Monatshefte für Chemie 136, 625–634 (2005)
DOI 10.1007/s00706-004-0264-9

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

4-Aminobicyclo[2.2.2]octan-2-ones and -ols *via* Enamine Intermediates

Werner Seebacher[1,*], **Marcel Kaiser**[2], **Reto Brun**[2], **Robert Saf**[3], and **Robert Weis**[1]

[1] Institute of Pharmaceutical Sciences, Pharmaceutical Chemistry, Karl-Franzens-University of Graz, A-8010 Graz, Austria
[2] Swiss Tropical Institute, CH-4002 Basel, Switzerland
[3] Institute of Chemical Technology of Organic Materials, Erzherzog-Johann University, A-8010-Graz, Austria

Received August 31, 2004; accepted September 9, 2004
Published online January 24, 2005

Summary. The synthesis of new bicyclo[2.2.2]octane derivatives is described and their structures were established by NMR experiments. All compounds were tested in *in vitro* assays for their activities against causative organisms of malaria and African sleeping sickness and compared to those of former synthesized compounds.

Keywords. Antiplasmodial activity; Antitrypanosomal activity; Amino alcohols; Cyclizations; Structure-activity relationship.

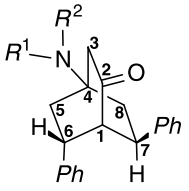
Introduction

Malaria remains one of the most important diseases of the developing world, killing 1–3 million people and causing disease in 300–500 million people annually. The two most widely used antimalarial drugs, chloroquine and sulfadoxine-pyrimethamine are failing at an accelerating rate in most malaria endemic regions. To combat malaria, new drugs are desperately needed [1].

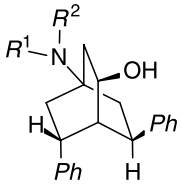
Trypanosomes cause African sleeping sickness, affecting millions of humans and animals. A total of 500000 people estimated to be infected per year with 60000 annual deaths [2]. The so far available trypanocidal drugs suramin, pentamidine, melarsoprol, and eflornithine are not effective against all stages, strains, and species of trypanosomes and can cause severe side effects [3, 4]. Therefore, new trypanocidal drugs with less side effects are urgently needed.

We have reported the synthesis of bicyclic 6,7-diphenyl substituted 4-amino compounds **1a**–**1d** from benzylidene acetone and thiocyanates of *sec.* amines [5].

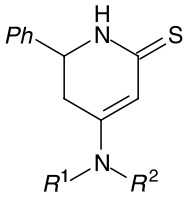
* Corresponding author. E-mail: we.seebacher@uni-graz.at



1a-1h



2a-2h



3f

a: $R^1 = R^2 = CH_3$ **d:** $R^1 + R^2 = -(CH_2)_5-$ **g:** $R^1 = R^2 = -(CH_2)_2-CH_3$
b: $R^1 + R^2 = -(CH_2)_2-O-(CH_2)_2-$ **e:** $R^1 = H$, $R^2 = CH_3$ **h:** $R^1 = R^2 = -(CH_2)_3-CH_3$
c: $R^1 + R^2 = -(CH_2)_4-$ **f:** $R^1 = R^2 = -CH_2-CH_3$

Fig. 1. Structure of 4-aminobicyclo[2.2.2]octane derivatives

In a further step, we have reduced **1a**–**1d** stereoselectively to alcohols **2a**–**2d** (Fig. 1). The ketones **1a**–**1d** and the alcohols **2a**–**2d** have been found to be active against *Plasmodium falciparum*, the causative agent of severe *Malaria tropica* and *Trypanosoma brucei rhodesiense*, the causative organism of East African trypanosomiasis [6]. Consequently, we have prepared a number of derivatives of ketones **1a**–**1d** and alcohols **2a**–**2d** [7–9].

Since some 4-aminobicyclo[2.2.2]octanones have been not available *via* the above-mentioned method, we were searching for alternative methods for their preparation. We succeeded in a two-step procedure using secondary amines and benzylidene acetone as starting materials. This paper presents their preparation and the discussion of their antiprotozoal activities compared to formerly synthesized analogues.

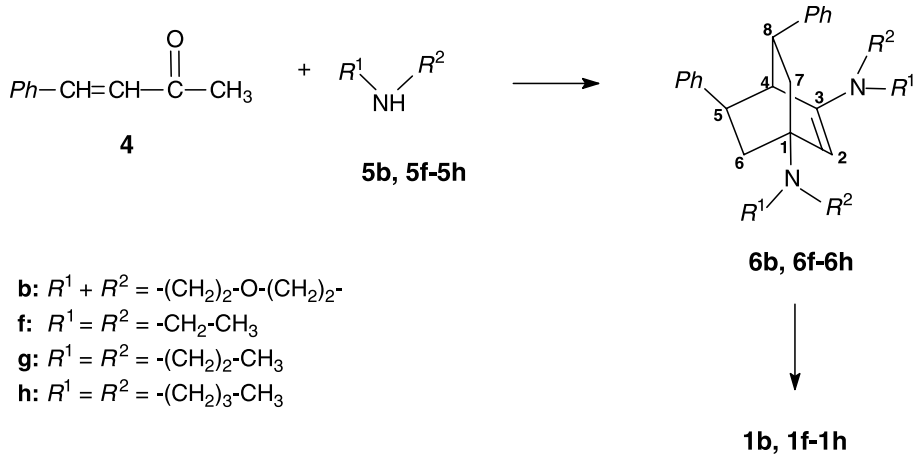
Results and Discussions

Syntheses

The 4-aminobicyclo[2.2.2]octan-2-one thiocyanates **1a**–**1d** have been prepared from benzylidene acetone and dialkylammonium thiocyanates in a one-pot reaction. Their structures have been elucidated by means of NMR experiments and a single crystal structure analysis [5]. But when diethylammonium thiocyanate was refluxed with benzylidene acetone under the same reaction conditions the pyridinethione **3f** has been isolated instead of the expected bicyclooctane derivative [10] (Fig. 1).

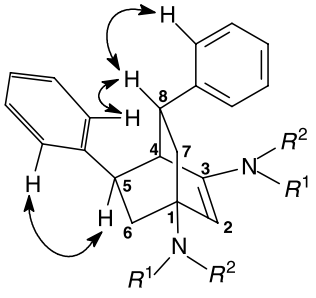
Benzylidene acetone (**4**) reacts with aniline in refluxing benzene in the presence of catalytic amounts of $ZnCl_2$ to 4-phenyl-3-buten-2-one-*N*-phenylimine [11]. However, with secondary aliphatic amines **5f**–**5g** the reaction yields bicyclic enamines **6** (Scheme 1).

The presence of compounds **6** in the reaction mixture was indicated by the appearance of the signal of the olefinic proton in position 2 at 4.7 ppm. Furthermore, evidence was given by the structural analysis of **6g**, which was mainly isolated for analytical purposes. The two identical chains in **6g** were distinguished using N*O*E-experiments: the proton in position 8 shows two N*O*Es (7 and 12%) to



b: $R^1 + R^2 =$ -$(CH_2)_2$-O-$(CH_2)_2$-
f: $R^1 = R^2 =$ -CH_2-CH_3
g: $R^1 = R^2 =$ -$(CH_2)_2$-CH_3
h: $R^1 = R^2 =$ -$(CH_2)_3$-CH_3

Scheme 1



6g: $R^1 = R^2 =$ -$(CH_2)_2$-CH_3

Fig. 2. N*O*Es observed for **6g**

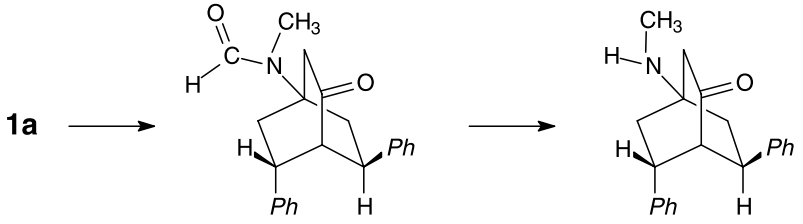
protons in *ortho* position of both aromatic rings whereas H-5 gives a 10% N*O*E to only one aromatic *ortho* proton (Fig. 2). Due to the workup in acidic milieu, the other enamines **6b**, **6f**–**6h** were cleaved to ketones **1b**, **1f**–**1h** (Scheme 1).

In order to investigate if the tertiary amino group is essential for the antiprotozoal activities, we removed one of the methyl groups of 4-dimethylaminobicyclo[2.2.2]octan-2-one **1a** by oxidation with $KMnO_4$ to the amide **7**. Subsequent saponification with KOH in diethylene glycol at 140°C yielded 4-methylaminobicyclo[2.2.2]octan-2-one **1e** (Scheme 2).

All new ketones **1e**–**1h** were reduced stereoselectively with $LiAlH_4$ in ether at room temperature to their corresponding alcohols **2e**–**2h** (Fig. 1). The configuration in position 2 of **2a** was proved by means of N*O*E experiments [6]. The same configuration was verified for the new compounds **2e**–**2h** by NMR measurements.

Antiprotozoal Acitivities and Cytotoxicity

All new compounds **1e**–**1h**, **2e**–**2h**, and **6g** were tested for their activities against *Trypanosoma b. rhodesiense* and *Plasmodium falciparum* K_1 using *in vitro* micro-



7 **1e**

Scheme 2

Table 1. Activities of compounds **1**, **2a**–**2h**, **6g** 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
1e	10.77	1.13	48.50
1f	1.18	7.81	117.7
1g	3.30	76.70	67.23
1h	2.67	58.26	44.99
2a	>15.55	2.95	132.5
2b	2.42	20.80	n.t.
2c	2.39	4.26	26.76
2d	0.84	5.34	37.34
2e	1.92	1.80	34.35
2f	0.95	1.88	81.34
2g	0.98	2.42	98.30
2h	0.78	2.08	38.68
6g	1.88	3.88	21.19
chl	0.062		
sur		0.011	
mef			4.3

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

plate assays. Their cytotoxicity was determined in a similar way. The results are presented in Table 1.

The new 4-dialkylaminobicyclo[2.2.2]octanones **1f**–**1h** exhibit noteworthy antiplasmodial activity. Compounds **1c** and **1f** are so far the most active ones of the bicyclooctanone series. Compound **1f** possesses at the same time an excellent selectivity index (IC_{50} cytotoxicity/IC_{50} activity is ~100). Compared to their bicyclooctanone analogues **1** the antiplasmodial activity of the alcohols **2** is generally higher. The so far most potent compound is **2d**. The new bicyclooctanol **2h** is slightly more active and possesses equal cytotoxicity.

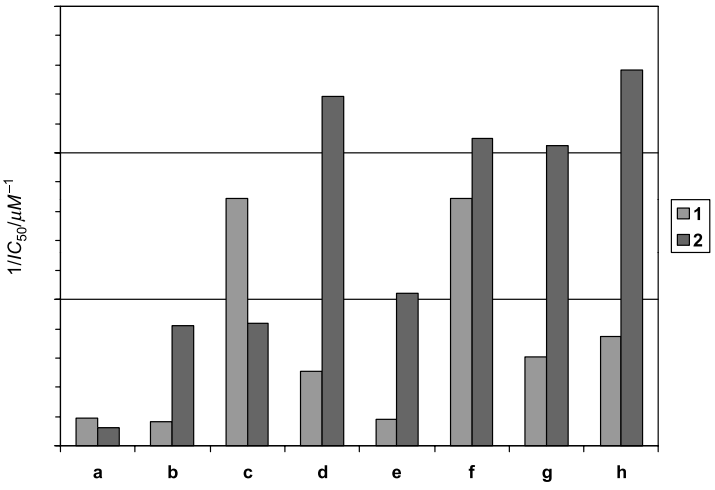


Fig. 3. Comparative presentation of the antiplasmodial activities of **1a**–**1h** and **2a**–**2h** as $1/IC_{50}$ values (ordinate)

Compounds **2f** and **2g** show almost the same potency, but a better selectivity index (Fig. 3).

The results of the antitrypanosomal properties of the new compounds reveal a clear supremacy of the two secondary amines **1e** and **2e** of these series. The alcohol **2e** is the most active compound of the bicyclooctanol series. But the only slightly less active **2f** features a better selectivity index. In general the ketones **1** possess decreased antitrypanosomal potency compared to their analogous alcohols **2**. However, ketone **1e** exhibits the highest trypanocidal activity of all of the so far tested bicyclooctanones and -ols and low cytotoxicity (Fig. 4).

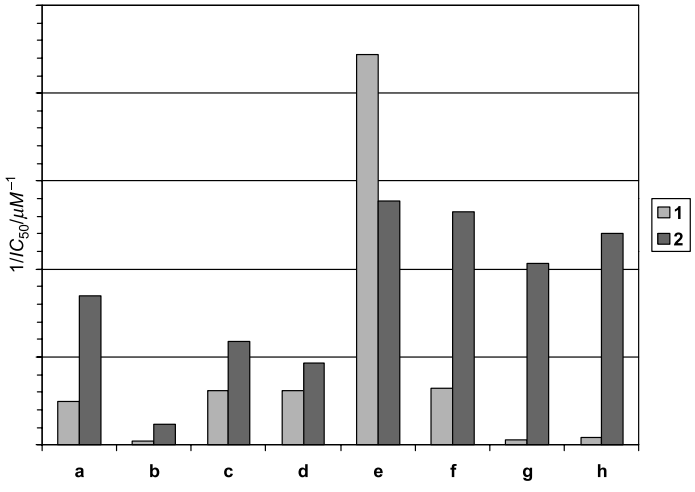


Fig. 4. Comparative presentation of the antitrypanosomal activities of **1a**–**1h** and **2a**–**2h** as $1/IC_{50}$ values (ordinate)

Conclusion

A new method for the synthesis of 4-aminobicyclo[2.2.2]octan-2-ones is presented. Compared to the so far reported bicyclooctan-2-ones **1a**–**1d** and -2-ols **2a**–**2d** the newly synthesized **1e**–**1h** and **2e**–**2h** possess equal or even better antiprotozoal properties and lower cytotoxicity. The 4-methylaminobicyclo[2.2.2]octan-2-one **1e** exhibits the highest antitrypanosomal activity whereas the 4-dibutylaminobicyclo[2.2.2]octan-2-ol **2h** is the compound with the highest antiplasmodial potency. Both compounds might serve as lead compounds for further investigations.

Experimental

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). 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 and HRMS: Kratos profile spectrometer 70 eV electron impact. Microanalyses: EA 1108 CHNS-O apparatus (Carlo Erba), Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; their values were in satisfactory agreement with the calculated ones. 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); the substances were detected in UV light at 254 nm. NMR spectra were collected from the bases, IR and UV spectra, melting points and biological tests from the hydrochlorides.

The preparation of ketones **1a**–**1d** and alcohols **2a**–**2d** has been reported [5, 6]. The preparation of **7** is described in Ref. [8].

(6RS,7RS)-(±)-4-Methylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one (**1e**, $C_{21}H_{23}NO$)

To a suspension of 2.88 g of **7** (8.6 mmol) in 36 cm^3 of diethylene glycol 2.67 g of KOH (47.6 mmol) were added, the reaction mixture was heated to 140°C and stirred at this temperature for 150 min. After cooling H_2O was added and the mixture was extracted 5× with CH_2Cl_2. The combined organic layers were washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was evaporated *in vacuo*. The residue was purified by means of CC over silica gel using CH_2Cl_2:CH_3OH = 20:1.5 as eluent giving 2.3 g (90%) of **1e** as colourless resin. Mp 181°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.76 (ddd, J = 13.1, 7.8, 2.8 Hz, 8-H), 2.08 (ddd, J = 13.0, 7.9, 2.6 Hz, 5-H), 2.19 (ddd, J = 13.4, 10.8, 2.9 Hz, 5-H), 2.27 (ddd, J = 13.1, 10.7, 3.2 Hz, 8-H), 2.36 (dd, J = 18.5, 2.5 Hz, 3-H), 2.44 (s, NCH_3), 2.54 (dd, J = 18.5, 3.2 Hz, 3-H), 2.67 (s, 1-H), 3.39 (br, t, J = 9.3 Hz, 6-H, 7-H), 7.03–7.40 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.60 (NCH_3), 34.93 (C-5), 35.43 (C-7), 38.35 (C-6), 40.28 (C-8), 47.88 (C-3), 54.38 (C-4), 54.55 (C-1), 126.44, 126.91, 127.51, 128.60, 128.64, 128.69 (aromatic C), 141.11, 144.13 (aromatic C_q), 213.06 (C-2) ppm; IR (KBr): $\bar{\nu}$ = 2938, 2779, 2688, 2433, 1730, 1496, 1477, 1450, 1064, 757, 699 cm^{-1}; UV-Vis (CH_3OH): λ_{max} (log ε) = 210 (4.049), 258 (2.701) nm; MS (70 eV): m/z = 305 (M^+), 200, 186, 173, 159, 144, 131, 124, 115, 103, 97, 91, 82, 77, 71, 56; HRMS (EI+): calcd. ($C_{21}H_{23}NO$): 305.17796, found: 305.17651.

(2SR,6RS,7RS)-(±)-4-Methylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ol (**2e**, $C_{21}H_{25}NO$)

To a solution of 190 mg of **1e** (0.62 mmol) in 7 cm^3 of dry ether 220 mg of $LiAlH_4$ (5.8 mmol) were added in portions under stirring and cooling on an ice bath. Then, the reaction mixture was stirred over night at room temperature. The reaction was quenched carefully by addition of H_2O under stirring and cooling. When the evolution of H_2 ceased, more H_2O was added and the mixture was extracted 5×

with CH_2Cl_2. The combined organic layers were washed 2× with H_2O and dried (Na_2SO_4). After filtration, the solvent was evaporated *in vacuo* giving **2e** as a colourless resin. Yield 176 mg (92%); mp 234°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.26$ (s, OH), 1.57 (br, d, $J = 13.3$ Hz, 3-H), 1.80–2.03 (m, 3-H, 5-H, 8-H), 2.18 (ddd, $J = 11.9$, 10.0, 1.9 Hz, 8-H), 2.44 (s, NCH_3), 2.44 (d, $J = 3.6$ Hz, 1-H), 2.96 (t, $J = 9.3$ Hz, 6-H), 3.23 (t, $J = 9.8$ Hz, 7-H), 4.30 (dd, $J = 8.4$, 4.1 Hz, 2-H), 7.11–7.40 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.43$ (NCH_3), 34.66 (C-5), 34.80 (C-7), 35.13 (C-8), 39.66 (C-6), 41.57 (C-3), 44.87 (C-1), 52.64 (C-4), 71.93 (C-2), 125.68, 126.24, 127.16, 127.39, 128.21, 128.49 (aromatic C), 143.34, 145.05 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3430$, 2962, 2944, 2792, 2720, 2438, 1601, 1497, 1478, 1450, 1334, 1076, 1032, 762, 749, 711, 698 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 212 (4.022), 259 (2.694) nm; MS (70 eV): $m/z = 307$ (M^+), 202, 186, 159, 126, 99, 91, 82, 71, 56; HRMS (EI+): calcd. ($C_{21}H_{25}NO$): 307.19361, found: 307.19447.

(6RS,7RS)-(±)-4-Diethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one (**1f**, $C_{24}H_{29}NO$)

To a solution of 46 g of benzylidene acetone (0.315 mol) and 23.06 g of diethylamine (0.315 mol) in 125 cm^3 of benzene 200 mg of $ZnCl_2$ were added. The mixture was refluxed over night at 140°C using a H_2O separator. After cooling to room temperature, the solid was filtered off and the solvent was removed *in vacuo* giving a resin. After purification by CC (diethylether, CH_2Cl_2:CH_3OH = 8:1) the solvent was evaporated. The residue was extracted with diethylether, filtered, and shaken 4× with 2 *M* NaOH, once with H_2O, dried (Na_2SO_4), and filtered. The solvent was evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2, and treated 2× with 10 cm^3 of 2 *M* HCl in ether. The solvent was evaporated *in vacuo* and the residue dissolved in acetone and ether was added. The oily emulsion was stirred over night giving a yellowish solid which was recrystallized from acetone. The base was set free by treatment of the hydrochloride with 2 *M* NaOH and subsequent extraction with diethylether. Yield 4.4 g (8%); mp 245°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.09$ (t, $J = 7.1$ Hz, $2CH_3$), 1.76 (ddd, $J = 12.0$, 8.5, 2.2 Hz, 8-H), 2.18 (ddd, $J = 13.2$, 8.3, 2.2 Hz, 5-H), 2.29 (ddd, $J = 13.2$, 10.5, 2.4 Hz, 5-H), 2.38–2.47 (m, 3-H, 8-H), 2.63–2.74 (m, 1-H, 3-H, $N(CH_2)_2$), 3.30 (br, t, $J = 9.5$ Hz, 6-H), 3.35 (br, t, $J = 9.5$ Hz, 7-H), 7.05–7.39 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.18$ ($2CH_3$), 33.11 (C-5), 35.82 (C-7), 38.47 (C-6), 39.01 (C-8), 42.35 ($N(CH_2)_2$), 46.42 (C-3), 54.34 (C-1), 59.06 (C-4), 126.40, 126.75, 126.93, 127.47, 128.57, 128.65 (aromatic C), 141.35, 144.37 (aromatic C_q), 213.63 (C-2) ppm; IR (KBr): $\bar{\nu} = 2932$, 2885, 2590, 2537, 2483, 1721, 1498, 1450, 1341, 1034, 757, 700 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 211 (4.188) nm; MS (70 eV): $m/z = 347$ (M^+), 304, 256, 243, 228, 215, 200, 186, 166, 131, 103, 98, 91, 78, 70, 42; HRMS (EI+): calcd. ($C_{24}H_{29}NO$): 347.22491, found: 347.22374.

(5RS,8RS)-(±)-5,8-Diphenyl-N,N,N′,N′-tetrapropylbicyclo[2.2.2]octan-2-en-1,3-diamine (**6g**, $C_{32}H_{46}N_2$)

A mixture of 46.12 g of benzylidene acetone (0.32 mol), 31.89 g of dipropylamine (0.32 mol) and 200 mg of $ZnCl_2$ in 125 cm^3 of benzene was refluxed over night at 140°C using a H_2O separator. After cooling to room temperature, the solid was filtered off and the solvent was removed *in vacuo* giving a resin which was purified by use of CC (CH_2Cl_2:CH_3OH = 4:1), the solvent was evaporated, giving 2.24 g (3%) of **6g** as a yellowish resin. The hydrochloride was prepared treating a solution of **6g** in CH_2Cl_2 with 2 *M* HCl in ether and evaporation of the solvents. The residue crystallized from acetone giving white needles. Mp 192°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.77$ (t, $J = 7.3$ Hz, $2CH_3$), 0.89 (t, $J = 7.3$ Hz, $2CH_3$), 1.30–1.46 (m, $2CH_2$), 1.50–1.60 (m, $2CH_2$), 1.78 (ddd, $J = 12.0$, 5.8, 3.4 Hz, 7-H), 1.87 (dd, $J = 12.1$, 7.0 Hz, 6-H), 1.97 (ddd, $J = 12.3$, 11.3, 3.4 Hz, 6-H), 2.20 (dd, $J = 12.0$, 10.2 Hz, 7-H), 2.61 (d, $J = 2.1$ Hz, 4-H), 2.61–2.74 (m, $2N(CH_2)_2$), 2.84–3.03 (m, 5-H), 3.18–3.22 (m, 8-H), 4.70 (d, $J = 1.7$ Hz, 2-H), 7.06–7.39 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.54$ ($2CH_3$), 11.96 ($2CH_3$), 20.79 ($2CH_2$), 24.28 ($2CH_2$), 34.94 (C-6), 37.66 (C-8), 40.78 (C-7), 45.31, 45.49 (C-4, C-5), 51.36, 53.46 ($2N(CH_2)_2$), 63.03 (C-1), 98.83 (C-2), 125.73, 126.03, 127.86, 127.96, 128.12,

128.39 (aromatic C), 144.28, 146.74 (aromatic C_q), 148.91 (C-3) ppm; IR (KBr): $\bar{\nu} = 3431$, 2968, 2936, 2878, 2611, 2469, 1654, 1495, 1474, 1453, 1365, 1353, 763, 708 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 208 (4.252) nm; MS (70 eV): $m/z = 458$ (M^+), 415, 375, 354, 311, 283, 271, 229, 200, 129, 104; HRMS (EI+): calcd. ($C_{32}H_{46}N_2$): 458.36610, found: 458.36638.

(6RS,7RS)-(±)-6,7-Diphenyl-4-dipropylaminobicyclo[2.2.2]octan-2-one (**1g**, $C_{26}H_{33}NO$)

A suspension of 200 mg of the hydrochloride of **6g** (0.40 mmol) in 200 cm^3 of 2 *M* HCl was refluxed on an oil-bath at 160°C over night. Then the solution was cooled and alkalized with NaOH under further cooling using an ice bath. The cold suspension was extracted 5× with ether, the organic layers were combined, washed 5× with H_2O, dried (Na_2SO_4), and filtered. The solvent was evaporated *in vacuo* giving 129 mg (85%) of **1g** as yellowish resin. The hydrochloride of **1g** was prepared by treatment of the base with a 2 *M* solution of HCl in ether and evaporation of the solvent *in vacuo*. The hydrochloride crystallized from *Et*OH/ether. Mp 160°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (t, $J = 7.3$ Hz, $2CH_3$), 1.42–1.51 (m, $2CH_2$), 1.73 (ddd, $J = 12.1$, 8.5, 2.7 Hz, 8-H), 2.16 (ddd, $J = 12.1$, 8.6, 2.5 Hz, 5-H), 2.26 (ddd, $J = 13.1$, 10.4, 2.7 Hz, 5-H), 2.36–2.44 (m, 3-H, 8-H), 2.48–2.60 (m, $N(CH_2)_2$), 2.62–2.67 (m, 1-H, 3-H), 3.33 (br, t, $J = 10.6$ Hz, 6-H), 3.36 (br, t, $J = 10.9$ Hz, 7-H), 7.06–7.39 (m, 10H, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.70$ ($2CH_3$), 24.33 ($2CH_2$), 32.98 (C-5), 35.89 (C-7), 38.53 (C-6), 39.06 (C-8), 46.56 (C-3), 51.85 ($N(CH_2)_2$), 54.33 (C-1), 58.88 (C-4), 126.42, 126.76, 126.98, 127.49, 128.60, 128.67 (aromatic C), 141.47, 144.49 (aromatic C_q), 213.81 (C-2) ppm; IR (KBr): $\bar{\nu} = 3428$, 2968, 2937, 2880, 2594, 2412, 1724, 1498, 1472, 1453, 1343, 1034, 760, 750, 700 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 209 (4.240) nm; MS (70 eV): $m/z = 375$ (M^+), 346, 284, 271, 256, 243, 200, 131, 103, 91; HRMS (EI+): calcd. ($C_{26}H_{33}NO$): 375.25621, found: 375.25668.

(6RS,7RS)-(±)-4-Dibutylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one (**1h**, $C_{28}H_{37}NO$)

To a solution of 46 g of benzylidene acetone (0.315 mol) and 40.7 g of dibutylamine (0.315 mol) in 125 cm^3 of benzene 200 mg of $ZnCl_2$ were added. The mixture was refluxed over night at 140°C using a H_2O separator. After cooling to room temperature, the solid was filtered off and the solvent was removed *in vacuo* giving a resin. Purification by CC (CH_2Cl_2, CH_2Cl_2:CH_3OH = 9:1, CH_3OH) gave after evaporation of the solvent a residue which was dissolved in CH_2Cl_2 and treated 2× with 15 cm^3 of a 2 *M* solution of HCl in ether. The solvent was evaporated *in vacuo* and to the residue acetone and ether were added. The oily emulsion was stirred for 3 d giving a yellowish solid which was recrystallized from acetone/ether. The base was set free by treatment of the hydrochloride with 2 *M* NaOH and subsequent extraction with ether. Yield 6.1 g (10%); mp 188°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.2$ Hz, $2CH_3$), 1.24–1.34 (m, $2CH_2$), 1.40–1.48 (m, $2CH_2$), 1.72 (ddd, $J = 12.0$, 8.5, 2.6 Hz, 8-H), 2.16 (ddd, $J = 13.3$, 8.6, 2.3 Hz, 5-H), 2.26 (ddd, $J = 13.3$, 10.4, 2.6 Hz, 5-H), 2.36–2.45 (m, 3-H, 8-H), 2.54–2.63 (m, 3-H, $N(CH_2)_2$), 2.67 (s, 1-H), 3.33 (br, t, $J = 9.8$ Hz, 6-H), 3.35 (br, t, $J = 9.8$ Hz, 7-H), 7.06–7.39 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.07$ ($2CH_3$), 20.53 ($2CH_2$), 32.93 (C-5), 33.37 ($2CH_2$), 35.88 (C-7), 38.51 (C-6), 38.99 (C-8), 46.59 (C-3), 49.50 ($N(CH_2)_2$), 54.33 (C-1), 58.96 (C-4), 126.39, 126.74, 126.96, 127.47, 128.58, 128.64 (aromatic C), 141.46, 144.45 (aromatic C_q), 213.74 (C-2) ppm; IR (KBr): $\bar{\nu} = 2959$, 2936, 2874, 2586, 2461, 1726, 1497, 1452, 1342, 1034, 758, 700 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 209 (4.255) nm; MS (70 eV): $m/z = 403$ (M^+), 360, 312, 299, 284, 242, 222, 180, 154, 143, 131, 104, 91; HRMS (EI+): calcd. ($C_{28}H_{37}NO$): 403.28752, found: 403.28708.

*Preparation of **2f–2h***

To a cooled etheral solution of bicyclo[2.2.2]octan-2-ones **1f–1h** $LiAlH_4$ was added in portions. The reaction mixture was stirred over night at room temperature, and quenched carefully by addition of

30% NaOH under stirring and cooling. After that, brine was added and the reaction mixture was extracted 5× with $CHCl_3$. The organic layers were washed 2× with H_2O and dried (Na_2SO_4). After filtration, the solvents were removed *in vacuo* at room temperature. The residue was further purified. The hydrochloride was prepared by repeated treatment of the residue with an excess of a 2 *M* solution of HCl in ether.

(2SR,6RS,7RS)-(±)-4-Diethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ol (**2f**, $C_{24}H_{31}NO$)

Reaction of 250 mg of **1f** (0.72 mmol) in 10 cm^3 of dry ether with 250 mg of $LiAlH_4$ (6.6 mmol) gave after purification using CC (*Me*OH) 200 mg (57%) of **2f** as a colourless resin. Mp 148°C (*Et*OH/*Et*OAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.11$ (t, $J = 7.2$ Hz, $2CH_3$), 1.71 (d, $J = 14.0$ Hz, 3-H), 1.99 (d, $J = 9.6$ Hz, 5-H), 2.07–2.13 (m, 3-H, 8-H), 2.26 (br, t, $J = 11.2$ Hz, 8-H), 2.45 (d, $J = 4.2$ Hz, 1-H), 2.67–2.79 (m, $N(CH_2)_2$), 2.91 (t, $J = 9.3$ Hz, 6-H), 3.22 (br, t, $J = 9.8$ Hz, 7-H), 4.30 (dd, $J = 8.1$, 4.4 Hz, 2-H), 7.10–7.40 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.33$ ($2CH_3$), 33.08, 33.20 (C-5, C-8), 34.86 (C-7), 39.37 (C-3), 39.66 (C-6), 42.35 ($N(CH_2)_2$), 44.27 (C-1), 57.81 (C-4), 72.13 (C-2), 125.68, 126.22, 127.10, 127.38, 128.24, 128.48 (aromatic C), 143.59, 145.32 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3320$, 2942, 2620, 1732, 1497, 1449, 1247, 1058, 1035, 762, 752, 699 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 209 (4.173) nm; MS (70 eV): $m/z = 349$ (M^+), 332, 304, 258, 244, 228, 214, 201, 186, 168, 154, 141, 124, 104, 91; HRMS (EI+): calcd. ($C_{24}H_{31}NO$): 349.24056, found: 349.23819.

(2SR,6RS,7RS)-(±)-6,7-Diphenyl-4-dipropylaminobicyclo[2.2.2]octan-2-ol (**2g**, $C_{26}H_{35}NO$)

Reaction of 750 mg of **1g** (2.0 mmol) in 20 cm^3 of dry ether with 750 mg of $LiAlH_4$ (10 mmol) gave 750 mg (99.5%) of pure **2g** as a colourless resin. Mp 180°C (*Et*$_2$O/*Et*OAc); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.4$ Hz, $2CH_3$), 1.43–1.54 (m, $2CH_2$), 1.68 (d, $J = 13.8$ Hz, 3-H), 1.96 (d, $J = 9.3$ Hz, 5-H), 2.06–2.13 (m, 3-H, 8-H), 2.32 (br, t, $J = 11.1$ Hz, 8-H), 2.46 (d, $J = 4.2$ Hz, 1-H), 2.49–2.63 (m, $N(CH_2)_2$), 2.91 (t, $J = 9.4$ Hz, 6-H), 3.22 (br, t, $J = 9.7$ Hz, 7-H), 4.30 (dd, $J = 7.9$, 4.4 Hz, 2-H), 7.10–7.41 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.83$ ($2CH_3$), 24.47 ($2CH_2$), 33.08, 33.18 (C-5, C-8), 34.89 (C-7), 39.44 (C-3), 39.70 (C-6), 44.24 (C-1), 51.97 ($N(CH_2)_2$), 57.54 (C-4), 72.21 (C-2), 125.68, 126.21, 127.11, 127.40, 128.27, 128.49 (aromatic C), 143.71, 145.40 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3316$, 2965, 2938, 2879, 2604, 2517, 1601, 1498, 1474, 1448, 1349, 1055, 1035, 753, 699 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 210 (4.109) nm; MS (70 eV): $m/z = 377$ (M^+), 348, 332, 286, 272, 256, 242, 229, 214, 196, 181, 169, 152, 131, 115, 104, 91, 69; HRMS (EI+): calcd. ($C_{26}H_{35}NO$): 377.27187, found: 377.27156.

(2SR,6RS,7RS)-(±)-4-Dibutylamino-6,7-diphenylbicyclo[2.2.2]octan-2-ol (**2h**, $C_{28}H_{39}NO$)

Reaction of 597 mg of **1h** (1.5 mmol) in 20 cm^3 of dry ether with 531 mg of $LiAlH_4$ (14 mmol) gave 590 mg (97%) of **2h** as a colourless resin. Mp 149°C (*Et*OAc, HC1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.94 (t, $J = 7.3$ Hz, $2CH_3$), 1.26–1.36 (m, $2CH_2$), 1.43–1.51 (m, $2CH_2$), 1.69 (d, $J = 13.8$ Hz, 3-H), 1.96 (d, $J = 9.4$ Hz, 5-H), 2.06–2.12 (m, 3-H, 8-H), 2.23 (br, t, $J = 11.0$ Hz, 8-H), 2.45 (d, $J = 4.2$ Hz, 1-H), 2.54–2.67 (m, $N(CH_2)_2$), 2.90 (t, $J = 9.4$ Hz, 6-H), 3.22 (br, t, $J = 9.6$ Hz, 7-H), 4.29 (dd, $J = 7.7$, 4.2 Hz, 2-H), 7.10–7.40 (m, aromatic H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.15$ ($2CH_3$), 20.70 ($2CH_2$), 33.08 (C-5, C-8), 33.58 ($2CH_2$), 34.88 (C-7), 39.40 (C-3), 39.70 (C-6), 44.24 (C-1), 49.58 ($N(CH_2)_2$), 57.67 (C-4), 72.18 (C-2), 125.68, 126.21, 127.12, 127.39, 128.25, 128.49 (aromatic C), 143.69, 145.38 (aromatic C_q) ppm; IR (KBr): $\bar{\nu} = 3300$, 2959, 2935, 2894, 2872, 2676, 2621, 2529, 1602, 1498, 1469, 1448, 1345, 1056, 1033, 748, 699 cm^{-1}; UV-Vis (CH_3OH): λ_{max} ($\log \varepsilon$) = 210 (4.194) nm; MS (70 eV): $m/z = 405$ (M^+), 362, 314, 300, 284, 242, 224, 214, 182, 168, 155, 145, 129, 104, 91; HRMS (EI+): calcd. ($C_{28}H_{39}NO$): 405.30317, found: 405.30311.

Antiprotozoal Tests, Cytotoxicity

A detailed description of the microplate assays against *Plasmodium falciparum* K_1 and *Trypanosoma brucei rhodesiense* (STIB900) as well as examination of the cytotoxicity using L6 cells have been reported [9].

Acknowledgements

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

References

[1] Fidock DA, Rosenthal PJ, Croft SL, Brun R, Nwaka S (2004) Nature Rev Drug Discov **3**: 509
[2] Wickware P (2002) Nat Med **8**: 908
[3] Gutteridge WE (1985) Brit Med Bull **41**: 162
[4] Doua F, Yapo FB (1993) Acta Trop **54**: 163
[5] Weis R, Schweiger K, Seebacher W, Belaj F (1998) Tetrahedron **54**: 14015
[6] Weis R, Brun R, Saf R, Seebacher W (2003) Monatsh Chem **134**: 1019
[7] Seebacher W, Brun R, Saf R, Weis R (2003) Monatsh Chem **134**: 1411
[8] Seebacher W, Brun R, Saf R, Kröpfl D, Weis R (2004) Monatsh Chem **135**: 313
[9] Seebacher W, Brun R, Weis R (2004) Eur J Pharm Sci **21**: 225
[10] Seebacher W, Michl G, Belaj F, Brun R, Saf R, Weis R (2003) Tetrahedron **59**: 2811
[11] Brady WT, Shieh CH (1983) J Org Chem **48**: 2499