Monatshefte für Chemie 138, 709–714 (2007)
DOI 10.1007/s00706-007-0670-x
Printed in The Netherlands

Monatshefte für Chemie
Chemical Monthly

Antiprotozoal Activities of Epimeric Aminobicycles

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Received February 16, 2007; accepted February 27, 2007; published online May 11, 2007

Summary. We synthesized several 4-aminobicyclo[2.2.2]octan-2-ols and 4-amino-2-azabicyclo[3.2.2]nonanes from epimerized 4-amino-bicyclo[2.2.2]octan-2-ones. The new compounds were tested for their activity against *Trypanosoma b. rhodesiense*, the causative organism of East African sleeping sickness, and *Plasmodium falciparum* K_1, a multiresistant protozoan parasite which causes Malaria tropica. The results are compared to the activities of their formerly synthesized stereoisomers and structure–activity relationships are discussed.

Keywords. East African sleeping sickness; Malaria tropica; Bicyclic compounds; Configuration; Structure–activity relationships.

Introduction

Recently we reported the izomerization of (6-*exo*,7-*syn*)-6,7-diphenylbicylo[2.2.2]octan-2-ones **1** to their (6-*endo*,7-*syn*)-analogues **2** by reaction with *t-Bu*OK [1]. Compounds **2** exhibit compared to **1** improved antiplasmodial activities and at the same time lower cytotoxicity [1]. Since the (2-*exo*,6-*exo*,7-*syn*)-bicylo[2.2.2]octan-2-ols **3** and 4-amino-2-azabicyclo[3.2.2]nonanes **4**, which have been derived from **1**, have shown good antiprotozoal properties [2, 3] we synthesized their 6-*endo*-analogues **5** and **6**. In order to investigate the influence of the bicyclic ring skeleton on the antiprotozoal activities of the latter, we determined those of the cyclohexene and cyclohexane derivatives **7** and **8** with analogous substitution pattern (Fig. 1).

Results and Discussion

Syntheses

The (6-*exo*)-4-amino-6,7-diphenylbicyclo[2.2.2]octan-2-ones **1a**–**1d** were accessible by a one-pot reaction of benzylidene acetone with isothiocyanates of *sec.* amines [4]. By stereoselective reduction with $LiAlH_4$ their corresponding alcohols **3a**–**3d** were obtained [2]. Compounds **4a**–**4d** were synthesized from **1a**–**1d** by a reported procedure [3]. The selective stereoinversion of the configuration in ring position 6 of compounds **1a**–**1d** succeeded upon heating with *t-Bu*OK. According to the findings of *Muir* [5] and *Nikon* [6] we assumed the following reaction mechanism: proton abstraction in ring position 6 of the bicyclo[2.2.2]octan-2-ones **1a**–**1d** gives the tricyclic β-enolates **9a**–**9d** as intermediates. The bicyclo[2.2.2]octane ring system is re-formed by selective addition of a proton in position 6 and cleavage of the bond between positions 2 and 6. The epimeric bicyclo[2.2.2]octanes **1** and **2** were separated by crystallization (Scheme 1) [1].

The reduction of the optically inactive (6-*endo*,7-*syn*)-6,7-diphenylbicylo[2.2.2]octan-2-ones **2a**–**2d** with $LiAlH_4$ gave the (2-*exo*,6-*endo*,7-*syn*)-6,7-diphenylbicylo[2.2.2]octan-2-ols **5a**–**5d**. Configura-

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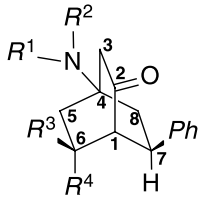
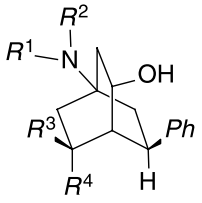
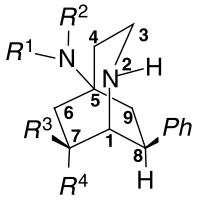


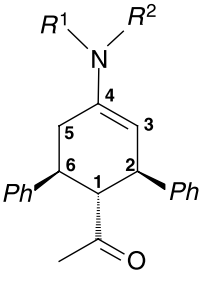
1a–1d: R^3 = H, R^4 = *Ph*
2a–2d: R^3 = *Ph*, R^4 = H



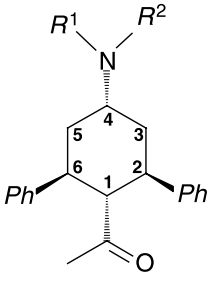
3a–3d: R^3 = H, R^4 = *Ph*
5a–5d: R^3 = *Ph*, R^4 = H



4a–4d: R^3 = H, R^4 = *Ph*
6a,6c,6d: R^3 = *Ph*, R^4 = H



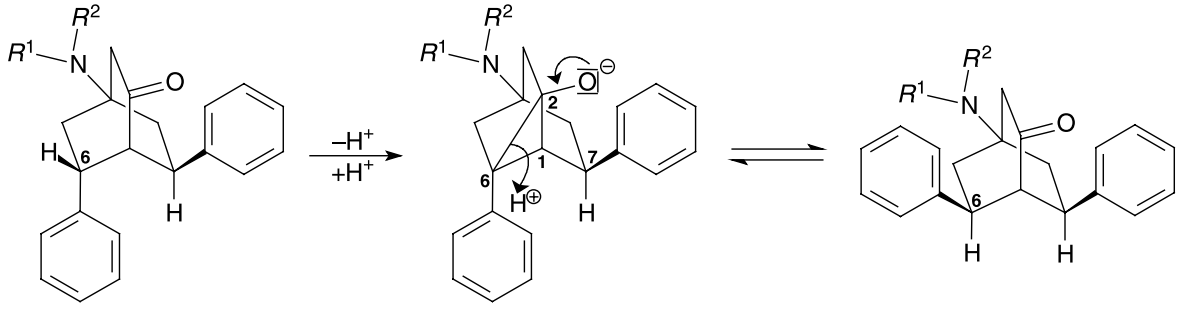
7b–7d



8b–8d

a: $R^1 = R^2 = -CH_3$
b: $R^1 + R^2 = -(CH_2)_2-O-(CH_2)_2-$
c: $R^1 + R^2 = -(CH_2)_4-$
d: $R^1 + R^2 = -(CH_2)_5-$

Fig. 1. Structures of compounds **1**–**8**



1a–1d **9a–9d** **2a–2d**

a: $R^1 = R^2 = CH_3$
b: $R^1 + R^2 = -(CH_2)_2-O-(CH_2)_2-$
c: $R^1 + R^2 = -(CH_2)_4-$
d: $R^1 + R^2 = -(CH_2)_5-$

Scheme 1

tions were established by means of N*O*E experiments: Through-space couplings were observed in **5c** from aromatic *ortho* protons to H-6 and from H-2 to the same aromatic ortho protons. Furthermore, we observed a w-coupling from H-7 to H-2 confirming the 6-*endo* position of the aromatic ring (Fig. 2).

The bicyclic diamines **6a**, **6c**, and **6d** were synthesized from ketones **2a**, **2c**, and **2d** *via* a *Beckmann* rearrangement and subsequent reduction with $LiAlH_4$.

The syntheses of compounds **7** and **8** started from benzylidene acetone **10** which formed in the presence of pyrrolidine the diketone **11** *via* a base-catalyzed intramolecular *Diels-Alder* reaction [7]. Several enamines of (cyclohex-3-en-1-yl)ethanones **7b**–**7d** were obtained by the reaction of **11** with secondary amines in the presence of *p*-toluene sulfonic acid. The selective hydrogenation of the enamine group of **7** was achieved by means of Pd/C (10%)

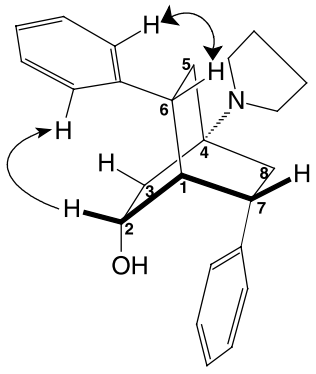
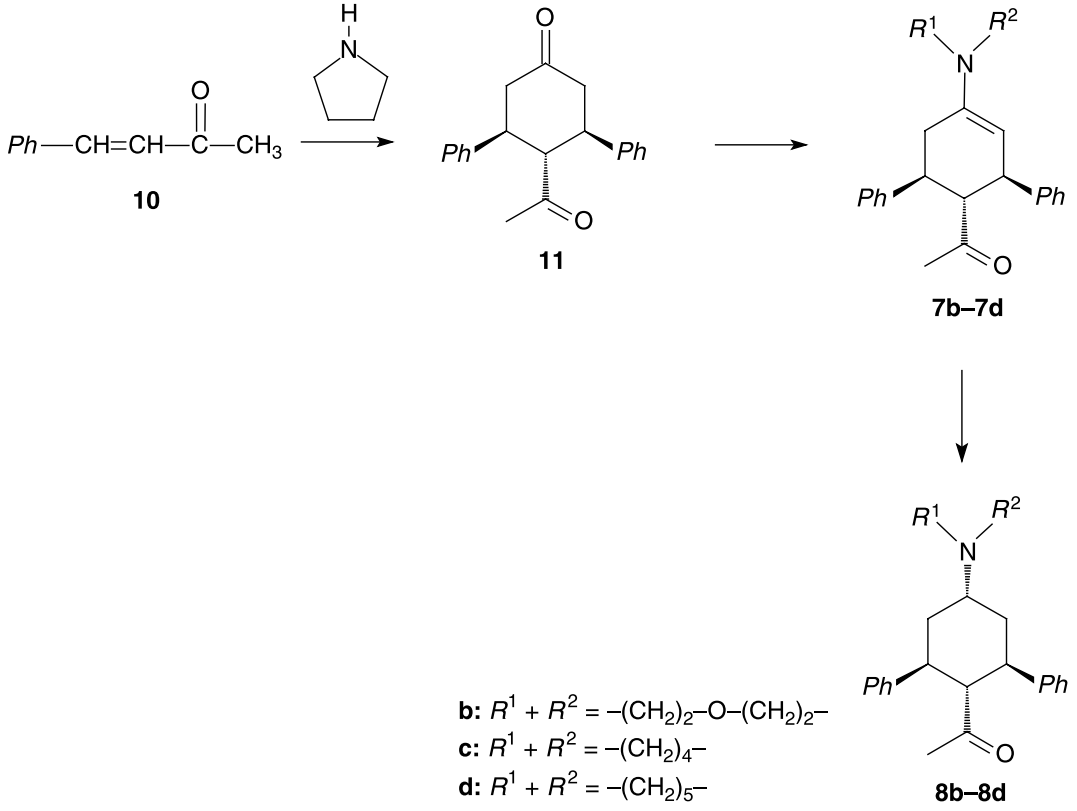


Fig. 2. N*O*Es in compound **5c**

as catalyst, whereupon the oxo group remained unchanged (Scheme 2). The structures of the thus obtained (cyclohexyl)ethanones **8b**–**8d** were established by NMR spectroscopy using N*O*E experiments [8].

Antiprotozoal Activities and Cytotoxicity

The antiprotozoal activities were investigated against *Trypanosoma b. rhodesiense* and *Plasmodium falciparum* K_1, and the IC_{50} values were determined. The cytotoxicity was measured using L-6 cells. In order to estimate the influence of the inverted configurations of the new bicyclooctane and -nonane derivatives their antiprotozoal activities were compared to those of the corresponding epimers. Compared to ketones **1** their (6-*endo*,7-*syn*) analogues **2** showed enhanced activity against protozoan parasites, especially against *Plasmodium falciparum* K_1, a strain which is resistant to chloroquine and pyrimethamine. Compound **2c** ($IC_{50} = 0.71\ \mu M$) is the most active antiplasmodial bicyclooctanone showing very low cytotoxicity ($IC_{50} \geq 235.6\ \mu M$). The antitrypanosomal activities of compounds **2** are negligible. Likewise, the antiprotozoal activities of compounds **5** and **6** were compared to those of their isomers. Although the selectivity indices for the antiplasmodial activities of the new alcohols **5a** and **5c** surpass those of their epimers, their antiprotozoal activities are in general to low. Most of the new bicyclooctanols **5** are far less cytotoxic than their epimers **3**. Similar observations were made for the 2-azabicyclo[3.2.2]nonanes which show in the (7-*exo*,8-*syn*) series **4** promising antiprotozoal activities. Their



Scheme 2

Table 1. Activities of compounds **1–8** expressed as IC_{50} (μM)[a]

Compd.	*P. falciparum* K_1	*T. b. rhodesiense*	Cytotox. L6-cells
1a	>10.57	9.99	24.57
1b	>11.89	116.3	n.t.
1c	1.19	8.03	26.45
1d	3.95	8.12	46.82
2a	1.17	10.82	158.8
2b	11.79	45.45	193.1
2c	0.71	14.01	>235.6
2d	1.90	12.52	114.7
3a	>15.55	2.95	132.5
3b	2.42	20.80	n.t.
3c	2.39	4.26	26.76
3d	0.84	5.34	37.34
4a	0.28	0.60	108.8
4b	6.84	9.44	>206.7
4c	0.56	1.16	120.4
4d	0.64	6.57	89.74
5a	1.35	9.67	131.9
5b	8.72	37.83	>247.6
5c	2.05	4.74	231.1
5d	16.20	3.67	>248.9
6a	3.05	79.77	>228.98
6c	7.63	46.88	214.6
6d	2.33	24.73	206.71
7b	>13.83	68.33	>249.0
7c	>14.47	81.63	244.9
7d	>13.91	117.7	>250.3
8b	8.42	>247.6	>247.6
8c	>14.39	44.31	259.0
8d	>13.83	73.58	>248.9
chl	0.12		188.5
sur		0.0075	4724.5
mef			11.37

[a] Values represent the average of four determinations (two determinations of two independent experiments), n.t.: not tested. *chl* = chloroquine, *mef* = mefloquine, *sur* = suramine

7-*endo* epimers **6** are less cytotoxic, but unfortunately also less active (Table 1).

Cyclohexenes **7** may be seen as ring cleavage products of **2**. Those and their reduction products **8** are completely inactive against both parasites indicating the positive influence of the bicyclic ring system on the antiprotozoal activity.

Conclusion

New bicyclo[2.2.2]octanols and 2-azabicyclo[3.2.2]-nonanes were synthesized and their antiprotozoal activities were compared to those of their epimers. In some cases the antiplasmodial activity was increased due to the stereoinversion, whereas the antitrypanosomal activity and the cytotoxicity were in general lowered indicating the influence of the position of the aromatic substituent.

Cyclohexene- and cyclohexane-derivatives with similar substitution pattern were inactive revealing the importance of the bicyclic ring system for the antiprotozoal activity.

Experimental

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). UV/VIS: Lambda 17 UV/VIS-spectrometer (Perkin Elmer). NMR spectra: Varian Inova 400 (300 K) 5 mm tubes, solvent resonance as internal standard. ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra. ^{1}H- and ^{13}C-resonances are numbered as given in the formulae. MS, HR-MS: Kratos profile spectrometer 70 eV electron impact. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba), Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; the values for compounds **5** were in satisfactory agreement with the calculated ones, compounds **6** are hygroscopic. Materials: column-chromatography (CC): silica gel 60 (Merck 70–230 mesh, pore-diameter 60 Å); thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm, 200×200 mm^2); the substances were detected in UV light at 254 nm.

The preparation of (6-*exo*,7-*syn*)-(±)-4-amino-6,7-diphenylbicylo[2.2.2]octan-2-ones **1a–1d**, (6-*endo*,7-*syn*)-(±)-4-amino-6,7-diphenylbicylo [2.2.2]octan-2-ones **2a–2d**, (2-*exo*,6-*exo*,7-*syn*)-(±)-6,7-diphenylbicylo[2.2.2]octan-2-ols **3a–3d**, (7-*exo*,8-*syn*)-(±)-(7,8-diphenyl-2-azabicyclo[3.2.2]-non-5-yl)amines **4a–4d**, cyclohexenes **7b–7d** and cyclohexanes **8b–8d** has been reported [1–3, 8].

*Preparation of (2-exo,6-endo,7-syn)-(±)-4-Amino-6,7-diphenylbicyclo[2.2.2]octan-2-ols **5a–5d***

The (6-*endo*,7-*syn*)-(±)-4-amino-6,7-diphenylbicyclo[2.2.2] octan-2-ones **2a–2d** were suspended in dry ether and $LiAlH_4$ was added in portions with cooling on an ice bath. After 1 h the ice bath was removed and the reaction mixture was stirred over night at room temperature. The reaction was quenched cautiously with H_2O under cooling and 2 *M* NaOH was added. The mixture was extracted 5 times with CH_2Cl_2 and the combined organic layers were washed 2 times with H_2O, dried (Na_2SO_4) and filtered. The solvent was evaporated *in vacuo* giving pure **5a–5d** as colourless resins. The products were recrystallized from ethanol/water.

(2-exo,6-endo,7-syn)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ol (**5a**, $C_{22}H_{27}NO$)

A suspension of 500 mg **2a** (1.57 mmol) in 10 cm^3 dry ether reacted with 300 mg $LiAlH_4$ (7.9 mmol) to 282 mg (49%) **5a**. Mp 115°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (d, $J = 7.4$ Hz, OH), 1.57 (ddd, $J = 13.5$, 4.8, 3.3 Hz, 3-H), 1.82

(ddd, $J = 13.1$, 6.5, 2.7 Hz, 5-H), 1.98–2.09 (m, 5-H, 8-H), 2.14 (ddd, $J = 13.3$, 10.0, 3.2 Hz, 3-H), 2.32 (ddd, $J = 13.3$, 5.7, 3.0 Hz, 8-H), 2.37 (s, $N(CH_3)_2$), 2.40 (d, $J = 2.5$ Hz, 1-H), 3.33 (ddd, $J = 9.8$, 6.7, 2.2 Hz, 6-H), 3.42 (br, dd, $J = 9.7$, 5.3 Hz, 7-H), 3.86–3.94 (m, 2-H), 7.17–7.49 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.27$ (C-8), 31.28 (C-5), 38.28 (C-3), 38.39 ($N(CH_3)_2$), 42.23 (C-7), 42.51 (C-6), 45.20 (C-1), 56.46 (C-4), 67.37 (C-2), 126.17, 127.25, 127.57, 128.37, 128.56 (aromatic C), 143.56, 144.99 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3171$, 3057, 2983, 2936, 2870, 2830, 2788, 1600, 1496, 1468, 1446, 1346, 1063, 1035, 745, 696 cm^{-1}; UV (CH_2Cl_2): λ ($\log \varepsilon$) = 231 (3.340) nm; MS (70eV): $m/z = 321$ (M^+), 216, 200, 172, 140, 128, 113, 104, 96, 91, 85, 78, 70; HRMS (EI+): calcd. ($C_{22}H_{27}NO$): 321.20926; found: 321.21135.

(2-exo,6-endo,7-syn)-(±)-4-Morpholino-6,7-diphenylbicyclo[2.2.2]octan-2-ol (**5b**, $C_{24}H_{29}NO_2$)

A suspension of 268 mg **2b** (0.74 mmol) in 10 cm^3 dry ether reacted with 250 mg $LiAlH_4$ (6.6 mmol) to 200 mg (74%) of **5b**. Mp 144°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (d, $J = 7.5$ Hz, OH), 1.57 (ddd, $J = 13.3$, 4.6, 3.4 Hz, 3-H), 1.82 (ddd, $J = 13.0$, 6.5, 2.7 Hz, 5-H), 2.00–2.09 (m, 5-H, 8-H), 2.14 (ddd, $J = 13.3$, 9.9, 3.2 Hz, 3-H), 2.34 (ddd, $J = 13.0$, 5.5, 2.7 Hz, 8-H), 2.44 (d, $J = 2.4$ Hz, 1-H), 2.68–2.78 (m, $N(CH_2)_2$), 3.34 (ddd, $J = 9.6$, 6.5, 2.0 Hz, 6-H), 3.43 (br, dd, $J = 9.7$, 5.0 Hz, 7-H), 3.75–3.78 (m, $O(CH_2)_2$), 3.87–3.95 (m, 2-H), 7.19–7.48 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.64$ (C-8), 31.34 (C-5), 38.76 (C-3), 42.13 (C-7), 42.38 (C-6), 45.25 (C-1), 46.20 ($N(CH_2)_2$), 56.80 (C-4), 67.43 (C-2), 67.63 ($O(CH_2)_2$), 126.23, 126.26, 127.22, 127.49, 128.39, 128.63 (aromatic C), 143.40, 144.81 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3214$, 2961, 2929, 2899, 2855, 1601, 1496, 1446, 1366, 1287, 1270, 1120, 1071, 1061, 1031, 872, 747, 702, 693 cm^{-1}; UV (CH_2Cl_2): λ ($\log \varepsilon$) = 230 (3.273) nm; MS (70 eV): $m/z = 363$ (M^+), 258, 242, 215, 182, 155, 138, 128, 115, 104, 91, 78, 51, 41, 28; HRMS (EI+): calcd. ($C_{24}H_{29}NO_2$): 363.21983; found: 363.21746.

(2-exo,6-endo,7-syn)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-ol (**5c**, $C_{24}H_{29}NO$)

A suspension of 375 mg **2c** (1.09 mmol) in 10 cm^3 dry ether reacted with 204 mg $LiAlH_4$ (5.4 mmol) to 375 mg (99%) **5c**. Mp 130°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.74$ (d, $J = 8.1$ Hz, OH), 1.64 (ddd, $J = 13.2$, 4.7, 3.4 Hz, 3-H), 1.85 (br, s, $(CH_2)_2$), 1.89 (ddd, $J = 13.2$, 6.5, 2.8 Hz, 5-H), 2.09–2.17 (m, 5-H, 8-H), 2.25 (ddd, $J = 13.4$, 9.9, 3.2 Hz, 3-H), 2.41 (ddd, $J = 13.4$, 5.5, 2.6 Hz, 8-H), 2.43 (d, $J = 2.3$ Hz, 1-H), 2.75–2.80 (m, $N(CH_2)_2$), 3.37 (br, t, $J = 8.7$ Hz, 6-H), 3.44–3.48 (m, 7-H), 3.90–4.00 (m, 2-H), 7.18–7.50 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.60$ ($(CH_2)_2$), 30.47 (C-8), 32.13 (C-5), 39.23 (C-3), 42.29 (C-7), 42.67 (C-6), 45.42 (C-1), 45.49 ($N(CH_2)_2$), 55.19 (C-4), 67.41 (C-2), 126.15, 126.19, 127.33, 127.57, 128.34, 128.60 (aromatic C), 143.66, 145.05 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3060$, 3023, 2942, 2920, 2862, 1601, 1495, 1446, 1345, 1289, 1137, 1062, 771, 750, 701 cm^{-1}; UV (CH_2Cl_2): λ ($\log \varepsilon$) = 230 (3.404) nm; MS (70 eV): $m/z = 347$ (M^+), 242, 226, 199, 166, 139, 131, 104, 91, 78; HRMS (EI+): calcd. ($C_{24}H_{29}NO$): 347.22491; found: 347.22228.

(2-exo,6-endo,7-syn)-(±)-6,7-Diphenyl-4-piperidino-bicyclo[2.2.2]octan-2-ol (**5d**, $C_{25}H_{31}NO$)

A suspension of 336 mg **2d** (0.93 mmol) in 10 cm^3 dry ether reacted with 176 mg $LiAlH_4$ (4.6 mmol) to 336 mg (99%) **5d**. Mp 148°C; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.75$ (d, $J = 8.0$ Hz, OH), 1.45–1.51 (m, CH_2), 1.60 (ddd, $J = 13.3$, 5.2, 3.0 Hz, 3-H), 1.62–1.67 (m, $2CH_2$), 1.84 (ddd, $J = 13.1$, 6.9, 2.7 Hz, 5-H), 2.01–2.11 (m, 5-H, 8-H), 2.16 (ddd, $J = 13.0$, 9.7, 3.2 Hz, 3-H), 2.39 (ddd, $J = 13.3$, 5.3, 2.7 Hz, 8-H), 2.43 (d, $J = 2.3$ Hz, 1-H), 2.65–2.71 (m, $N(CH_2)_2$), 3.31 (br, t, $J = 9.8$ Hz, 6-H), 3.40–3.47 (m, 7-H), 3.85–3.93 (m, 2-H), 7.18–7.49 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.94$ (CH_2), 26.84 ($2CH_2$), 29.60 (C-8), 31.79 (C-5), 38.96 (C-3), 42.19 (C-7), 42.44 (C-6), 45.29 (C-1), 46.82 ($N(CH_2)_2$), 57.11 (C-4), 67.70 (C-2), 126.13, 126.19, 127.28, 127.55, 128.34, 128.60 (aromatic C), 143.65, 145.07 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3172$, 3056, 2985, 2934, 2868, 2856, 2820, 1601, 1497, 1446, 1349, 1289, 1264, 1107, 1060, 1030, 743, 701 cm^{-1}; UV (CH_2Cl_2): λ ($\log \varepsilon$) = 231 (3.351) nm; MS (70 eV): $m/z = 361$ (M^+), 270, 256, 240, 213, 180, 153, 136, 115, 104, 91, 78; HRMS (EI+): calcd. ($C_{25}H_{31}NO$): 361.24056; found: 361.24264.

*Preparation of (7-endo,8-syn)-(±)-(7,8-Diphenyl-2-azabicyclo[3.2.2]non-5-yl)amines **6a**, **6c**, and **6d***

Compounds **2a**, **2c**, and **2d** were suspended in glacial acetic acid and hydroxylamine-*O*-sulfonic acid was added. The mixture was refluxed over night at 145°C. The brown solution was poored on ice, alkalized with 2 *M* NaOH, and extracted 5 times with CH_2Cl_2. The combined organic layers were washed 3 times with H_2O, dried (Na_2SO_4), and filtered. After evaporation of the solvent *in vacuo*, the residues were either recrystallized from ethanol (for compounds **6c** and **6d**) or used directly after drying by repeated distillation with dry benzene (for compound **6a**). They were suspended in dry ether and $LiAlH_4$ was added in portions under cooling on an ice bath. The reaction mixture was refluxed at 55°C for 48 h. After cooling to room temperature, it was cooled with an ice bath and quenched carefully with ice water and 2 *M* NaOH. The mixture was extracted 5 times with ether, the combined organic layers were washed 3 times with H_2O, dried (Na_2SO_4), filtered, and the solvent was evaporated giving **6a**, **6c**, and **6d** as oils. In case of compound **6a**, it was purified by Kugelrohr distillation. The dihydrochlorides were prepared by treatment of a solution of the diamine in CH_2Cl_2 with etheral HCl (2 *M*) and subsequent evaporation of the solvents *in vacuo*. The residues were recrystallized.

(7-endo,8-syn)-(±)-(7,8-Diphenyl-2-azabicyclo[3.2.2]non-5-yl)dimethylamine (**6a**, $C_{22}H_{28}N_2$)

A suspension of 1.58 g **2a** (4.9 mmol) in 14 cm^3 glacial acetic acid reacted with 1.45 g hydroxylamine-*O*-sulfonic acid (12.8 mmol) to 1.215 g of a residue which was suspended in 50 cm^3 dry ether. This mixture reacted with 0.55 g $LiAlH_4$ (14.5 mmol) to 336 mg (66%) **6a**. Mp (HCl, CH_2Cl_2): 252°C;

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.80$ (t, $J = 6.0$ Hz, 4-H), 2.20–2.84 (m, 6-H, 9-H), 2.32 (s, $N(CH_3)_2$), 2.64 (t, $J = 6.1$ Hz, 3-H), 3.23 (ddd, $J = 10.4$, 6.5, 3.2 Hz, 7-H, 8-H), 3.60 (t, $J = 3.4$ Hz, 1-H), 7.20–7.47 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 34.29$ (C-4), 37.17 (C-6, C-9), 38.07 ($N(CH_3)_2$), 40.14 (C-3), 43.72 (C-7, C-8), 57.52 (C-1), 57.95 (C-5), 125.97, 127.73, 128.37, 145.00 (aromatic C) ppm; IR (KBr): $\bar{\nu} = 3423$, 2932, 2743, 2676, 2360, 1580, 1500, 1451, 1411, 1379, 743, 731, 701 cm^{-1}; UV (CH_3OH): λ ($\log \varepsilon$) = 210 (4.114) nm; MS (70 eV): $m/z = 320$ (M^+), 275, 244, 215, 188, 176, 145, 130, 104, 91, 85; HRMS (EI+): calcd. ($C_{22}H_{28}N_2$): 320.22525; found: 320.22327.

(7-endo,8-syn)-(±)-(7,8-Diphenyl-2-azabicyclo[3.2.2]non-5-yl)pyrrolidine (**6b**, $C_{24}H_{30}N_2$)

A suspension of 1.5 g **2b** (4.3 mmol) in 12 cm^3 glacial acetic acid reacted with 1.46 g hydroxylamine-*O*-sulfonic acid (13 mmol) to 790 mg of a precipitate which was suspended in 25 cm^3 dry ether. This mixture reacted with 330 mg $LiAlH_4$ (8.65 mmol) to 600 mg (40%) **6b**. Mp (HCl, ethanol/ethyl acetate): 237°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.75$–1.78 (m, $(CH_2)_2$), 1.89 (t, $J = 6.0$ Hz, 4-H), 2.22 (dd, $J = 13.6$, 4.9 Hz, 6-H, 9H), 2.35 (dd, $J = 13.6$, 12.0 Hz, 6-H, 9-H), 2.66 (t, $J = 6.0$ Hz, 3-H), 2.72–2.78 (m, $N(CH_2)_2$), 3.21–3.26 (m, 7-H, 8-H), 3.61 (t, $J = 3.4$ Hz, 1-H), 7.20–7.48 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.61$ ($(CH_2)_2$), 36.43 (C-4), 37.31 (C-6, C-9), 40.24 (C-3), 43.74 (C-7, C-8), 45.14 ($N(CH_2)_2$), 57.12 (C-5), 57.84 (C-1), 125.92, 127.73, 128.34, 144.96 (aromatic C) ppm; IR (KBr): $\bar{\nu} = 3422$, 2955, 2623, 2940, 1637, 1601, 1499, 1449, 1380, 1033, 746, 703 cm^{-1}; UV (CH_3OH): λ ($\log \varepsilon$) = 208 (4.231) nm; MS (70 eV): $m/z = 346$ (M^+), 301, 255, 241, 214, 202, 170, 145, 124, 111, 91; HRMS (EI+): calcd. ($C_{24}H_{30}N_2$): 346.24090; found: 346.23957.

(7-endo,8-syn)-(±)-(7,8-Diphenyl-2-azabicyclo[3.2.2]non-5-yl)piperidine (**6d**, $C_{25}H_{32}N_2$)

A suspension of 1.7 g **2d** (4.7 mmol) in 15 cm^3 glacial acetic acid reacted with 1.6 g hydroxylamine-*O*-sulfonic acid (14 mmol) to 843 mg of a precipitate which was suspended in 28 cm^3 dry ether. This mixture reacted with 336 mg $LiAlH_4$ (8.85 mmol) to 723 mg (42%) **6d**. Mp (HCl, CH_2Cl_2): 280°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.43$–1.47 (m, CH_2), 1.57–1.63 (m, $2CH_2$), 1.82 (t, $J = 6.0$ Hz, 4-H), 2.20–2.32 (m, 6-H, 9-H), 2.60–2.64 (m, 3-H, $N(CH_2)_2$), 3.20 (ddd, $J = 10.2$, 5.8, 3.1 Hz, 7-H, 8-H), 3.61 (t, $J = 3.4$ Hz, 1-H), 7.19–7.47 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.05$ (CH_2), 26.98 ($2CH_2$), 35.81 (C-4), 37.38 (C-6, C-9), 40.24 (C-3), 43.76 (C-7, C-8), 46.15 ($N(CH_2)_2$), 57.39 (C-1), 58.40 (C-5), 125.88, 127.66, 128.31, 145.16 (aromatic C) ppm; IR (HCl, KBr): $\bar{\nu} = 3406$, 3033, 2942, 2656, 2534, 1602, 1585, 1500, 1445, 1405, 1384, 1372, 984, 771, 746, 700 cm^{-1}; UV (CH_3OH): λ ($\log \varepsilon$) = 209 (4.225) nm; MS (70 eV): $m/z = 360$ (M^+), 315, 269, 228, 216, 198, 172, 145, 125, 104, 91, 84; HRMS (EI+): calcd. ($C_{25}H_{32}N_2$): 360.25655; found: 360.25542.

Antiprotozoal Tests, Cytotoxicity

A detailed description of the *in vitro* microplate assays for the determination of the activities against *Plasmodium falciparum* K_1, *Trypanosoma b. rhodesiense* (STIB 900), and cytotoxicity against L-6 cells has been reported [9].

Acknowledgements

This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung (Austrian Science Fund) grant Nr. P-15928.

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