), 12.90 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 16.15 (SCH_3), 35.28 (C-3), 46.60 (C-2), 105.90 (C-5), 125.30, 127.65,

129.28, 129.30, 129.35, 129.74, 134.25, 134.47 (aromatic C), 166.61 (C-4), 183.32 (C-6) ppm. **12b** (minor constituent): ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 2.72 (s, 3H, SCH_3), 3.30 (dd, J=17.6, 2.9 Hz, 1H, 3-H), 3.53 (dd, J=17.6, 13.9 Hz, 1H, 3-H), 4.77 (dd, J=13.9, 2.9 Hz, 1H, 2-H), 7.29–7.56 (m, 10H, aromatic H), 8.14 (s, 1H, 5-H), 12.90 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 17.58 (SCH_3), 33.73 (C-3), 46.56 (C-2), 109.39 (C-5), 125.14, 127.66, 129.26, 129.30, 129.42, 129.62, 133.83, 135.05 (aromatic C), 168.25 (C-4), 179.10 (C-6); Anal. Calcd for $C_{18}H_{18}INS_2$ (439.38): C, 49.21; H, 4.13; I, 28.88; N, 3.19; S, 14.60%. Found: C, 49.03; H, 4.15; I, 28.68; N, 3.16; S, 14.53%.

3.4. *N*-Phenyl-6-phenylimino-3,6-dihydro-2*H*-thiopyran-4-amines (13)

General procedure. The respective *N*-phenyl-6-methylthio-2*H*-thiopyran-4(3*H*)-iminiumiodides **11** and **12** (0.09 mol) were dissolved in aniline (2 moles). The mixture was stirred at 60°C for 18 h, while a stream of nitrogen was passed through. The formed mercaptan was captured in a gas-washing bottle with dilute caustic soda. The excess of aniline was removed in vacuo. The residue was triturated with ethyl acetate, filtered with suction, dried and subsequently stirred in a 2 M solution of sodium hydroxide (0.8 mol) in water for 1 h. The resulting suspension was extracted with ether or toluene repeatedly. The combined extracts were washed three times with water and dried over Na_2SO_4. The solvent was evaporated. The residue was triturated with ethanol/water, filtered with suction, dried and recrystallized.

3.4.1. (*RS*)-(±)-2-(1-Methylethyl)-*N*-phenyl-6-phenylimino-3,6-dihydro-2*H*-thiopyran-4-amine (13a). Yield: 24.4 g (84.1%); mp 143°C (ethanol/water); IR (KBr): $\tilde{\nu}$= 2958 (w), 1585 (m), 1531 (s), 1494 (m), 1229 (m), 695 (m) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 400 MHz): 0.93, 0.94 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.80–1.87 (m, 1H, $CH(CH_3)_2$), 2.66 (dd, J=16.2, 11.2 Hz, 1H, 3-H), 2.76 (dd, J=16.2, 2.5 Hz, 1H, 3-H), 3.18–3.26 (m, 1H, 2-H), 5.84 (s, 1H, 5-H), 6.72–7.42 (m, 10H, aromatic H), 8.42 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d$_6$, δ, 100 MHz): 19.88 ($CH(CH_3)_2$), 31.63 ($CH(CH_3)_2$), 33.28 (C-3), 46.80 (C-2), 96.87 (C-5), 120.84, 122.56, 123.67, 128.79, 129.36, 140.14, 151.45 (aromatic C), 152.40 (C-4), 159.44 (C-6); Anal. Calcd for $C_{20}H_{22}N_2S$ (322.47): C, 74.49; H, 6.88; N, 8.69; S, 9.94%. Found: C, 74.30; H, 7.02; N, 8.68; S, 9.82%.

3.4.2. (*RS*)-(±)-*N*,2-Diphenyl-6-phenylimino-3,6-dihydro-2*H*-thiopyran-4-amine (13b). Yield: 25.0 g (77.1%); mp 165°C (ethanol); IR (KBr): $\tilde{\nu}$=3200 (w), 3040 (m), 1620 (m), 1590 (s), 1530 (s), 1490 (s), 1445 (s), 1290 (m), 1230 (s), 1170 (s), 695 (s) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, δ, 400 MHz): 2.89 (dd, J=16.3, 2.9 Hz, 1H, 3-H), 3.23 (dd, J=16.3, 12.1 Hz, 1H, 3-H), 4.62 (dd, J=12.1, 2.9 Hz, 1H, 2-H), 5.92 (s, 1H, 5-H), 6.74–7.52 (m, 15H, aromatic H), 8.39 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d$_6$, δ, 100 MHz): 36.42 (C-3), 43.72 (C-2), 96.55 (C-5), 120.80, 122.80, 122.99, 123.89, 127.90, 128.12, 128.75, 128.85, 129.44, 139.84, 139.91, 151.27 (aromatic C), 152.40 (C-4), 159.56 (C-6); Anal. Calcd for $C_{23}H_{20}N_2S$+0.2 H_2O (360.09): C, 76.72; H, 5.71; N, 7.78; S, 8.90%. Found: C, 76.82; H, 5.74; N, 7.89; S, 8.73%.

3.5. 4-Anilino-1-phenyl-5,6-dihydropyridine-2(1*H*)-thiones (16)

General procedure. Compounds **13** (0.05 mol) were added to 200 ml of freshly distilled DMF. A stream of argon was passed through the suspension for 5 min. The reflux condenser was closed with a balloon and the reaction mixture was refluxed for 16 h. The solvent was removed in vacuo. The residue was triturated with ethanol/ethyl acetate, filtered with suction and recrystallized.

3.5.1. (*RS*)-(±)-4-Anilino-6-(1-methylethyl)-1-phenyl-5,6-dihydropyridine-2(1*H*)-thione (16a). Yield: 11.5 g (71.3%); mp 199°C (ethanol); IR (KBr): $\tilde{\nu}$=3174 (w), 3029 (w), 2960 (w), 1611 (m), 1583 (s), 1534 (m), 1492 (m), 1444 (m), 1427 (m), 1276 (m), 1163 (m), 699 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 0.89, 1.01 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 2.19–2.28 (m, 1H, $CH(CH_3)_2$), 2.49 (dd, J=16.4, 3.1 Hz, 1H, 5-H), 3.01 (dd, J=16.4, 7.8 Hz, 1H, 5-H), 3.83–3.88 (m, 1H, 6-H), 5.98 (s, 1H, NH), 6.28 (s, 1H, 3-H), 7.13–7.44 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 17.49, 19.75 ($CH(CH_3)_2$), 28.11 (C-5), 30.27 ($CH(CH_3)_2$), 65.15 (C-6), 101.83 (C-3), 123.03, 125.05, 127.29, 128.66, 128.84, 129.32, 138.36 (aromatic C), 145.70 (C-4), 191.99 (C-2); Anal. Calcd for $C_{20}H_{22}N_2S$ (322.47): C, 74.49; H, 6.88; N, 8.69; S, 9.94%. Found: C, 74.27; H, 7.05; N, 8.74; S, 9.77%.

3.5.2. (*RS*)-(±)-4-Anilino-1,6-diphenyl-5,6-dihydropyridine-2(1*H*)-thione (16b). Yield: 14.4 g (80.8%); mp 216°C (ethanol); IR (KBr): $\tilde{\nu}$=3260 (m), 3190 (w), 3120 (w), 3050 (w), 1580 (s), 1530 (s), 1490 (s), 1425 (s), 1370 (m), 1240 (m), 1160 (s), 755 (s), 695 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 2.59 (dd, J=16.1, 2.5 Hz, 1H, 5-H), 3.48 (dd, J=16.1, 6.2 Hz, 1H, 5-H), 5.07 (dd, J=6.2, 2.5 Hz, 1H, 6-H), 5.94 (s, 1H, NH), 6.42 (s, 1H, 3-H), 7.07–7.35 (m, 15H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 36.63 (C-5), 63.99 (C-6), 103.48 (C-3), 123.18, 125.27, 126.91, 127.30, 127.51, 128.01, 128.71, 128.95, 129.40, 138.09, 139.36 (aromatic C), 143.77 (C-4), 146.11 (aromatic C), 192.76 (C-2); Anal. Calcd for $C_{23}H_{20}N_2S$ (356.49): C, 77.49; H, 5.65; N, 7.86; S, 9.00%. Found: C, 77.08; H, 5.78; N, 7.70; S, 8.92%.

3.6. 6-Methylthio-*N*,1-diphenyl-2,3-dihydropyridine-4(1*H*)-iminiumiodides (17, 18)

General method. A solution of iodomethane (0.036 mol) in 20 ml of chloroform was added through a dropping funnel to a suspension of **16** (0.03 mol) in 80 ml of chloroform within 1 h. The solution was stirred for 18 h at room temperature. The solvent was removed in vacuo. The residue was triturated with ethanol/ethyl acetate, filtered with suction and recrystallized.

3.6.1. (*RS*)-(±)-2-(1-Methylethyl)-6-methylthio-*N*,1-diphenyl-2,3-dihydropyridine-4(1*H*)-iminiumiodide (17a, 18a). Yield: 12.4 g (87.1%); mp 215°C (chloroform/ethyl acetate); IR (KBr): $\tilde{\nu}$=3036 (m), 2960 (m), 1602 (m), 1579 (s), 1560 (s), 1479 (s), 1408 (m), 1281 (s), 764 (m),

697 (m) cm^{-1}; **17a** (main component): ^1H NMR (DMSO-d_6, δ, 400 MHz): 0.90, 0.97 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 2.04–2.14 (m, 1H, $CH(CH_3)_2$), 2.39 (s, 1H, SCH_3), 3.01–3.09 (m, 1H, 3-H), 3.49–3.59 (m, 1H, 3-H), 4.12–4.17 (m, 1H, 2-H), 5.65 (s, 1H, 5-H), 7.33–7.62 (m, 10H, aromatic H), 11.07 (br, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, δ, 100 MHz): 15.56 (SCH_3), 17.32, 19.03 ($CH(CH_3)_2$), 27.53 (C-3), 29.53 ($CH(CH_3)_2$), 65.52 (C-2), 86.19 (C-5), 123.89, 127.56, 128.37, 130.01, 130.14, 136.69, 140.75 (aromatic C), 159.34 (C-4), 175.83 (C-6) ppm. **18a** (minor constituent): ^1H NMR (DMSO-d_6, δ, 400 MHz): 0.70, 0.80 (2d, J=6.2 Hz, 6H, $CH(CH_3)_2$), 1.96–2.06 (m, 1H, $CH(CH_3)_2$), 2.53 (s, 1H, SCH_3), 2.73–2.81 (m, 1H, 3-H), 3.41-3.51 (m, 1H, 3-H), 4.01–4.08 (m, 1H, 2-H), 5.86 (s, 1H, 5-H), 7.33–7.62 (m, 10H, aromatic H), 11.07 (br, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6, δ, 100 MHz): 15.86 (SCH_3), 17.79, 18.95 ($CH(CH_3)_2$), 23.12 (C-3), 29.45 ($CH(CH_3)_2$), 66.10 (C-2), 90.14 (C-5), 162.67 (C-4), 173.66 (C-6), residual ^{13}C resonances were not detected; Anal. Calcd for $C_{21}H_{25}IN_2S+0.5\ H_2O$ (474.43): C, 53.17; H, 5.74; I, 26.75; N, 5.90; S, 6.76%. Found: C, 53.15; H, 5.59; I, 26.78; N, 5.85; S, 6.42%.

3.6.2. (*RS*)-(±)-6-Methylthio-*N*,1,2-triphenyl-2,3-dihydropyridine-4(1*H*)-iminiumiodide (17b, 18b). Yield: 14.7 g (98.3%); mp 223°C (chloroform/ethyl acetate); IR (KBr): $\tilde{\nu}$=3170 (w), 3130 (w), 2980 (m), 2930 (m), 1610 (m), 1570 (s), 1470 (s), 1340 (s), 1230 (m), 1170 (m), 770 (s), 700 (s) cm^{-1}; **17b** (main component): ^1H NMR ($CDCl_3$, δ, 400 MHz): 2.34 (s, 3H, SCH_3), 4.01 (d, J=6.3 Hz, 2H, 3-H), 5.16 (t, J=6.3 Hz, 1H, 2-H), 5.72 (s, 1H, 5-H), 7.20–7.53 (m, 15H, aromatic H), 11.10 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 16.05 (SCH_3), 35.15 (C-3), 64.91 (C-2), 87.18 (C-5), 124.65, 127.14, 127.69, 127.83*, 128.96*, 129.09, 129.44*, 129.58, 129.78*, 135.55, 135.90, 140.46 (aromatic C), 159.58 (C-4), 175.54 (C-6) ppm. **18b** (minor constituent): ^1H NMR ($CDCl_3$, δ, 400 MHz): 2.61 (s, 3H, SCH_3), 3.24 (dd, J=17.2, 6.1 Hz, 1H, 3-H), 3.68 (dd, J=17.2, 7.0 Hz, 1H, 3-H), 5.09 (dd, J=7.0, 6.1 Hz, 1H, 2-H), 7.23 (s, 1H, 5-H), 7.20–7.53 (m, 15H, aromatic H), 11.10 (br, 1H, NH) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 16.96 (SCH_3), 31.18 (C-3), 64.74 (C-2), 92.01 (C-5), 124.88, 127.16, 127.53*, 127.88*, 129.05*, 129.15*, 135.32, 136.26, 140.51 (aromatic C), 160.35 (C-4), 174.99 (C-6); Anal. Calcd for $C_{24}H_{23}IN_2S$ (498.43): C, 57.85; H, 4.65; I, 25.46; N, 5.62; S, 6.43%. Found: C, 57.98; H, 4.66; I, 25.39; N, 5.49; S, 6.50%.

3.7. 4-Anilino-1-phenylpiperidines (19, 20)

General method. 25 g of freshly prepared Raney nickel W-2[36] were added to a solution of compounds **17** and **18** (0.005 mol) in 50 ml of ethanol. The mixture was shaken at room temperature at 30 psi for 8 h. The reaction mixture was sucked off. The residue was washed with ethanol. The filtrate was concentrated in vacuo. The isomers were separated by CC over silica gel eluting with cyclohexane/ethyl acetate (19:1). The dihydrochlorides of **19** and **20** were afforded by treatment with equivalent amounts of a 1 M solution of hydrogen chloride in diethylether. The solvent was evaporated and the residues recrystallized.

3.7.1. (2*RS*,4*SR*)-(±)-4-Anilino-2-(1-methylethyl)-1-phenylpiperidine (19a). Yield: 1.16 g (56.1%); mp (diHCl): 196°C (ethanol/ethyl acetate); R_f (base)=0.39 (cyclohexane:ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3386 (s), 2969 (s), 2637 (s), 2488 (s), 1599 (m), 1495 (s), 1452 (m), 1409 (m), 1031 (m), 757 (s), 697 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.78, 0.82 (2d, J=6.8 Hz, 6H, $CH(CH_3)_2$), 1.30 (ddd, J=11.6, 11.6, 11.0 Hz, 1H, 3-H_{ax}), 1.49 (dddd, J=11.4, 11.4, 10.8, 4.1 Hz, 1H, 5-H_{ax}), 1.76–1.86 (m, 1H, $CH(CH_3)_2$), 2.05–2.18 (m, 2H, 3-H_{eq}, 5-H_{eq}), 2.88–2.99 (m, 2H, 6-H_{ax}, 2-H_{ax}), 3.19 (ddd, J=12.5, 4.4, 4.4 Hz, 1H, 6-H_{eq}), 3.37–3.45 (m, 1H, 4-H_{ax}), 3.56 (br, s, 1H, NH), 6.60–7.32 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 15.62, 19.73 ($CH(CH_3)_2$), 28.48 ($CH(CH_3)_2$), 31.30 (C-3), 33.05 (C-5), 50.26 (C-4), 54.06 (C-6), 63.20 (C-2), 113.20, 117.21, 123.37, 123.69, 129.03, 129.36, 147.13, 152.25 (aromatic C); Anal. Calcd for $C_{20}H_{28}Cl_2N_2+C_2H_5OH$ (413.43): C, 63.91; H, 8.29; Cl, 17.15; N, 6.78%. Found: C, 63.57; H, 8.10; Cl, 17.12; N, 6.83%.

3.7.2. (2*RS*,4*RS*)-(±)-4-Anilino-2-(1-methylethyl)-1-phenylpiperidine (20a). Yield: 0.43 g (23.4%); mp (diHCl): 207°C (ethanol/ethyl acetate); R_f (base)=0.48 (cyclohexane:ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3417 (m), 3044 (m), 2970 (m), 2510 (s), 1597 (m), 1492 (s), 1445 (s), 1405 (m), 750 (s), 698 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 0.92, 1.04 (2d, J=6.5 Hz, 6H, $CH(CH_3)_2$), 1.37 (ddd, J=12.5, 12.5, 4.9 Hz, 1H, 3-H_{ax}), 1.36–1.44 (m, 1H, 5-H_{ax}), 2.01–2.05 (m, 1H, 5-H_{eq}), 2.17–2.22 (m, 1H, 3-H_{eq}), 2.23–2.30 (m, 1H, $CH(CH_3)_2$), 3.19 (ddd, J=13.6, 13.6, 2.4 Hz, 1H, 6-H_{ax}), 3.32 (br, s, 1H, NH), 3.55 (dddd, J=9.7, 4.9, 2.0, 1.5 Hz, 1H, 2-H_{eq}), 3.66–3.74 (m, 2H, 4-H_{ax}, 6-H_{eq}), 6.58–7.22 (m, 10H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 20.55, 20.57 ($CH(CH_3)_2$), 27.81 ($CH(CH_3)_2$), 31.40 (C-5), 32.36 (C-3), 41.08 (C-6), 46.56 (C-4), 62.40 (C-2), 113.24, 114.69, 116.97, 117.35, 129.21, 129.33, 146.91, 150.71 (aromatic C); Anal. Calcd for $C_{20}H_{28}Cl_2N_2$ (367.36): C, 65.39; H, 7.68; Cl, 19.30; N, 7.63%. Found: C, 65.38; H, 7.68; Cl, 18.96; N, 7.47%.

3.7.3. (2*RS*,4*SR*)-(±)-4-Anilino-1,2-diphenylpiperidine (19b). Yield: 1.59 g (71.1%); mp (diHCl): 195°C (ethanol/ethyl acetate); R_f (base)=0.36 (cyclohexane:ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3386 (m), 2968 (w), 2612 (s), 2490 (s), 1598 (m), 1562 (m), 1496 (s), 1451 (m), 1414 (m), 1044 (m), 756 (s), 695 (s) cm^{-1}; NMR (base): ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.63 (ddd, J=11.7, 11.7, 10.3 Hz, 1H, 3-H_{ax}), 1.74 (dddd, J=12.0, 12.0, 11.5, 4.1 Hz, 1H, 5-H_{ax}), 2.21–2.28 (m, 1H, 5-H_{eq}), 2.33–2.39 (m, 1H, 3-H_{eq}), 3.04 (ddd, J=12.0, 12.0, 2.6 Hz, 1H, 6-H_{ax}), 3.44 (br, s, 1H, NH), 3.54–3.61 (m, 1H, 4-H_{ax}), 3.60 (ddd, J=12.0, 4.1, 4.1 Hz, 1H, 6-H_{eq}), 4.20 (dd, J=10.3, 3.2 Hz, 1H, 2-H_{ax}), 6.57–7.25 (m, 15H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 33.12 (C-5), 42.73 (C-3), 50.11 (C-4), 54.60 (C-6), 62.62 (C-2), 113.31, 117.30, 122.05, 122.65, 126.42, 126.93, 128.16, 128.41, 129.21, 143.69, 146.81, 151.78 (aromatic C); Anal. Calcd for $C_{23}H_{26}Cl_2N_2+C_2H_5OH$ (447.45): C, 67.11; H, 7.21; Cl, 15.85; N, 6.26%. Found: C, 67.15; H, 7.22; Cl, 15.90; N, 6.55%.

3.7.4. (2*RS*,4*RS*)-(±)-4-Anilino-1,2-diphenylpiperidine (20b). Yield: 0.35 g (17.0%); mp (diHCl): 220°C (ethanol/

ethyl acetate); R_f (base)=0.45 (cyclohexane:ethyl acetate=4:1); IR (KBr): $\tilde{\nu}$=3424 (w), 3030 (m), 2994 (m), 2640 (s), 2601 (s), 2566 (s), 2469 (s), 1598 (m), 1569 (m), 1492 (s), 1442 (m), 758 (s), 694 (s) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 400 MHz): 1.60 (dddd, J=13.3, 10.9, 8.8, 4.3 Hz, 1H, 5-H_{ax}), 1.86 (ddd, J=13.3, 10.5, 5.0 Hz, 1H, 3-H_{ax}), 2.08–2.16 (m, 1H, 5-H_{eq}), 2.59–2.65 (m, 1H, 3-H_{eq}), 3.37 (ddd, J=13.7, 10.9, 3.3 Hz, 1H, 6-H_{ax}), 3.48–3.56 (m, 1H, 4-H_{ax}), 3.79 (dddd, J=13.7, 4.3, 4.3, 1.0 Hz, 1H, 6-H_{eq}), 5.13 (ddd, J=5.0, 3.3, 1.0 Hz, 1H, 2-H_{eq}), 6.52–7.33 (m, 15H, aromatic H) ppm. ^{13}C NMR ($CDCl_3$, δ, 100 MHz): 31.77 (C-5), 36.46 (C-3), 43.17 (C-6), 45.95 (C-4), 57.29 (C-2), 113.20, 114.88, 117.36, 117.94, 126.54, 126.85, 128.59, 129.22, 129.27, 141.15, 146.71, 150.15 (aromatic C); Anal. Calcd for $C_{23}H_{26}Cl_2N_2$+0.2 C_2H_5OH (410.59): C, 68.45; H, 6.68; Cl, 17.27; N, 6.82%. Found: C, 68.32; H, 6.59; Cl, 17.40; N, 6.81%.

References

1. Kallischnigg, R. (Knoll AG) Ger. 891547, 1953; *Chem. Abstr.* **1958**, *52*, 13805h.
2. Stoll, A.; Bourquin, J. P. (Sandoz) US 2757175, 1956; *Chem. Abstr.* **1957**, *51*, 2055e.
3. Janssen, P. A. J.; Gardocki, J. F. (N V Res Lab Dr C Janssen) US 3141823, 1962; *Chem. Abstr.* **1964**, *61*, 10689a.
4. Sandoz Ltd. Brit. 717227, 1954; *Chem. Abstr.* **1956**, *50*, 2684f.
5. Knoll A.-G. Brit. 700097, 1953; *Chem. Abstr.* **1955**, *49*, 6318g.
6. Aboul-Enein, M. N.; Khalifa, M.; El-Azouny, A. A. *Pharm. Acta Helv.* **1973**, *48*, 151–156.
7. Van Bever, W. F. M.; Niemegeers, C. J. E.; Janssen, P. A. J. *J. Med. Chem.* **1974**, *17*, 1047–1051.
8. Fifer, E. K.; Davis, W. M.; Borne, R. F. *Eur. J. Med. Chem. Chim. Ther.* **1984**, *19*, 519–524.
9. Burke Jr., T. R.; Jacobson, A. E.; Rice, K. C.; Silverton, J. V.; Simonds, W. F.; Streaty, R. A.; Klee, W. A. *J. Med. Chem.* **1986**, *29*, 1087–1093.
10. Lalinde, N.; Moliterni, J.; Wright, D.; Spencer, H. K.; Ossipov, M. H.; Spaulding, T. C.; Rudo, F. G. *J. Med. Chem.* **1990**, *33*, 2876–2882.
11. Brine, G. A.; Stark, P. A.; Liu, Y.; Carroll, F. I.; Singh, P.; Xu, H.; Rothman, R. B. *J. Med. Chem.* **1995**, *38*, 1547–1557.
12. Wang, Z.-X.; Zhu, Y.-C.; Jin, W.-Q.; Chen, X.-J.; Chen, J.; Ji, R.-Y.; Chi, Z.-Q. *J. Med. Chem.* **1995**, *38*, 3652–3659.
13. Micovic, I. V.; Roglic, G. M.; Ivanovic, M. D.; Dosen-Micovic, L.; Kiricojevic, V. D.; Popovic, J. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, *16*, 2041–2050.
14. Thomas, J. B.; Herault, X. M.; Rothman, R. B.; Burgess, J. P.; Mascarella, S. W.; Xu, H.; Horel, R. B.; Dersch, C. M.; Carroll, F. I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3053–3056.
15. Riley, T. N.; Hale, D. B.; Wilson, M. C. *J. Pharm. Sci.* **1973**, *62*, 983–986.
16. Casy, A. F.; Ogungbamila, F. O. *Eur. J. Med. Chem. Chim. Ther.* **1983**, *18*, 56–60.
17. Feldman, P. L.; James, M. K.; Brackeen, M. F.; Bilotta, J. M.; Schuster, S. V.; Lahey, A. P.; Lutz, M. W.; Johnson, M. R.; Leighton, H. J. *J. Med. Chem.* **1991**, *34*, 2202–2208.
18. Essawi, M. Y. H. *Pharmazie* **1999**, *54*, 307–308.
19. Kung, P.-P.; Casper, M. D.; Cook, K. L.; Wilson-Lingardo, L.; Risen, L. M.; Vickers, T. A.; Ranken, R.; Blyn, L. B.; Wyatt, J. R.; Cook, P. D.; Ecker, D. J. *J. Med. Chem.* **1999**, *42*, 4705–4713.
20. Nadler, G.; Faivre, J.-F.; Forest, M.-C.; Cheval, B.; Martin, M.; Souchet, M.; Gout, B.; Bril, A. *Bioorg. Med. Chem.* **1998**, *6*, 1993–2011.
21. Nerenberg, J. B.; Erb, J. M.; Thompson, W. J.; Lee, H.-Y.; Guare, J. P.; Munson, P. M.; Bergman, J. M.; Huff, J. R.; Broten, T. P.; Chang, R. S. L.; Chen, T. B.; O'Malley, S.; Schorn, T. W.; Scott, A. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2467–2472.
22. Fukushi, H.; Mabuchi, H.; Itoh, K.; Terashita, Z.-I.; Nishikawa, K.; Sugihara, H. *Chem. Pharm. Bull.* **1994**, *42*, 541–550.
23. Williams, P. D.; Clineschmidt, B. V.; Erb, J. M.; Freidinger, R. M.; Guidotti, M. T.; Lis, E. V.; Pawluczyk, J. M.; Pettibone, D. J.; Reiss, D. R.; Veber, D. F.; Woyden, C. J. *J. Med. Chem.* **1995**, *38*, 4634–4636.
24. Bell, I. M.; Erb, J. M.; Freidinger, R. M.; Gallicchio, S. N.; Guare, J. P.; Guidotti, M. T.; Halpin, R. A.; Hobbs, D. W.; Homnick, C. F.; Kuo, M. S.; Lis, E. V.; Mathre, D. J.; Michelson, S. R.; Pawluczyk, J. M.; Pettibone, D. J.; Reiss, D. R.; Vickers, S.; Williams, P. D.; Woyden, C. J. *J. Med. Chem.* **1998**, *41*, 2146–2163.
25. Ogawa, H.; Yamamura, Y.; Miyamoto, H.; Kondo, K.; Yamashita, H.; Nakaya, K.; Chihara, T.; Mori, T.; Tominaga, M.; Yabuuchi, Y. *J. Med. Chem.* **1993**, *36*, 2011–2017.
26. Ismaiel, A. M.; De Los Angeles, J.; Teitler, M.; Ingher, S.; Glennon, R. A. *J. Med. Chem.* **1993**, *36*, 2519–2525.
27. Remond, G.; Portevin, B.; Bonnet, J.; Canet, E.; Regoli, D.; De Nanteuil, G. *Eur. J. Med. Chem.* **1997**, *32*, 843–868.
28. Ryder, T. R.; Hu, L.-Y.; Rafferty, M. F.; Lotarski, S. M.; Rock, D. M.; Stoehr, S. J.; Taylor, C. P.; Weber, M. L.; Miljanich, G. P.; Millerman, E.; Szoke, B. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2453–2458.
29. Hu, L.-Y.; Ryder, T. R.; Rafferty, M. F.; Feng, M. R.; Lotarski, S. M.; Rock, D. M.; Sinz, M.; Stoehr, S. J.; Taylor, C. P.; Weber, M. L.; Bowersox, S. S.; Miljanich, G. P.; Millerman, E.; Wang, Y.-X.; Szoke, B. G. *J. Med. Chem.* **1999**, *42*, 4239–4249.
30. Hu, L.-Y.; Ryder, T. R.; Rafferty, M. F.; Taylor, C. P.; Feng, M. R.; Kuo, B.-S.; Lotarski, S. M.; Miljanich, G. P.; Millerman, E.; Siebers, K. M.; Szoke, B. G. *Bioorg. Med. Chem.* **2000**, *8*, 1203–1212.
31. Hahn, V.; Cerkovnikov, E.; Prelog, V. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 1658–1660.
32. Hahn, V.; Cerkovnikov, E.; Prelog, V. *Helv. Chim. Acta.* **1943**, *26*, 1132–1142.
33. Wahren, M. *Z. Chem.* **1969**, *9*, 241–252.
34. Schweiger, K. *Monatsh. Chem.* **1980**, *111*, 1175–1184.
35. Adkins, H.; Billica, H. R. *J. Am. Chem. Soc.* **1948**, *70*, 695–698.
36. Mozingo, R. *Organic Syntheses Collect.*; Horning, E. C., Ed.; Wiley: New York, 1967; Vol. 3, pp. 181–183.
37. Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; 2nd ed.; Pergamon: Oxford, 1969; pp 334–341.