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Hydrazones and new Oximes of 4-Aminobicyclo[2.2.2]octanones and their Antiprotozoal Activities

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Summary. 4-Aminobicyclo[2.2.2]octan-2-ones and -ols showed activity against the causative organisms of East African sleeping sickness and Malaria tropica. Several imino derivatives of the ketones were more active. Now hydrazono analogues and 3-hydroximino derivatives of the ketones and alcohols were synthesized. The structures of the obtained isomers were elucidated by NMR spectroscopy. A single phenylhydrazone exhibited quite good antitrypanosomal activity in the range of already known imino analogues.

Keywords. Antiprotozoal activity; Imines; Isomers; Ketones; NMR spectroscopy.

Introduction

Malaria is a global health problem killing 2–3 million people every year [1]. The multidrug-resistant strains of the causative protozoon, *Plasmodium falciparum*, are becoming increasingly prevalent around the world [2–4]. Since traditional therapeutics have become ineffective in many parts of the world there is still need of new antimalarials with potency against drug-resistant strains [5, 6].

East African sleeping sickness is caused by the protozoan parasite *Trypanosoma brucei rhodesiense*. If untreated the infection is fatal and every year more than 50,000 people die from the disease [7, 8]. Since many decades not a single novel drug against this parasite has been developed and at the time there are only three drugs available. Patients suffer from painful application, severe side-effects,

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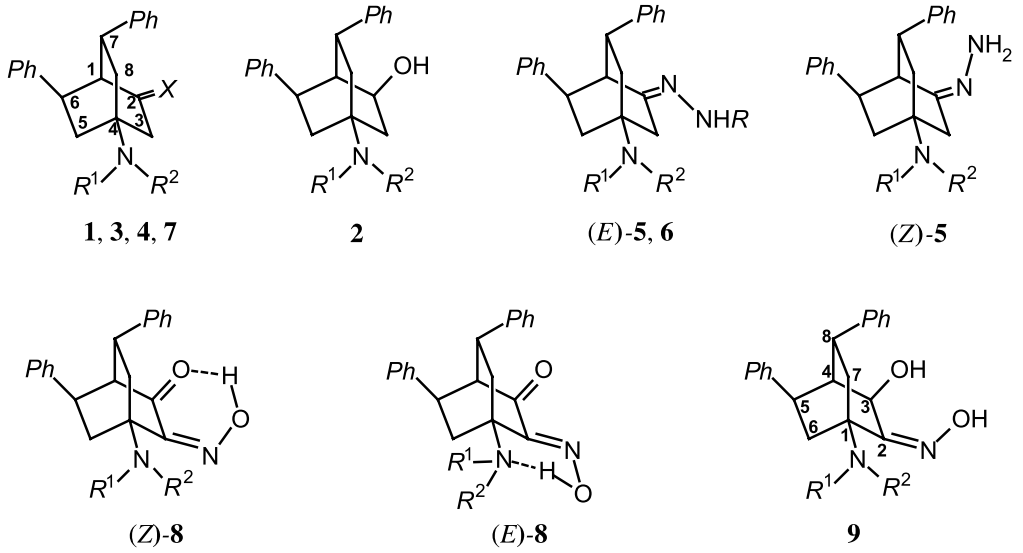

1, **3**, **4**, **7** **2** (*E*)-**5**, **6** (*Z*)-**5**

(*Z*)-**8** (*E*)-**8** **9**

a: $R^1{=}R^2 = Me$; **b:** $R^1{+}R^2 = -(CH_2)_4-$; **c:** $R^1{+}R^2 = -(CH_2)_5-$

	R
1	=O
3	=NOH
4	=N–NH–C(=S)–NH–*Ph*
5	H
6	*Ph*
7	H_2

Fig. 1. Structures of compounds **1–9**

and increasing resistance against these drugs. Therefore, there is an urgent need for new compounds against sleeping sickness [9].

4-Aminobicyclo[2.2.2]octan-2-ones **1** and -ols **2** have shown antiprotozoal activities [10]. Recently, we have reported the synthesis of several more potent imino derivatives of **1**. The oximes **3b** and **3c** and the phenylthiosemicarbazone **4a** have been the most active antiplasmodial compounds, whereas **4a**–**4c** have shown the highest antitrypanosomal potency in this series [11–14] (Fig. 1). In order to investigate if an oxime group in position 3 of compounds **1** and **2** has a similar effect, we prepared their 3-hydroximino derivatives. In addition, hydrazono analogues of compounds **3** were synthesized. All of the new compounds were tested for their activity against *P. falciparum* and *T.b. rhodesiense*.

Results and Discussion

Syntheses

Compounds **1a**–**1c** are available from benzylideneacetone and dialkylammonium thiocyanates in a one-pot synthesis [10, 15]. Those were treated with hydrazine or

its derivatives giving hydrazones **5**–**6**. The reactions proceeded quantitatively when a large excess of hydrazine was used, but the isolation of the phenylhydrazones **6** was difficult. The chromatographic purification of the latter was unsuccessful as long as phenylhydrazine was present in the mixture. During a high vacuum distillation in a Kugelrohr oven only a part of the excess phenylhydrazine could be removed and several decomposition products were formed. Finally, the quantitative elimination of phenylhydrazine succeeded by conversion to its osazone. The subsequent chromatographic purification afforded the pure (*E*)-isomers of compounds **6** in acceptable yields.

In the NMR spectra of the hydrazones we observed the presence of two isomers with the (*E*)-isomers of **5** as main constituents. In the ^{13}C NMR spectra the (*Z*)-isomers of **5** were recognizable by the typical 6 ppm upfield shifts [16] of the signals for their C-1 due to sterical interactions.

The synthesis of bicyclooctan-3-one oximes was inspired by the observation that oximes **3** exhibit far higher antiplasmodial activity than the corresponding ketones **1**. Since they are also more active than the bicyclo[2.2.2]octanes **7** [11] the effect can rather be attributed to the insertion of the oxime group than to the replacement of the oxo group. Preparing the 3-hydroximino derivatives of compounds **1** and **2** we examined if the insertion of a hydroximino group in position 3 has a similar effect. The monoximes **8** of bicyclo[2.2.2]octan-2,3-diones were obtained by treatment of monoketones **1** with isoamyl nitrite under strong alkaline conditions. In polar solvents the oximes **8** predominantly exist in the (*Z*)-form, whereas treatment with $CHCl_3$ affords their (*E*)-isomers. In this way compound (*Z*)-**8c** was quantitatively transformed to (*E*)-**8c**. In ^1H NMR spectra of compounds **8** the signals for the NOH protons were shifted to at least 14 ppm due to hydrogen bridge formation. The distinction between the (*E*)- and (*Z*)-isomers succeeded *via* ^{13}C NMR spectroscopy. The hydrogen bridge in (*Z*)-**8a**–**8c** causes a typical downfield shift for the resonance of the carbonyl carbon. Moreover, the two signals of the aminoalkyl carbons of (*E*)-**8a**–**8c** have differing chemical shifts due to the hindered rotation of the dialkylamino group establishing the formation of an N–H bridge.

Since the bicyclooctan-2-ols **2** exhibit in general better antiprotozoal activity than the corresponding ketones **1**, we were interested, if the activities of the corresponding 3-hydroximino analogues show a similar proportion. Therefore we reduced compounds **8a** and **8b** with $NaBH_4$ and obtained almost stereoselectively the (*Z*)-(3*RS*, 5*RS*, 8*RS*)-isomers **9a** and **9b** in good yields. Only traces of (*E*)-isomers

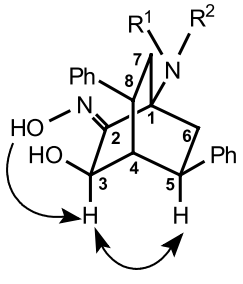

Fig. 2. N*O*Es in compounds **9a** and **9b**

were visable in their NMR spectra whereas the formation of (3*SR*, 5*RS*, 8*RS*)-analogues was not observed. The configuration in position 3 of **9a** and **9b** was established by N*O*Es between 3-H and 5-H. An N*O*E from NOH to 3-H detected their (*Z*)-configuration (Fig. 2).

Antiprotozoal Activities and Cytotoxicity

The antiprotozoal activities of all new compounds **5–6** and **8–9** were tested against *Trypanosoma b. rhodesiense*, and *Plasmodium falciparum* K_1 using *in vitro* microplate assays. Their cytotoxicity was determined using L-6 cells. The results are presented in Table 1.

Unfortunately, the hydrazones **5–6** were in general less active than the corresponding oximes **3** with the exception of phenylhydrazone **6a**. The antitrypanosomal activity and the cytotoxicity of the latter are comparable to that of the already known phenylthiosemicarbazones **4**. The insertion of the oxime group in position 3

Table 1. Activities of compounds **1–9** expressed as $IC_{50}/\mu M$[a]

Compd.	*P. falciparum* K_1	*T.b. rhodesiense*	Cytotox. L-6 cells
1a	>10.57	9.99	24.57
1b	1.19	8.03	26.45
1c	3.95	8.12	46.82
2a	>15.55	2.95	132.5
2b	2.39	4.26	26.76
2c	0.84	5.34	37.34
3a	1.26	7.67	150.4
3b	0.08	1.84	13.45
3c	0.15	3.66	24.16
4a	0.23	0.26	3.98
4b	0.56	0.24	5.08
4c	0.72	0.46	16.09
5a	3.13	3.44	47.86
5b	3.81	4.05	41.64
5c	3.65	3.52	59.01
6a	1.46	0.44	9.30
6b	2.33	1.77	10.70
7a	2.50	1.64	23.40
7b	3.64	1.47	16.03
7c	1.55	1.49	11.52
8a	3.14	3.23	8.00
8b	2.13	3.52	5.89
8c	3.45	54.05	21.27
9a	1.78	4.15	82.39
9b	1.91	2.79	64.04
chl	0.062		
sur		0.011	
mef			4.3

[a] Values represent the average of four determinations (two determinations of two independent experiments), *chl* = chloroquine, *mef* = mefloquine, *sur* = suramine

of the bicyclooctan-2-ones **1** and -ols **2** caused in most cases an increase of antiprotozoal potencies, however, those still were unsatisfactory compared to the drugs in use.

Conclusion

Bicyclooctan-2-one hydrazones and 3-hydroximino derivatives of bicyclooctan-2-ones and -ols were prepared. Their structures were elucidated by NMR spectroscopy revealing their (*E*)- or (*Z*)-configuration. Although a number of the newly prepared oximes showed higher antiprotozoal activities than their parent alcohols and ketones, they are still less active than the drugs in use. At least a single phenylhydrazone showed distinct antitrypanosomal activity in the range of already known imines of bicyclooctanones.

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. Assignments marked with an asterisk are interchangeable. 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; 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 compounds were detected in UV light at 254 nm.

The preparation of ketones **1a**–**1c** and alcohols **2a**–**2c** has been reported [10, 15].

*Preparation of Bicyclo[2.2.2]octan-2-one Hydrazones **5a**–**5c***

In an atmosphere of Ar $NH_2NH_2 \cdot H_2O$ and activated molecular sieves (0.3 nm) were added to a solution of ketones **1** in dry *Et*OH. The mixture was refluxed at 100°C over night. After cooling to room temperature, the solids were filtered off and the solvent was evaporated *in vacuo*. The residue was dissolved in the minimum of *Et*OH and H_2O was added. The mixture was cooled with liquid nitrogen and lyophilized.

(6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one Hydrazone ((*E*)-**5a**, (*Z*)-**5a**, $C_{22}H_{27}N_3$)

The reaction of 1.34 g **1a** (4.2 mmol), 4.1 g $NH_2NH_2 \cdot H_2O$ (82 mmol), and 3.6 g molecular sieves in 50 cm^3 *Et*OH gave 1.0 g (72%) of the isomers (*E*)-**5a** and (*Z*)-**5a**. NMR: *Main component* (*E*)-**5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.58$ (ddd, $J = 11.8$, 8.5, 2.7 Hz, 8-H), 1.99–2.05 (m, 5-H), 2.20–2.30 (m, 5-H, 8-H), 2.33–2.44 (m, 3-H, $N(CH_3)_2$), 2.70 (s, 1-H), 3.16–3.23 (m, 7-H), 3.26–3.31 (m, 6-H), 4.97 (br, s, NH_2), 7.08–7.40 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 30.92$ (C-3), 31.88 (C-5), 36.09 (C-7), 36.92 (C-8), 38.48 ($N(CH_3)_2$), 40.72 (C-6), 45.84 (C-1), 57.32 (C-4), 126.02, 126.32, 127.35, 127.44, 128.24, 128.44, 142.62, 145.16 (aromatic C), 154.31 (C-2) ppm; *minor constituent* (*Z*)-**5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.78$ (ddd, $J = 12.1$, 9.5, 2.6 Hz, 8-H), 1.94–1.99 (m, 5-H), 2.14 (ddd, $J = 12.5$, 10.6, 1.9 Hz, 8-H), 2.20–2.30 (m, 5-H), 2.37 (s, $N(CH_3)_2$), 2.54–2.63 (m, 3-H), 2.99 (s, 1-H), 3.16–3.23 (m, 6-H), 3.26–3.31 (m, 7-H), 4.44 (br, s, NH_2), 7.08–7.40 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.94$ (C-5), 34.69 (C-8), 36.80, 36.82 (C-3, C-7), 38.42

($N(CH_3)_2$), 39.34 (C-6), 40.02 (C-1), 57.50 (C-4), 126.54, 126.64, 127.08, 127.44, 128.56, 128.76, 142.54, 144.23 (aromatic C), 154.71 (C-2) ppm; (*E*)-**5a**, (*Z*)-**5a**: IR (KBr): $\bar{\nu} = 2944$, 2869, 2780, 1601, 1494, 1447, 753, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.733) nm; MS (EI^+): $m/z = 333$ (M^+), 317, 213, 185, 172, 158, 128, 104, 91, 84, 70; HRMS (EI^+): calcd ($C_{22}H_{27}N_3$) 333.22050, found 333.22289.

(6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-one Hydrazone
((*E*)-**5b**, (*Z*)-**5b**, $C_{24}H_{29}N_3$)
The reaction of 1.38 g **1b** (4 mmol), 4.0 g $NH_2NH_2 \cdot H_2O$ (80 mmol), and 3.0 g molecular sieves in 50 cm^3 *Et*OH gave 1.33 g (89%) of the isomers (*E*)-**5b** and (*Z*)-**5b**. NMR: *Main component* (*E*)-**5b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.65$ (ddd, $J = 12.9$, 7.9, 3.0 Hz, 8-H), 1.78–1.84 (m, $(CH_2)_2$), 2.06–2.28 (m, 5-H), 2.25–2.34 (m, 8-H), 2.36–2.47 (m, 3-H), 2.67 (s, 1-H), 2.72–2.82 (m, $N(CH_2)_2$), 3.23 (br, t, $J = 9.2$ Hz, 7-H), 3.31 (br, t, $J = 9.4$ Hz, 6-H), 4.96 (br, s, NH_2), 7.06–7.41 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.58$ ($(CH_2)_2$), 31.79 (C-3), 32.77 (C-5), 36.04 (C-7), 37.58 (C-8), 40.80 (C-6), 45.55 ($N(CH_2)_2$), 46.17 (C-1), 56.01 (C-4), 125.98, 126.30, 127.36, 127.54, 128.22, 128.42, 142.66, 145.19 (aromatic C), 154.55 (C-2) ppm; *minor constituent* (*Z*)-**5b**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.78$–1.84 (m, $(CH_2)_2$), 1.86 (ddd, $J = 13.1$, 8.2, 2.7 Hz, 8-H), 2.01–2.09 (m, 5-H), 2.13–2.21 (m, 8-H), 2.21–2.31 (m, 5-H), 2.62 (dd, $J = 16.4$, 2.5 Hz, 3-H), 2.66 (dd, $J = 16.4$, 3.0 Hz, 3-H), 2.72–2.82 (m, $N(CH_2)_2$), 2.97 (s, 1-H), 3.21 (br, t, $J = 9.2$ Hz, 6-H), 3.31 (br, t, $J = 9.1$ Hz, 7-H), 4.41 (br, s, NH_2), 7.11–7.42 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.52$ ($(CH_2)_2$), 32.82 (C-5), 35.55 (C-8), 36.72 (C-7), 37.47 (C-3), 39.39 (C-6), 40.34 (C-1), 45.55 ($N(CH_2)_2$), 56.18 (C-4), 126.51, 126.60, 127.11, 127.54, 128.54, 128.73, 142.59, 144.26 (aromatic C), 154.94 (C-2) ppm; (*E*)-**5b**, (*Z*)-**5b**: IR (KBr): $\bar{\nu} = 2942$, 2871, 2806, 1601, 1494, 1449, 755, 700 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.744) nm; MS (EI^+): $m/z = 359$ (M^+), 343, 239, 199, 91, 70; HRMS (EI^+): calcd ($C_{24}H_{29}N_3$) 359.23615, found 359.23725.

(6RS,7RS)-(±)-6,7-Diphenyl-4-piperidinobicyclo[2.2.2]octan-2-one Hydrazone
((*E*)-**5c**, (*Z*)-**5c**, $C_{25}H_{31}N_3$)
The reaction of 1.44 g **1c** (4 mmol), 4.0 g $NH_2NH_2 \cdot H_2O$ (80 mmol), and 3.0 g molecular sieves in 50 cm^3 *Et*OH gave 1.17 g (76%) of the isomers (*E*)-**5c** and (*Z*)-**5c**. NMR: *Main component* (*E*)-**5c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.43$–1.50 (m, CH_2), 1.57 (ddd, $J = 12.5$, 8.9, 2.7 Hz, 8-H), 1.58–1.66 (m, $2CH_2$), 2.03 (ddd, $J = 13.1$, 8.4, 2.5 Hz, 5-H), 2.22–2.32 (m, 3-H, 5-H, 8-H), 2.33 (dd, $J = 16.6$, 3.2 Hz, 3-H), 2.45 (dd, $J = 16.6$, 2.5 Hz, 3-H), 2.59–2.73 (m, $N(CH_2)_2$), 2.70 (s, 1-H), 3.19 (br, t, $J = 9.2$ Hz, 7-H), 3.25 (br, t, $J = 9.3$ Hz, 6-H), 4.95 (br, s, NH_2), 7.09–7.41 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.86$ (CH_2), 26.82 ($2CH_2$), 31.42 (C-3), 32.26 (C-5), 36.24 (C-7), 37.79 (C-8), 40.80 (C-6), 45.93 (C-1), 46.91 ($N(CH_2)_2$), 57.90 (C-4), 125.99, 126.29, 127.37, 127.49, 128.25, 128.43, 142.72, 145.28 (aromatic C), 154.78 (C-2) ppm; *minor constituent* (*Z*)-**5c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.43$–1.50 (m, CH_2), 1.58–1.66 (m, $2CH_2$), 1.79 (ddd, $J = 12.7$, 9.3, 2.6 Hz, 8-H), 1.95–2.01 (m, 5-H), 2.14 (ddd, $J = 12.7$, 10.0, 2.4 Hz, 8-H), 2.22–2.27 (m, 5-H), 2.57–2.72 (m, 3-H, $N(CH_2)_2$), 2.99 (s, 1-H), 3.14 (br, t, $J = 9.2$ Hz, 6-H), 3.26 (br, t, $J = 9.5$ Hz, 7-H), 4.41 (br, s, NH_2), 7.10–7.42 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.86$ (CH_2), 26.75 ($2CH_2$), 32.39 (C-5), 35.33 (C-8), 36.95 (C-7), 37.28 (C-3), 39.39 (C-6), 40.22 (C-1), 46.88 ($N(CH_2)_2$), 58.13 (C-4), 126.51, 126.64, 127.14, 127.49, 128.55, 128.76, 142.65, 144.33 (aromatic C), 155.16 (C-2) ppm; (*E*)-**5c**, (*Z*)-**5c**: IR (KBr): $\bar{\nu} = 2932$, 2853, 2791, 1601, 1495, 1467, 753, 700 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.794) nm; MS (EI^+): $m/z = 359$ (M^+), 343, 239, 199, 91, 70; HRMS (EI^+): calcd ($C_{25}H_{31}N_3$) 373.25180, found 373.25216.

*Preparation of Bicyclo[2.2.2]octan-2-one Phenylhydrazones **6a** and **6b***
In an atmosphere of Ar activated molecular sieves (0.3 nm) were added to a solution of ketones **1** and freshly distilled phenylhydrazine in dry *Et*OH. The mixture was refluxed at 100°C over night. After cooling to room temperature, the solids were filtered off and the solvent was evaporated *in vacuo*. The

residue was dissolved in a small amount of *Et*OH and a solution of glucose in H_2O was added. The mixture was heated at 90°C until the solution became yellowish. Then it was cooled and evaporated to dryness. The residue was partitioned between H_2O and ether. The organic layer was dried and evaporated. The residue was chromatographed twice over a column filled with aluminum oxide eluting with CH_2Cl_2:*Me*OH (49:1) and subsequently with CH_2Cl_2:*Me*OH (79:1). The fractions containing compounds **6** were combined and the solvent was evaporated.

(E)-(6RS,7RS)-(±)-4-Dimethylamino-6,7-diphenylbicyclo[2.2.2]octan-2-one Phenylhydrazone (**6a**, $C_{28}H_{31}N_3$)

The reaction of 1.28 g **1a** (4 mmol), 1.57 g phenylhydrazine (14 mmol), and 3 g molecular sieves in 50 cm^3 *Et*OH gave a mixture of **6a** and phenylhydrazine. The ethanolic solution of the residue was treated with 7.6 g glucose in 24 cm^3 H_2O. Chromatographic purification of the crude phenylhydrazone gave 0.32 g (19%) **6a**. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.56$ (ddd, $J = 12.0$, 8.4, 2.9 Hz, 8-H), 2.05 (ddd, $J = 13.0$, 8.3, 2.4 Hz, 5-H), 2.17 (s, NH), 2.26–2.32 (m, 5-H, 8-H), 2.41 (s, $N(CH_3)_2$), 2.43 (dd, $J = 16.5$, 3.2 Hz, 3-H), 2.53 (dd, $J = 16.5$, 2.5 Hz, 3-H), 2.89 (s, 1-H), 3.24 (dd, $J = 10.6$, 8.4 Hz, 7-H), 3.24 (dd, $J = 10.2$, 8.2 Hz, 6-H), 6.83–7.40 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 31.50$ (C-3), 32.18 (C-5), 36.20 (C-7), 37.39 (C-8), 38.56 ($N(CH_3)_2$), 40.89 (C-6), 45.23 (C-1), 57.63 (C-4), 113.18, 119.82, 126.08, 126.40, 127.51, 128.27, 128.50, 129.16, 142.58, 145.25, 145.62 (aromatic C), 149.69 (C-2) ppm; IR (KBr): $\bar{\nu} = 2948$, 2872, 2782, 1602, 1498, 1240, 751, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 276$ (4.263) nm.

(E)-(6RS,7RS)-(±)-6,7-Diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-one Phenylhydrazone (**6b**, $C_{30}H_{33}N_3$)

The reaction of 1.38 g **1b** (4 mmol), 2.16 g phenylhydrazine (20 mmol), and 3 g of molecular sieves in 60 cm^3 *Et*OH gave a mixture of **6b** and phenylhydrazine. The ethanolic solution of the residue was treated with 10.8 g glucose in 35 cm^3 H_2O. Chromatographic purification of the crude phenylhydrazone gave 0.30 g (17%) **6b**. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.63$ (ddd, $J = 12.8$, 8.3, 2.8 Hz, 8-H), 1.78–1.87 (m, $(CH_2)_2$), 2.13 (br, dd, $J = 13.2$, 8.1 Hz, 5-H), 2.25–2.35 (m, 5-H, 8-H), 2.46–2.56 (m, 3-H), 2.73–2.83 (m, $N(CH_2)_2$), 2.86 (s, 1-H), 3.26 (br, dd, $J = 10.3$, 8.1 Hz, 7-H), 3.35 (br, dd, $J = 10.3$, 8.3 Hz, 6-H), 6.81–7.42 (m, aromatic H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.61$ $(CH_2)_2$), 32.47 (C-3), 32.99 (C-5), 36.16 (C-7), 37.95 (C-8), 40.96 (C-6), 45.52 (C-1), 45.64 ($N(CH_3)_2$), 56.33 (C-4), 113.14, 119.74, 126.00, 126.35, 127.52, 128.22, 128.45, 129.13, 142.64, 145.28, 145.63 (aromatic C), 149.79 (C-2) ppm; IR (KBr): $\bar{\nu} = 2949$, 2872, 2809, 1601, 1497, 1238, 751, 698 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 276$ (4.233) nm.

*Preparation of 4-Amino-3-hydroximinobicyclo[2.2.2]octan-2-ones **8a–8c***

Potassium *tert*-butoxide was suspended in dry *THF* and cooled under stirring to −30°C in an atmosphere of Ar. A solution of the corresponding bicyclooctanone **1** in dry *THF* was added *via* a dropping funnel within 15 min. The mixture was stirred for a further 10 min at −30°C, then isoamyl nitrite was added dropwise using a syringe. The colour of the mixture changed from pale yellow to deep violet. The mixture was allowed to warm up to room temperature and was stirred over night. Then, the solvent was removed *in vacuo* and the residue dissolved in H_2O, acidified with 2 *N* acetic acid and extracted once with ether to remove neutral impurities. After alkalization with 2 *N* NaOH the aqueous phase was extracted five times with ether. The combined organic layers were washed with H_2O, dried over sodium sulfate, and filtered. The solvent was evaporated *in vacuo* and the residue treated with hot heptane giving a precipitate which was further purified.

(6RS,7RS)-(±)-4-Dimethylamino-3-hydroximino-6,7-diphenyl-bicyclo[2.2.2]octan-2-one ((*E*)-**8a**, (*Z*)-**8a**, $C_{22}H_{24}N_2O_2$)

The reaction of 1.14 g potassium *tert*-butoxide (9.33 mmol) in 10 cm^3 *THF* and 1.218 g **1a** (3.8 mmol) in 14 cm^3 *THF* gave with 1.2 cm^3 isoamyl nitrite (1.06 g, 9.07 mmol) a precipitate which was

recrystallized from *Et*OH giving 250 mg (19%) of yellow needles of a pure mixture (82:18) of the isomers (*E*)-**8a** and (*Z*)-**8a**. Mp 147°C; NMR: *Main component* (*Z*)-**8a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.14$ (ddd, $J = 13.5$, 7.5, 3.2 Hz, 8-H), 2.27 (dd, $J = 13.3$, 8.2 Hz, 5-H), 2.43–2.56 (m, 5-H, 8-H), 2.59 (s, $N(CH_3)_2$), 2.86 (t, $J = 1.7$ Hz, 1-H), 3.37–3.45 (m, 6-H, 7-H), 6.99–7.43 (m, aromatic H), 14.16 (s, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 33.30$ (C-5), 35.17 (C-7), 35.79 (C-8), 38.23 (C-6), 39.21 ($N(CH_3)_2$), 55.02 (C-1), 61.85 (C-4), 126.87, 126.90, 127.29, 127.35, 128.88, 128.92, 139.92, 143.28 (aromatic C), 150.95 (C-3), 200.60 (C-2) ppm; *minor constituent* (*E*)-**8a**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.02$ (ddd, $J = 13.2$, 9.2, 2.9 Hz, 5-H* or 8-H*), 2.11–2.68 (m, 5-H, 8-H, $N(CH_3)_2$), 2.97 (s, 1-H), 3.37–3.47 (m, 6-H, 7-H), 6.99–7.43 (m, aromatic H), 15.36 (s, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 30.12$, 33.03 (C-5*, C-8*), 35.43 (C-7), 37.06 (NCH_3), 38.39 (C-6), 40.23 (NCH_3), 53.81 (C-1), 65.61 (C-4), 126.97, 127.11, 127.25, 128.85, 139.84, 142.82 (aromatic C), 154.77 (C-3), 197.32 (C-2) ppm; (*E*)-**8a**, (*Z*)-**8a**: IR (KBr): $\bar{\nu} = 3224$, 2945, 2827, 2783, 1720, 1630, 1493, 1447, 1013, 981, 891, 752, 696 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 260$ (3.793) nm; MS (EI^+): $m/z = 348$ (M^+), 331, 321, 276, 199, 172, 158, 115, 96; HRMS (EI^+): calcd ($C_{22}H_{24}N_2O_2$) 348.18378, found 348.18702.

(6RS,7RS)-(±)-3-Hydroximino-6,7-diphenyl-4-pyrrolidinobicyclo[2.2.2]octan-2-one ((*E*)-**8b**, (*Z*)-**8b**, $C_{24}H_{26}N_2O_2$)

The reaction of 1.03 g potassium *tert*-butoxide (8.4 mmol) in 10 cm^3 *THF* and 1.32 g **1b** (3.8 mmol) in 14 cm^3 *THF* gave with 1.2 cm^3 isoamyl nitrite (1.06 g, 9.07 mmol) a precipitate which was purified by means of CC using CH_2Cl_2:*Me*OH (16:1) as eluent affording 200 mg (14%) (*Z*)-**8b** as a yellow resin including only traces of (*E*)-**8b**. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.85$–1.88 (m, $2CH_2$), 2.26 (ddd, $J = 13.7$, 7.0, 3.2 Hz, 8-H), 2.33 (dd, $J = 13.5$, 8.0 Hz, 5-H), 2.55 (dd, $J = 13.7$, 11.4 Hz, 8-H), 2.61 (ddd, $J = 13.7$, 10.6, 3.4 Hz, 5-H), 2.81 (t, $J = 1.9$ Hz, 1-H), 3.04–3.11 (m, $N(CH_2)_2$), 3.39–3.45 (m, 6-H, 7-H), 6.96–7.43 (m, aromatic H), 14.30 (s, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.78$ ($2CH_2$), 34.57 (C-5), 35.09 (C-7), 38.38 (C-6), 38.89 (C-8), 46.91 ($N(CH_2)_2$), 55.68 (C-1), 60.94 (C-4), 126.90, 126.96, 127.32, 127.56, 128.89, 128.93, 140.00, 143.34 (aromatic C), 150.16 (C-3), 201.42 (C-2) ppm; IR (KBr): $\bar{\nu} = 3412$, 2962, 2872, 1712, 1673, 1602, 1564, 1495, 1451, 1339, 1021, 982, 794, 760, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 265$ (3.790) nm; MS (EI^+): $m/z = 374$ (M^+), 357, 329, 270, 253, 225, 198, 156, 131, 115, 91; HRMS (EI^+): calcd ($C_{24}H_{26}N_2O_2$) 374.19943, found 374.19856.

(6RS,7RS)-(±)-3-Hydroximino-6,7-diphenyl-4-piperidinobicyclo[2.2.2]octan-2-one ((*E*)-**8c**, (*Z*)-**8c**, $C_{25}H_{28}N_2O_2$)

The reaction of 1.03 g potassium *tert*-butoxide (8.4 mmol) in 10 cm^3 *THF* and 1.37 g **1c** (3.8 mmol) in 14 cm^3 *THF* gave with 1.2 cm^3 isoamyl nitrite (1.06 g, 9.07 mmol) a precipitate which was purified by means of CC using CH_2Cl_2:*Me*OH (16:1) as eluent affording 250 mg (17%) (*Z*)-**8c** as a yellow resin. (*Z*)-**8c** was dissolved in $CHCl_3$ over night at room temperature. The solvent was removed *in vacuo* giving pure (*E*)-**8c**. NMR: (*Z*)-**8c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.46$–1.52 (m, CH_2), 1.61–1.67 (m, $2CH_2$), 2.08 (ddd, $J = 13.3$, 7.9, 3.1 Hz, 8-H), 2.30 (dd, $J = 13.0$, 8.5 Hz, 5-H), 2.53 (br, dd, $J = 13.0$, 11.6 Hz, 5-H, 8-H), 2.78–2.92 (m, $N(CH_2)_2$), 2.88 (s, 1-H), 3.33–3.43 (m, 6-H, 7-H), 6.99–7.42 (m, aromatic H), 14.18 (s, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.83$ (CH_2), 26.66 ($2CH_2$), 33.45 (C-5), 35.28 (C-7), 35.34 (C-8), 38.32 (C-6), 47.42 ($N(CH_2)_2$), 54.59 (C-1), 62.39 (C-4), 126.87, 127.11, 127.28, 127.33, 128.87, 128.90, 140.02, 143.40 (aromatic C), 151.55 (C-3), 200.97 (C-2) ppm; (*E*)-**8c**: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.19$–1.29 (m, CH_2), 1.56–1.70 (m, CH_2), 1.74–1.84 (m, CH_2), 2.05 (ddd, $J = 13.1$, 9.0, 2.7 Hz, 8-H), 2.31–2.46 (m, 5-H, 8-H, 2NCH), 2.65 (ddd, $J = 12.1$, 10.1, 2.7 Hz, 5-H), 2.97–2.99 (m, 1-H, NCH), 3.20 (br, d, $J = 9.9$ Hz, NCH), 3.36–3.44 (m, 6-H, 7-H), 7.12–7.40 (m, aromatic H), 15.60 (s, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 23.91$, 25.66, 26.26 ($3CH_2$), 31.43 (C-8), 33.31 (C-5), 35.50 (C-7), 38.35 (C-6), 45.85, 49.75 ($N(CH_2)_2$), 53.61 (C-1), 66.22 (C-4), 126.91, 126.96, 127.09, 127.20, 128.82, 128,88, 139.91, 142.91 (aromatic C), 155.07 (C-3), 197.45 (C-2) ppm; (*E*)-**8c**, (*Z*)-**8**c: IR (KBr): $\bar{\nu} = 3027$, 2932, 2853, 1714,

1672, 1602, 1562, 1495, 1450, 1029, 998, 981, 881, 795, 759, 699 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 266$ (3.782) nm; MS (EI^+): $m/z = 388$ (M^+), 371, 343, 267, 239, 212, 193, 156, 115, 91; HRMS (EI^+): calcd ($C_{25}H_{28}N_2O_2$) 388.21508, found 388.21494.

(Z)-(3RS,5RS,8RS)-(±)-1-Dimethylamino-3-hydroxy-5,8-diphenyl-bicyclo[2.2.2]octan-2-one oxime (**9a**, $C_{22}H_{26}N_2O_2$)

To an ice cooled suspension of 160 mg **8a** (0.46 mmol) in 10 cm^3 dry *Et*OH, 22 mg $NaBH_4$ (0.58 mmol) were added in portions. The ice bath was removed and the mixture was stirred over night at room temperature. Then it was cooled again with an ice bath and quenched carefully with H_2O. The resulting mixture was extracted 5 times with $CHCl_3$, the organic layers were combined, washed once with H_2O, dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* giving 153 mg (95%) as a resinous residue which crystallized from *Et*OH in form of white crystals of **9a**. Mp 176°C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 2.17$ (dd, $J = 12.3$, 9.6 Hz, 6-H), 2.26–2.32 (m, 6-H, 7-H), 2.49 (s, $N(CH_3)_2$), 2.81 (d, $J = 3.8$ Hz, 4-H), 2.91 (br, t, $J = 9.6$ Hz, 5-H), 3.34 (br, t, $J = 10.0$ Hz, 8-H), 4.99 (d, $J = 3.1$ Hz, 3-H), 7.14–7.41 (m, aromatic H), 10.10 (br, s, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 29.56$ (C-7), 34.56 (C-6), 34.87 (C-8), 39.09 (C-5), 39.12 ($N(CH_3)_2$), 40.89 (C-4), 60.52 (C-1), 69.10 (C-3), 125.75, 126.51, 127.09, 127.55, 127.86, 128.61, 142.47, 144.15 (aromatic C), 161.75 (C-2) ppm; IR (KBr): $\bar{\nu} = 3553$, 2969, 2953, 2885, 1496, 1475, 1444, 1326, 1063, 1033, 950, 930, 907, 787, 769, 737, 697 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 231$ (3.043) nm; MS (EI^+): $m/z = 350$ (M^+), 333, 305, 276, 201, 186, 172, 158, 144, 128, 96, 91, 84, 70, 49; HRMS (EI^+): calcd ($C_{22}H_{26}N_2O_2$) 350.19943, found 350.19726.

(Z)-(3RS,5RS,8RS)-(±)-3-Hydroxy-5,8-diphenyl-1-pyrrolidinobicyclo[2.2.2]octan-2-one oxime (**9b**, $C_{24}H_{28}N_2O_2$)

To an ice cooled suspension of 160 mg (0.43 mmol) **8b** in 10 cm^3 dry *Et*OH, 22 mg $NaBH_4$ (0.58 mmol) were added in portions. The ice bath was removed and the mixture was stirred for 3 h. Then it was cooled again with an ice bath and further 30 mg $NaBH_4$ (0.79 mmol) were added. The mixture was stirred over night at room temperature, cooled with an ice bath, and quenched carefully with H_2O. The resulting mixture was extracted 5 times with $CHCl_3$, the organic layers were combined, washed once with H_2O, dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* giving 150 mg (93%) as a resinous residue which crystallized from ether in form of white crystals of **9b**. Mp 176°C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.78$ (br, s, $(CH_2)_2$), 2.19 (dd, $J = 11.6$, 10.2 Hz, 6-H), 2.32–2.42 (m, 6-H, 7-H), 2.78 (d, $J = 3.4$ Hz, 4-H), 2.94 (br, t, $J = 9.6$ Hz, 5-H), 2.96–3.10 (m, $N(CH_2)_2$), 3.36 (br, t, $J = 9.9$ Hz, 8-H), 3.55 (br, s, OH), 4.94 (d, $J = 3.8$ Hz, 3-H), 7.09–7.55 (m, aromatic H), 10.10 (br, s, OH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 24.22$ ($2CH_2$), 32.94 (C-7), 34.41 (C-6), 34.73 (C-8), 39.28 (C-5), 41.61 (C-4), 46.68 ($N(CH_2)_2$), 59.12 (C-1), 69.74 (C-3), 125.75, 126.55, 127.19, 127.49, 127.85, 128.63, 141.95, 143.88 (aromatic C), 161.87 (C-2) ppm; IR (KBr): $\bar{\nu} = 3462$, 2966, 2952, 2871, 2831, 2690, 1496, 1447, 1350, 1321, 1073, 926, 884, 758, 696 cm^{-1}; UV-Vis (CH_2Cl_2): $\lambda(\log\varepsilon) = 233$ (3.098) nm; MS (EI^+): $m/z = 359$ $(M\text{-}OH)^+$, 331, 302, 240, 212, 199, 184, 157, 129, 91, 78; HRMS (EI^+): calcd ($C_{24}H_{28}N_2O_2$-OH) 359.21234, found 359.21651.

Antiprotozoal Tests, Cytotoxicity

A detailed description of the microplate assays against *Plasmodium falciparum* K_1 and *Trypanosoma brucei rhodesiense* (STIB900) as well as the examination of the cytotoxicity using L-6 cells has been reported [11].

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