Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 2105–2111

BIOORGANIC & MEDICINAL CHEMISTRY

The Structure of McN-5652

Oliver Schulze,[a,b] Ulrich Schmidt,[a] Jürgen Voss,[a,*] Bruno Nebeling,[b] Gunadi Adiwidjaja[c] and Klaus Scharwächter[a]

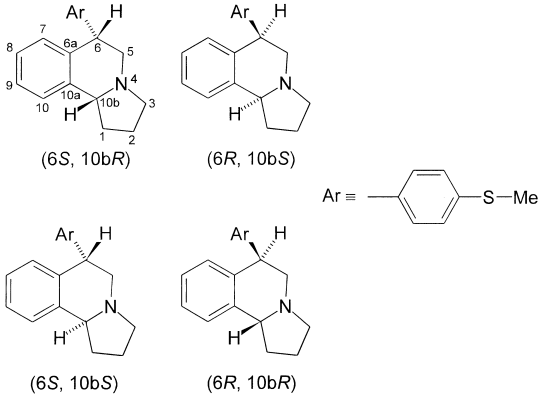
[a]*Institut für Organische Chemie der Universität Hamburg, Martin-Luther-King-Platz 6, 20146 Hamburg, Germany*
[b]*Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Radiologie, Abt. für Nuklearmedizin, UKE-Zyklotron, Luruper Chaussee 149, 22761 Hamburg, Germany*
[c]*Mineralogisch-Petrographisches Institut der Universität Hamburg, Grindelallee 48, 20146 Hamburg, Germany*

Received 8 August 2000; accepted 9 April 2001

Abstract—The configuration of the diastereoisomers of 6-(4-methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline **1** (McN-5652) is determined and unequivocally assigned by NMR spectroscopy (NOE measurements) and an X-ray structural analysis of the *trans* diastereoisomer. The enantiomers of *cis*-**1** are separated by preparative HPLC on a chiral phase. One of the enantiomers of *cis*-**1** represents the precursor for imaging the serotonin 5-HT transporter with positron emission tomography (PET).

Introduction

McN-5652-Z is a highly potent serotonin 5-HT transporter uptake blocker. Its [$^{11}CH_3$] derivative allows the visualization and evaluation of the serotonergic transporter density by the method of positron emission tomography (PET).[1–4] These studies might reveal what damage is caused to the brain by drug (MDMA, e.g., Ecstasy) abuse and whether the damaged brain can regenerate after the drug abuse is stopped. The chemical name of this compound is 6-(4-methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**1**). Due to the fact that this compound possesses two centres of asymmetry there are four stereoisomers (6*S*, 10b*R*)-**1**, (6*R*, 10b*S*)-**1**, (6*S*, 10b*S*)-**1** and (6*R*, 10b*R*)-**1** (Scheme 1). Regarding the position of the hydrogen atoms at C-6 and C-10b the two enantiomeric pairs should be called '*cis*' or '*trans*'. Because it is known that these four isomers possess different K_i values for the serotonin 5-HT transporter uptake inhibition,[3–7] it is important to characterize their chemical configuration correctly. Although a lot of work has been performed on these compounds there is still a lack of information about the correct stereochemistry of the individual isomers. The information that can be found in the literature is misleading and contradictory,[5,6] that is a *cis*-stereoisomer can be found in a scheme but in the text it is called *trans*.[6] Furthermore, to the best of our knowledge, there has never been an unequivocal proof of the correct identification of any isomer.



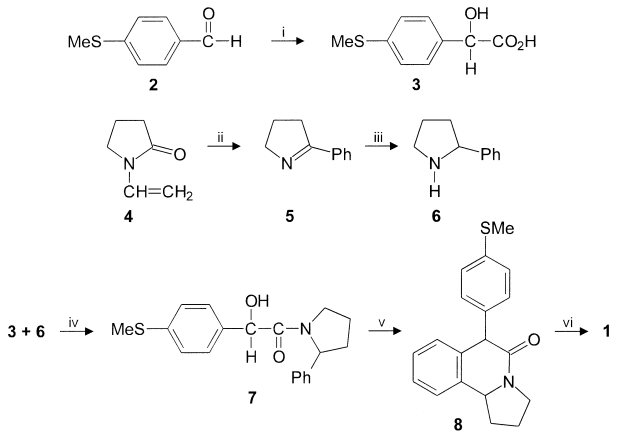
Scheme 1. The four stereoisomers of **1**: two *cis*-enantiomers (top) and two *trans*-enantiomers (bottom).

*Corresponding author. Tel.: +49-428-38-2803; fax: +49-428-38-5592; e-mail: voss@chemie.uni-hamburg.de

0968-0896/01/$ - see front matter
PII: S0968-0896(01)00117-1

Results and Discussion

Since we are involved in the pharmacological studies mentioned at the beginning, we were interested to synthesize and to characterize definitely the four stereoisomers. We used the synthetic route published by Maryanoff et al.,[6] in which general procedures for the preparation of **1** and numerous related compounds are described. Here, we will report the details of our synthesis only for those steps in which we were deviating from the literature. Furthermore, all spectroscopic data of **1** and its precursors **3** and **5**–**8** (Scheme 2) are given, which are lacking in ref 6.



Scheme 2. Reagents and conditions: (i) $CHBr_3$, NaOH, LiBr, dioxane; (ii) PhCOOEt, NaH, THF; (iii) $NaBH_4$, EtOH; (iv) xylene, TsOH; (v) H^+, TFA; (vi) BH_3•THF.

We were able to separate the pair of *trans*-enantiomers from the pair of *cis*-enantiomers by preparative column chromatography. The chemical purity of the diastereoisomers was verified by HPLC.

Our structural assignment was firstly based on ^{1}H NMR spectroscopic and, in particular, NOE measurements. The essential data are presented in Figures 1 and 2. The interpretation is unequivocal. For example the double dublet signal at $\delta = 3.65$ ppm of *trans*-**1**, which obviously belongs to H-10b, exhibits an NOE contact with one of the two protons ($\delta = 2.69$ ppm) at C-5. The latter is, therefore, located in *cis*-position with respect to H-10b and represents H-5b. The signal at $\delta = 3.43$ ppm thus represents H-5a, which exhibits an NOE contact with H-6 ($\delta = 4.35$ ppm). Consequently, H-5a and H-10b and thus H-6 and H-10b exhibit *trans*-configurations. This is only possible for the *trans*-diastereoisomer of **1**. The assignment is also supported by a coupling constant of $J_{5b,6} = 11$ Hz revealing a *trans*-configuration between these two protons, whereas $J_{5a,6} = 6.4$ Hz is typical of a *cis*-configuration. Analogous reasoning applies for the ^{1}H NMR data of the *cis*-diastereoisomer, although no suitable NOE contacts could be observed in this case. The NOE spectra also revealed that the *ortho*-positions of the 4-methylthiophenyl residue are not equivalent, that is the dihedral angle C24–C23–C41–C42 (crystallographic numbering, cf. Fig. 3) should deviate significantly from 180°. Furthermore, the 4-methylthiophenyl substituent is obviously not able to rotate freely at room temperature.

Fortunately, we could grow a suitable single crystal of one diastereoisomer. An X-ray structural analysis of this crystal proved the compound to be racemic *trans*-**1** and thus confirmed our NMR and NOE results.

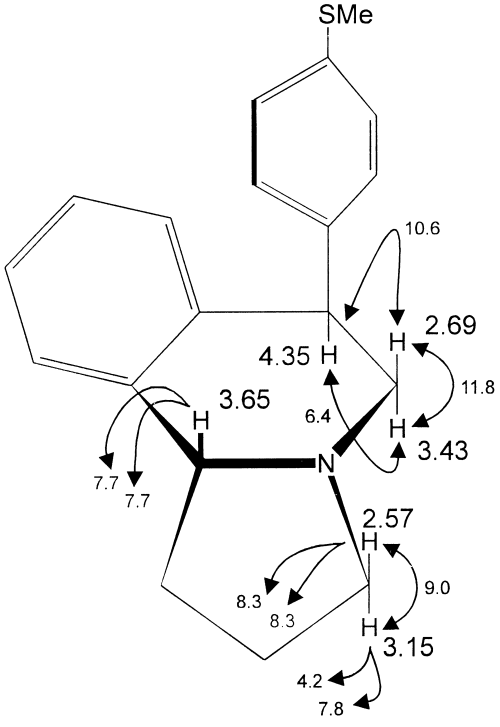


Figure 1. Chemical shifts (ppm) and coupling constants (↔, Hz) of *trans*-**1**.

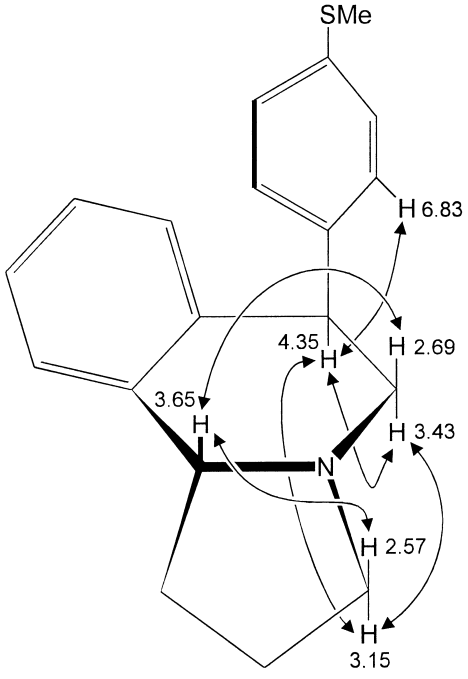


Figure 2. Observed NOE contacts (↔) in *trans*-**1**.

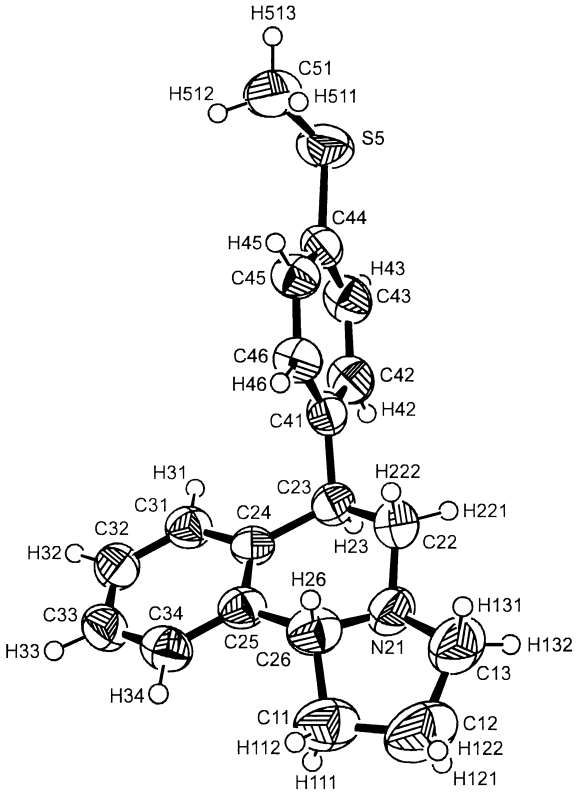


Figure 3. ORTEP view of the X-ray diffraction structure of racemic *trans*-**1** [only the (6*R*, 10b*R*)-enantiomer is shown] with atom numbering. Thermal ellipsoids are drawn at the 50% probability level.

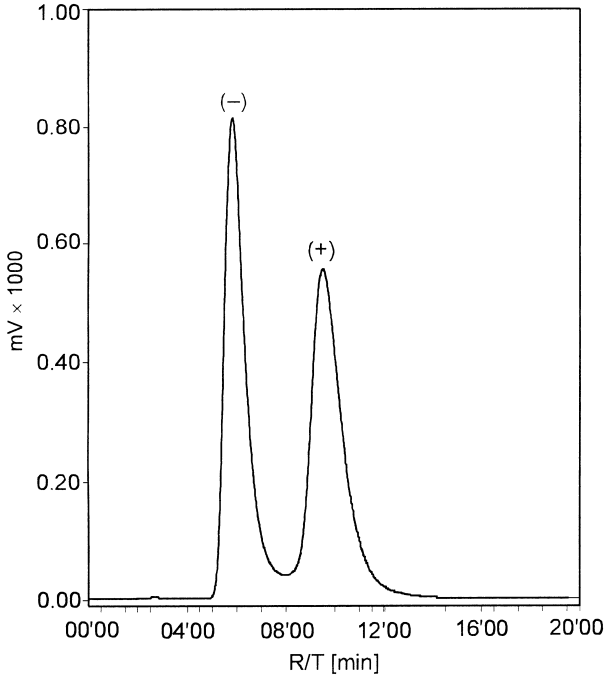


Figure 4. HPLC separation of the two enantiomers of *cis*-**1**.

Nevertheless, we did not know, whether the *cis*- or the *trans*-diastereoisomer was the more potent serotonin uptake blocker. Comparison with an authentic sample of the most active isomer proved, however, that it was identical with our *cis*-diastereoisomer. In order to find out which of the two *cis*-enantiomers was the previously described (+)-enantiomer,[5] we had to separate and compare them with an authentic sample of the (+)-McN-5652-Z enantiomer.[8] Therefore, we developed a separation on a chiral column. The chiralpak® AD material [amylose tris(3,5-dimethylphenyl)carbamate] showed very good separation of the (+)/(−)-enantiomers. A representative chromatogram of the separation of the *cis*-enantiomers is given in Figure 4. The (−)-enantiomer was eluted first as compared with the reference sample.

Since **1** is a compound of high physiological activity we have, finally, performed a 3-D QSAR calculation based on our X-ray structural data using the HyperChem® software.[9] The calculated data are compiled in Table 1.

Experimental

General procedures

Melting points were determined by the use of an Electrothermal apparatus (values are corrected). IR spectra were measured with an ATI Mattson Genesis spectrometer. NMR spectra were recorded with Bruker AMX 400 and DRX 500 spectrometers. Chemical shifts (ppm) are related to Me_4Si (^1H and ^{13}C). Coupling constants J are given in Hz. Multiplicity abbreviations: multiplet (m), singlet (s), dublet (d). Standard correlation techniques were used for assignments. Mass spectra were measured on Varian CH 7 (EI, 70 eV) and VG Analytical 70-250 S (HRMS) apparatus. TLC was carried out on E. Merck PF_{254} foils (detection: UV light, EtOH–H_2SO_4 spray/200 °C), and column chromatography on E. Merck Kieselgel 60 (70–230 mesh). Solvents were purified and dried according to standard laboratory procedures.[10] The purity of the separated diastereoisomers was analyzed with HPLC on nucleosil 100 3 C18, 125×3 mm. The mobile phase was 50% acetonitrile/50% water with 0.02 mol ammonium formate.

The preparative separation of the (+)/(−)-enantiomers was performed on a 250×10 mm column packed with chiralpak® AD 25 μm. The mobile phase was 97% *n*-hexane/3% 2-propanol/0.05% triethylamine.

Table 1. Theoretical QSAR parameters for *trans*-**1**

Partial charge	Net charge = 0.00 e
Surface area (approx.)	428.20 Å^2
Surface area (grid)	508.27 Å^2
Volume	850.66 Å^3
Hydration energy	−1.04 kcal mol^{-1}
LogP	1.44
Refractivity	100.02 Å^3
Polarizability	35.74 Å^3
Mass	295.44 amu

Table 2. Crystal data and structure refinement for *trans*-**1**[a]

Diffractometer	KappaCCD Nonius
Molecular formular	$C_{19}H_{21}NS$
Molecular weight (g mol^{-1})	295.43
Temperature (K)	293(2)
Wavelength (Å)	0.7107, MoK_α, graphite monochromated
Scan mode	Rotation Φ
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 17.278(1)$ Å
	$b = 5.661(1)$ Å
	$c = 25.069(1)$ Å
	$\alpha = \gamma = 90°$
	$\beta = 138.39(1)°$
Volume (Å^3)	1628.3(3)
Z (molecules per cell)	4
D_{calcd} (g cm^{-3})	1.205
Absorption coefficient (mm^{-1})	0.192
$F(000)$	632
Crystal size (mm)	0.39×0.35×0.32
θ Range for data collection (°)	1.63–25.02
Index ranges	$0 \le h \le 20$; $0 \le k \le 6$;-29 $\le l \le 19$
Reflections collected	7579
Independent reflections	2810
Reflections with $I \ge 2\sigma(I)$	2218
Refinement method	Full-matrix-block least-squares on F^2
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2, w = 1/[\sigma^2(F_o^2) + (0.1160P)^2 + 0.7813P]$, where $P = (F_o^2 + 2F_c^2)/3$
H-Atom refinement	Geom. and difmap
Data/restraints/parameters	2810/0/245
Goodness-of-fit on F^2	1.050
Final R indices [$I \ge 2\sigma(I)$]	$R_1 = 0.0556$, $wR_2 = 0.1556$
R Indices (all data)	$R_1 = 0.0773$, $wR_2 = 0.2012$
Largest difference peak and hole (e Å^{-3})	0.248 and −0.336

[a]Full crystallographic details, excluding structure features, have been deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel.: +44-1223-336408; fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk (deposition number CCDC-142696).

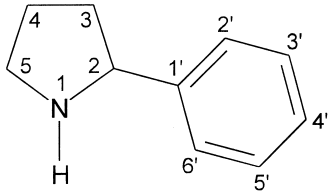
Table 3. Selected bond lengths (pm), bond angles (°) and torsion angles (°) of *trans*-**1**

S(5)−C(44)	176.3 (3)	C(23)−C(24)−C(25)	121.6 (2)
S(5)−C(51)	176.5 (4)	C(24)−C(25)−C(26)	119.4 (3)
N(21)−C(13)	145.4 (4)	C(24)−C(25)−C(34)	119.3 (3)
N(21)−C(22)	144.5 (4)	C(11)−C(26)−C(25)	119.2 (3)
N(21)−C(26)	145.2 (5)	C(23)−C(41)−C(42)	121.5 (2)
C(11)−C(12)	151.2 (7)	C(22)−N(21)−C(13)−C(12)	165.4 (4)
C(11)−C(26)	152.9 (5)	C(26)−N(21)−C(13)−C(12)	42.8 (4)
C(12)−C(13)	151.9 (7)	C(13)−N(21)−C(22)−C(23)	172.5 (3)
C(22)−C(23)	152.5 (4)	C(26)−N(21)−C(22)−C(23)	−68.5 (4)
C(23)−C(24)	152.5 (4)	C(13)−N(21)−C(26)−C(11)	−46.2 (3)
C(24)−C(25)	139.9 (4)	C(22)−N(21)−C(26)−C(11)	−172.1 (3)
C(25)−C(26)	150.5 (4)	C(13)−N(21)−C(26)−C(25)	−174.1 (3)
C(23)−C(41)	151.2 (4)	C(22)−N(21)−C(26)−C(25)	60.0 (3)
C(41)−C(42)	138.4 (4)	C(11)−C(12)−C(13)−N(21)	−22.4 (5)
C(44)−S(5)−C(51)	105.14 (17)	C(12)−C(11)−C(26)−N(21)	30.3 (4)
C(13)−N(21)−C(22)	116.1 (3)	N(21)−C(22)−C(23)−C(24)	40.9 (4)
C(13)−N(21)−C(26)	104.4 (3)	N(21)−C(22)−C(23)−C(41)	169.9 (3)
C(22)−N(21)−C(26)	111.1 (3)	C(24)−C(25)−C(26)−N(21)	−26.5 (4)
N(21)−C(13)−C(12)	102.3 (3)	C(26)−C(11)−C(12)−C(13)	−4.7 (5)
N(21)−C(22)−C(23)	109.6 (2)	C(12)−C(11)−C(26)−C(25)	152.3 (4)
N(21)−C(26)−C(25)	110.3 (3)	C(22)−C(23)−C(24)−C(25)	−10.1 (4)
N(21)−C(26)−C(11)	102.3 (3)	C(41)−C(23)−C(24)−C(25)	−137.4 (2)
C(12)−C(11)−C(26)	103.4 (4)	C(22)−C(23)−C(41)−C(42)	113.2 (3)
C(11)−C(12)−C(13)	106.3 (3)	C(24)−C(23)−C(41)−C(42)	−118.8 (3)
C(22)−C(23)−C(24)	112.2 (3)	C(23)−C(24)−C(25)−C(26)	3.0 (4)
C(22)−C(23)−C(41)	111.0 (2)	C(24)−C(25)−C(26)−C(11)	−144.5 (4)
C(24)−C(23)−C(41)	114.1 (2)		

X-ray structure analysis. The crystal data and a summary of experimental details for racemic *trans*-**1** are given in Table 2. Cell parameters were determined by least-squares refinement of the angular settings of 159 centred reflections with $\Theta = 9–25°$. The structure was solved by direct methods using the SIR-97 program,[11] and refined by full-matrix-block least-squares on F^2 using all data and the SHELXL-97 program.[12]Hydrogen positions were obtained in the mixed mode. Selected bond lengths and angles are given in Table 3.

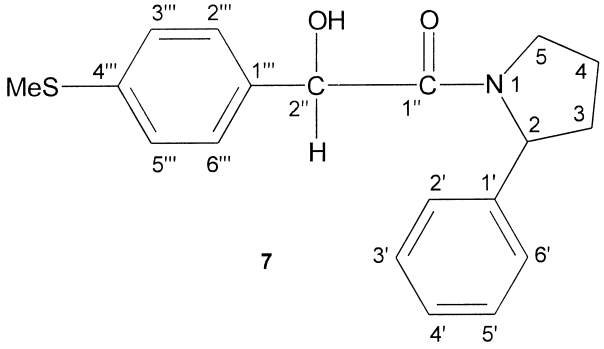
2-Hydroxy-2-(4-methylthiophenyl)ethanoic acid (3). The crude product obtained according to the literature[6] was treated with 1 N NaOH and the resulting sodium salt of **3** was filtered and washed intensively with diethyl ether. Then aq HCl (20%) was added and the solution was extracted with diethyl ether. After drying with $MgSO_4$ and evaporation of the solvent racemic **3** was isolated as a pale yellow solid, mp. 132 °C (138–140 °C).[6] Yield: 98%. ^{1}H NMR (400 M Hz, acetone-d_6): δ 10.27 (bs, 1H, COOH), 7.43 (ddd, 2H, H_{ar}, $J = 8.6, 2.0, 2.0$), 7.25 (ddd, 2H, H_{ar}, $J = 8.7, 2.1, 2.1$), 5.21 (s, 1H, C**H**(OH)), 2.46 (s, 3H, SMe). ^{13}C NMR (101 M Hz, acetone-d_6): δ = 207.5 (acetone), 175.0 (C_q, COOH), 139.9 (C_q), 137.8 (C_q), 128.6 (2 CH), 127.3 (2 CH), 73.5 (CH, CH(OH)), 30.4 (acetone), 15.9 (CH_3, SMe). IR (KBr): ν = 3439, 3053, 2925, 2638, 1708, 1597, 1493, 1433, 1408, 1381, 1349, 1321, 1286, 1255, 1231, 1195, 1185, 1093, 1073, 1013, 946, 919, 891, 858, 813, 759, 726, 688, 651, 576, 494, 435 cm^{-1}. MS (FAB): *m*/*z* (%) 199 (37, $M^+ + 1$), 198 (100, M^+), 181 (97, $M^+ + 1 - H_2O$). $C_9H_{10}O_3S$ (198.2): calcd C 54.53, H 5.08, S 16.18; found C 54.74, H 5.02, S 16.29.

2-Phenyl-Δ^1-pyrroline (5). Purification of the crude product was accomplished by distillation in vacuo to yield the pure pyrroline which crystallized on standing. ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.86–7.81 (m, 2H, 2′-H, 6′-H), 7.43–7.36 (m, 3H, 3′-H, 4′-H, 5′-H), 4.06 (tt, 2H, 5_a-H, 5_b-H, $J = 7.4, 2.0$), 2.93 (tt, 2H, 3_a-H, 3_b-H, $J = 8.2, 2.0$), 2.02 (m, 2H, H_a-H, 4_b-H). ^{13}C NMR (101 M Hz, $CDCl_3$): δ 173.3 (C_q, C2), 134.6 (C_q, C1′), 130.3 (CH, C2′, C6′), 128.4 (CH, C3′, C5′), 127.6 (CH, C4′), 61.5 (CH_2, C5), 34.9 (CH_2, C3), 22.7 (CH_2, C4).



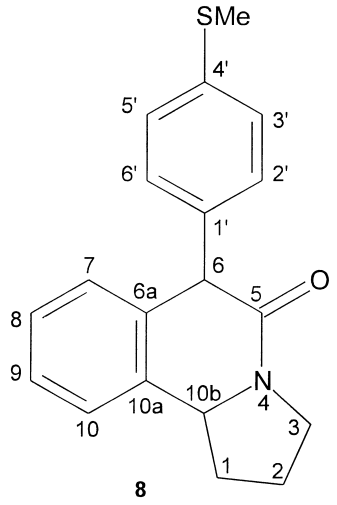
6

2-Phenylpyrrolidine (6). ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.42–7.19 (m, 5H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 4.12 (dd, 1H, 2-H, $J = 7.7, 7.7$), 3.20 (ddd, 1H, 5a-H, $J = 10.2, 7.7, 5.4$), 3.01 (ddd, 1H, 5b-H, $J = 10.2, 8.3, 6.7$), 2.26 (br s, 1H, NH), 2.23–1.62 (m, 4H, 3a-H, 3b-H, 4a-H, 4b-H). ^{13}C NMR (101 M Hz, $CDCl_3$): δ 138.8 (C_q, C1′) 129.1, 128.7, 127.2 (2:2:1, each CH, C2′, C3′, C4′, C5′, C6′), 70.5 (CH, C2), 55.4 (CH_2, C5), 33.4 (CH_2, C3), 24.7 (CH_2, C4).



7

1-[2-Hydroxy-2-(4-methylthiophenyl)]ethanoyl-2-phenylpyrrolidine (7). Deviating from Maryanoff's procedure,[6] a catalytic amount of 4-toluenesulphonic acid was added to the reaction mixture. After filtration through silica gel the product crystallized from ethyl acetate as a colourless solid, mp. 135 °C. The mother liquor was concentrated and again filtered through silica gel. According to the ^{1}H NMR spectrum the ratio of the two diastereoisomers (total yield 83%) was 2.7:1. Major diastereoisomer: ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.35–7.21 (m, 7H, 3′-H, 4′-H, 5′-H, 2‴-H, 3‴-H, 5‴-H, 6‴-H), 7.16–7.13 (m, 2H, 2′-H, 6′-H), 5.21 (dd, 1H, 2-H, $J = 8.1, 2.5$), 5.13 (s, 1H, 2″-H), 4.12 (bs, 1H, OH), 3.83 (ddd, 1H, 5a-H, $J = 10.1, 8.1, 3.4$), 3.07 (ddd, 1H, 5b-H, $J = 10.0, 9.0, 7.1$), 2.48 (s, 3H, SMe), 2.17–2.08 (m, 1H, 3a-H), 2.00–1.70 (m, 3H, 3b-H, 4a-H, 4b-H). ^{13}C NMR (101 M Hz, $CDCl_3$): δ 170.6 (C_q, C1″), 142.2 (C_q, C1′), 139.2, 135.4 (each C_q, C1‴, C4‴), 128.5, 128.3, 127.0, 126.8 (2:2:1:2, each CH, C3′, C4′, C5′, C2‴, C3‴, C5‴, C6‴), 125.3 (CH, C2′, C6′), 72.4 (CH, C2″), 61.9 (CH, C2), 46.8 (CH_2, C5), 33.6 (CH_2, C3), 23.4 (CH_2, C4), 15.56 (S-CH_3). Minor diastereoisomer: ^{1}H NMR (400 M Hz, $CDCl_3$): δ 7.02 (dddd, 1H, 4′-H, $J = 7.2, 7.2$ 1.3, 1.3), 6.96 (dddd, 2H, 3′-H, 5′-H, $J = 7.2, 7.2, 0.8$, 0.8), 6.78 (ddd, 2H, 3‴-H, 5‴-H or 2‴-H, 6‴-H, $J = 8.5$, 1.9, 1.9), 6.74 (ddd, 2H, 3‴-H, 5‴-H or 2‴-H, 6‴-H, $J = 8.5, 1.9, 1.9$), 6.62 (dddd, 2H, 2′-H, 6′-H, $J = 7.2, 1.6$, 1.6, 1.6), 5.09 (d, 1H, 2-H, $J = 7.5$), 5.04 (s, 1H, 2″-H), 4.12 (bs, 1H, OH), 3.83 (ddd, 1H, 5a-H, $J = 12.2, 10.0$, 7.6), 3.69 (ddd, 1H, 5b-H, $J = 12.5, 8.7, 2.3$), 2.33 (s, 3H, SMe), 2.31–2.22 (m, 1H, 3a-H), 2.00–1.70 (m, 3H, 3b-H, 4a-H, 4b-H). ^{13}C NMR (101 M Hz, $CDCl_3$): δ = 171.9 (C_q, C1″), 141.2 (C_q, C1′), 138.0, 135.3 (each C_q, C1‴, C4‴), 128.1, 128.0, 126.43, 126.38 (2:2:1:2, each CH, C3′, C4′, C5′, C2‴, C3‴, C5‴, C6‴), 125.1 (CH, C2′, C6′), 72.2 (CH, C2″), 61.2 (CH, C2), 47.6 (CH_2, C5), 35.9 (CH_2, C3), 20.5 (CH_2, C4), 15.78 (S–CH_3). Diastereoisomeric mixture: IR (KBr): ν = 3400, 3254, 3081, 3063, 3028, 2979, 2946, 2922, 2882, 1827 (s), 1581, 1493, 1441, 1357, 1339, 1317, 1285, 1244, 1198, 1185, 1161, 1112, 1072, 1044, 1027, 1016, 992, 965, 955, 926, 898, 870, 850, 824, 803, 791, 772, 754, 700, 662, 629, 597, 563, 548, 532, 491, 463 cm^{-1}. MS (FAB): *m*/*z* (%) 328 (100, $M^+ + 1$), 310 (34, $M^+ + 1 - H_2O$). $C_{19}H_{21}NO_2S$ (327.4): calcd C 69.69, H 6.46, N 4.28, S 9.79; found C 69.40, H 6.50, N 4.21, S 10.13.



8

6-(4-Methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-one (8). According to a modified literature synthesis[13] the amide **7** was cyclodehydrated with concd H_2SO_4 in a trifluoroacetic acid (TFA) medium. After stirring overnight at room temperature the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated to give **8** as a brown syrup. Yield: 92%. Diastereoisomeric mixture: ^{1}H NMR (400 M Hz): δ 7.42–7.02 (m, 8H, 7-H, 8-H, 9-H, 10-H and 2′-H, 3′-H, 5′-H, 6′-H), 4.89 (s, 1H, 6-H), 4.53 (dd, 1H, 10b-H, J = 6.3, 9.1), 3.66–3.51 (m, 2H, 3a-H, 3b-H), 2.64–2.59 (m, 1H, 1a-H), 2.42 (s, 3H, MeS), 2.14–2.09 (m, 1H, 2a-H), 1.98–1.88 (m, 2H, 1b-H, 2b-H). ^{13}C NMR (101 M Hz, $CDCl_3$): δ 169.0 (C_q, C5), 137.7, 137.3, 135.9, 135.2 (each C_q, C6a, C10a, C1′, C4′), 131.9, 128.9, 128.6, 128.2, 127.9, 127.3, 124.8 (each CH, C7, C8, C9, C10 and C2′, C3′, C5′, C6′), 59.4 (CH, C10b), 54.0 (CH, C6), 45.8 (CH_2, C3), 32.1 (CH_2, C1), 23.4 (CH_2, C2), 16.3 (SMe). IR: ν = 3435, 2972, 2949, 2920, 2879, 1647 (s, CO), 1491(s), 1439, 1404, 1344, 1317, 1304, 1236, 1198, 1161, 1093, 1016, 910, 812, 758, 731, 685 cm^{-1}.

6-(4-Methylthiophenyl)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (1). This was obtained as described in ref 6. The diastereoisomers were separated by column chromatography with ethyl acetate as mobile phase. The pair of *trans*-enantiomers was eluted first (R_f = 0.20, ethyl acetate) and crystallized as a pale brown solid, mp. 79–81 °C. The pair of *cis*-enantiomers followed (R_f = 0.07, ethyl acetate) and was isolated as a brown syrup. The ratio of the diastereoisomers *trans*/*cis* was 5:1.

trans-**1**: ^{1}H NMR (500 M Hz, $CDCl_3$): δ 7.22–7.19 (m, 2H, H_{ar}), 7.19–7.15 (m, 1H, H_{ar}), 7.13–7.11 (m, 1H, H_{ar}), 7.10–7.08 (m, 2H, H_{ar}), 7.08–7.04 (m, 1H, H_{ar}), 6.83 (ddd, 1H, H-2′, J = 7.8, 0.9, 0.9), 4.35 (dd, 1H, 6-H, J = 10.6, 6.4), 3.65 (dd, 1H, 10b-H, J = 7.7, 7.7), 3.43 (dd, 1H, 5a-H, J = 11.8, 6.4), 3.15 (ddd, 1H, 3a-H, J = 9.0, 7.8, 4.2), 2.69 (dd, 1H, 5b-H, J = 11.3, 11.3), 2.57 (ddd, 1H, 3b-H, J = 8.3, 8.3, 8.3), 2.47 (s, 3H, SMe), 2.49–2.42 (m, 1H, 1b-H), 2.00–1.87 (m, 2H, 2a-H, 2b-H), 1.86–1.77 (m, 1H, 1a-H). ^{13}C NMR (101 M Hz, $CDCl_3$): δ 141.2, 139.0, 137.5, 136.4 (each C_q, C6a, C10a, C1′, C4′), 129.7 (CH, C2′, C6′ or C3′, C5′), 129.1 (CH, C7 or C10), 127.0 (CH, C2′, C6′ or C3′, C5′), 126.3 (CH, C8, C9), 125.3 (CH, C7 or C10), 63.8 (CH, C10b), 57.9 (CH_2, C5), 53.0 (CH_2, C3), 44.6 (CH, C6), 30.7 (CH_2, C1), 22.1 (CH_2, C2), 16.0 (CH_3, SMe). IR (KBr): ν = 3064, 3035, 3022, 2968, 2924, 2914, 2881, 2870, 2781, 2740, 2725, 2673, 1597, 1491(s), 1448, 1431, 1408, 1371, 1346, 1327, 1284, 1261, 1234, 1215, 1203, 1180, 1163, 1134, 1109, 1092, 1061, 1036, 1016, 976, 953, 918, 868, 820, 785, 752, 721, 648, 633, 609, 584, 552, 480, 444 cm^{-1}. $C_{19}H_{21}NS$ (295.4): calcd C 77.24, H 7.16, N 4.74, S 10.85; found C 77.14, H 7.36, N 4.26, S 10.69.

cis-**1**: ^{1}H NMR (500 M Hz, $CDCl_3$): δ 7.19–7.12 (m, 6H), 7.09–7.05 (m, 1H), 6.88 (ddd, 1H, 2′-H, J = 7.7, 1.0, 1.0), 4.17 (dd, 1H, 6-H, J = 5.3, 5.3), 3.61 (dd, 1H, 10b-H, J = 9.6, 6.9), 3.01 (dd, 1H, 5a-H or 5b-H, J = 11.1, 5.6), 2.95 (ddd, 1H, 3a-H or 3b-H, J = 10.2, 8.2, 3.1), 2.91 (dd, 1H, 5a-H or 5b-H, J = 11.0, 5.1), 2.69 (ddd, 1H, 3a-H or 3b-H, J = 8.9, 8.9, 8.9), 2.45 (s, 3H, MeS), 2.40–2.34 (m, 1H, 1-H or 2-H), 2.04–1.94 (m, 1H, 1-H or 2-H), 1.91–1.80 (m, 2H, 1-H or 2-H). ^{13}C NMR (101 M Hz, $CDCl_3$): δ 143.1, 138.7, 137.2, 135.9 (each C_q, C6a, C10a, C1′, C4′), 129.4, 129.3, 126.7, 126.2, 126.1, 125.8 (2:1:2:1:1:1, each CH, C7, C8, C9, C10, C2′, C3′, C5′, C6′), 63.6 (CH, C10b), 56.1 (CH_2, C5), 54.3 (CH_2, C3), 45.6 (CH, C6), 30.5 (CH_2, C1), 22.3 (CH_2, C2), 16.1 (CH_3, SMe). IR (KBr): ν = 3070, 3060, 3018, 2964, 2939, 2922, 2873, 2785, 2731, 1651, 1601, 1491(s), 1448, 1439, 1404, 1375, 1348, 1323, 1292, 1215, 1163, 1132, 1117, 1092, 1016, 966, 823, 752 cm^{-1}.

(+)-McN-5652-Z. As mentioned above we separated the two *cis*-enantiomers of **1** on a 250×10 mm column packed with chiralpak® AD 25μm. The mobile phase was 97% *n*-hexane/3% 2-propanol/0.05% triethylamine. The flow rate was 4.7 mL min^{-1}. The capacity factors were 1.12 for the (−)-enantiomer and 2.99 for the (+)-enantiomer.

Acknowledgements

The authors thank the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) for financial support (Project No. Z12.01-68503-206). Professor Dr. A. Krebs and Dr. V. Sinnwell, Univ. Hamburg, are gratefully acknowledged for supporting our HPLC and NMR studies. We thank J. Zessin, Forschungszentrum Rossendorf, for providing an authentic sample of (+)-McN-5652-Z.

References and Notes

1. Suehiro, M.; Ravert, H. T.; Dannals, R. F.; Scheffel, U.; Wagner, H. N., Jr. *J. Labelled Compd. Radiopharm.* **1992**, *31*, 841.
2. Suehiro, M.; Scheffel, U.; Dannals, R. F.; Ravert, H. T.; Ricaurte, G. A.; Wagner, H. N., Jr. *J. Nucl. Med.* **1993**, *34*, 120.

3. Szabo, Z.; Kao, P. F.; Scheffel, U.; Suehiro, M.; Mathews, W. B.; Ravert, H. T.; Musachio, J. L.; Marenco, S.; Kim, S. E.; Ricaurte, G.; Wong, D. F.; Wagner, H. N., Jr.; Dannals, R. F. *Synapse* **1995**, *20*, 37.
4. McCann, U. D.; Szabo, Z.; Scheffel, U.; Dannals, R. F.; Ricaurte, G. A. *Lancet* **1998**, *352*, 1433.
5. Maryanoff, B. E.; McComsey, D. F.; Costanzo, M. J.; Setler, P. E.; Gardocki, J. F.; Shank, R. P.; Schneider, C. R. *J. Med. Chem*. **1984**, *27*, 943.
6. Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem*. **1987**, *30*, 1433.
7. Maryanoff, B. E.; Vaught, J. L.; Shank, R. P.; McComsey, D. F.; Costanzo, M. J.; Nortey, S. O. *J. Med. Chem*. **1990**, *33*, 2793.
8. Zessin, J.; Gucker, P.; Ametamey, S. M.; Steinbach, J.; Brust, P.; Vollenweider, F. X.; Johannsen, B.; Schubiger, P. A. *J. Labelled Compd. Radiopharm*. **1999**, *42*, 1301.
9. *HyperChem 6.0*, Hypercube, Inc.: Waterloo, Ontario, Canada, 2000.
10. Autorenkollektiv. *Organikum*, 19th ed.; Johann Ambrosius Barth: Leipzig, 1993; pp 659–681.
11. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Burla, M. C.; Polidori, G.; Camalli, M.; Spagna, R.; SIR97: *A Package for Crystal Structure Solution by Direct Methods and Refinement*; Bari, Perugia, Rome, Italy, 1997.
12. Sheldrick, G. M. *SHELXL-97: Program for Crystal Structure Refinement*; University of Göttingen, Göttingen, Germany, 1997.
13. Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc*. **1990**, *112*, 3567.