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Synthesis of Novel Diazabicycles and their Antiprotozoal Activities

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We describe the synthesis of new diaryl substituted diazabicyclo[3.2.1]octanes from diazepanes which were prepared by the reduction of diazepanones. The formation of the bicyclic system was optimized by microwave irradiation and the structures of the new compounds were established by single crystal structure analysis and NMR spectroscopy. All new compounds were tested for their potencies against *Plasmodium falciparum* K_1 and *Trypanosoma b. rhodesiense*, the causative organisms of malaria tropica and the East African form of sleeping sickness.

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Introduction

Recently we reported the synthesis of diaryl substituted bicyclo[2.2.2]octane-1,3-diamines **1**, 2-azabicyclo[3.2.2]nonan-5-amines **2**, and 3-azatricyclo[3.2.2.0^{2,3}]nonan-1-amines **3** (Fig. 1).[1,2] These compounds exhibit activities against *Plasmodium falciparum*, the causative organism of the most deadly form of malaria, malaria tropica, and *Trypanosoma b. rhodesiense*, the causative organism of the East African form of sleeping sickness. Enhanced resistance has been observed for both protozoal organisms, even against newly introduced drugs. Therefore there is an urgent need for both, new antiplasmodial and new antitrypanosomal agents.

Compounds **1–3** each contain two nitrogen atoms separated by 2–3 carbon atoms. In compound **1** both amines are exocyclic, whereas compounds **2** and **3** each conatin one endocyclic amine. We have subsequently prepared compounds with a ring structure containing two endocyclic amines. Because we observed the necessity of both aromatic residues for the antiprotozoal activity of bicyclooctane derivatives,[3] we included them in our new structures. The substitution pattern of the aromatic rings influences the biological activities of **2**.[4] Therefore we prepared bicycles with differing substitution patterns of the aromatic residues.

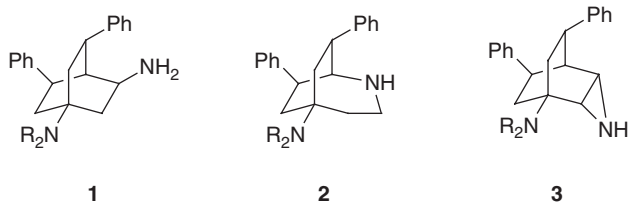
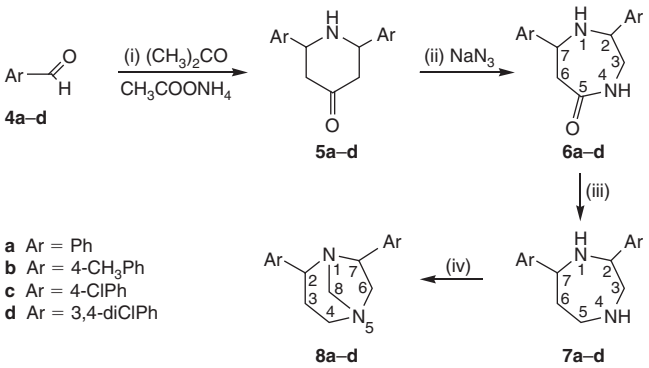


Fig. 1. Structures of bicyclic bases.



Scheme 1. Reagents and conditions: (i) refluxing ethanol, 5 min; (ii) conc. H_2SO_4, rt; (iii) $LiAlH_4$, ether, reflux, 16 h; (iv) paraformaldehyde, K_2CO_3, ethanol, reflux, 16 h.

Results and Discussion

The synthesis started from ammonium acetate, acetone and an arylaldehyde **4** giving diaryl piperidones **5** via a double Mannich reaction. The insertion of a second nitrogen was achieved via a Schmidt reaction[5,6] to afford diaryl[1,4]diazepan-5-ones **6**. The reduction of this compounds with lithium aluminiumhydride led to diaryl[1,4]diazepanes **7**, which were converted to the bicyclic ring system **8** by reaction with formaldehyde (Scheme 1).

The new compounds were investigated using NMR spectroscopy. The overlapping resonances of the two CH and the two

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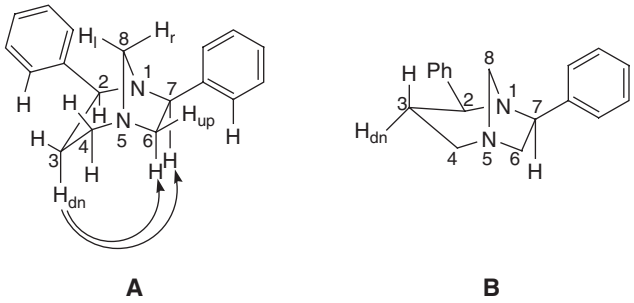


Fig. 2. Two conformers (**A**) and (**B**) of **8a**.

Table 1. Observed NOE effects of 8a

Proton-proton	NOE [%]	Distance [Å]
$H3_{up}$-arom. H	3.8	2.058
H7-H2	3.6	2.282
$H3_{dn}$-H7	3.2	2.314
$H8_{l}$-$H4_{up}$	2.7	2.300
$H3_{dn}$-$H6_{dn}$	2.4	2.428
$H8_{r}$-$H6_{up}$	1.9	2.679

CH_2 groups of the symmetrical educt **5**, were replaced by separate signals for each CH and CH_2 group in the ^{1}H NMR spectra of the non-symmetrical amides **6**. The signal of the amide carbon disappeared upon reduction to diamines **7**, and an additional signal corresponding to the newly formed CH_2 group was observed in ^{13}C spectra. The ^{1}H resonance for the two corresponding protons appeared at 3.1 ppm. The ring closure to compounds **8** was detected by the appearence of proton signals of the additional CH_2 group at 3.1 ppm and 3.9 ppm and its corresponding carbon resonance at 70 ppm; comparable data to that of unsubstituted 1,5-diazabicyclo[3.2.1]nonane.[7] Due to the aromatic substitution, the signals of H2 and H7 are shifted to lower fields compared with H3, H4, and H6. Evidence of the ring formation was given by long range couplings from C8 to H2, H4, H6, and H7 in HMBC spectra. From nuclear Overhauser effect (NOE) measurements of compound **8a**, the through-space couplings from $H3_{dn}$ to $H6_{dn}$ and H7 indicate a strong preference for conformation **A** versus conformation **B** (Fig. 2). The observed NOE effects are listed in Table 1, and compared with the distances derived from the crystal structure analysis of **8c**.

The crystal structure analysis of **8c** confirmed our observations and showed that the compound is 2,7-bis(4-chlorophenyl)-1,5-diazabicyclo[3.2.1]octane (Figs 3 and 4). Due to the presence of racemic twinning the substance is a racemate of *R*,*S*- and *S*,*R*-configuration of the chiral molecules. The two phenyl rings are almost co-planar (angle of 13.44(14)° between their normals). Hitherto the structures of only two 1,5-diazabicyclo[3.2.1]octanes are determined: 4-(1,5-diazabicyclo[3.2.1]oct-8-yl)-pyridine[8] and 8-(*p*-anisyl)-7-phenyl-1,5-diazabicyclo[3.2.1]octan-6-one.[9]

The formation of bicyclic compounds **8** was optimized for compound **8a** via microwave irradiation. We investigated the reaction of **7a** to **8a** at different temperatures from 70 to 120°C over 10 min, with highest yields of **8a** obtained at 70–80°C. It seems that temperatures beyond the boiling point of the mixture are disadvantageous for this reaction (Table 2).

We investigated the course of the reaction under conventional conditions (reflux, open vessel, 100°C oil bath temperature) and the course of the microwave assisted reaction using 60 W irradiation at 80°C and at 100°C. Compound **7a** was treated with paraformaldehyde and potassium carbonate in ethanol, aliquots were taken, and the ratios of educt to product, as well as the percentage yield, determined by integration of the proton signals in ^{1}H NMR spectra (Fig. 5).

Obviously, the advantage of the microwave assisted reaction is the enhanced conversion from **7a** to **8a** in only a few minutes. At 80°C a transformation to 91% of **8a** is observed after 20 min. At longer reaction times, a slight decrease of **8a** and an increase of **7a** is observed, and after 300 min some decomposition products begin to appear in the mixture. The course of the microwave assisted reaction at 100°C starts with 58% conversion to **8a** and runs parallel to that of the conventional heating method of boiling ethanol (100°C oil bath temperature).

However, complete conversions were achieved for the conventional method over night and for the microwave assisted method in 1 h at 120°C using 250 W irradiation. The solution of the microwave assisted reaction was colourless after the reaction, whereas the solution of the conventional reaction was brownish and an insoluble gum was formed, probably due to polymerized formaldehyde.

For the sake of comparison of antiprotozoal activities, we prepared the known bicyclic and tricyclic diamines **9**–**12** by Mannich reaction of dibenzylketone, ammonium acetate, and paraformaldehyde as reported (Fig. 6).[11]

The antitrypanosomal and the antiplasmodial activities of compounds **6**–**12** were determined using microplate assays of *T. b. rhodesiense* (STIB 900) and the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). Cytotoxicity was tested with L-6 rat skeletal myoblasts. Melarsoprol and chloroquine were used as standards with the results presented in Table 3.

The diaryl[1,4]diazepan-5-ones **6** show only weak activities, but a clear trend is observable: The antiprotozoal activities and the cytotoxicity are in direct proportion to the lipophilicity of compounds **6**. The reduction of the amides **6** to diamines **7** caused a distinct increase of both antiplasmodial and antitrypanosomal activities. Clearly the second basic centre promotes these activities. The most promising antiplasmodial compound in this group is **7a** with good activity and low cytotoxicity. The dichloro-diaryl[1,4]diazepan **7c** has the highest antitrypanosomal potency of all new compounds. The conversion of diaryl[1,4]diazepanes **7** to bicyclic compounds **8** changed the biological activities only marginally. As observed for compounds **7**, the 2,7-diphenyl derivative **8a** was the most active antiplasmodial and the dichloro-compound **8c** was the most potent antitrypanosomal agent (Table 3). In the series of 1,3-diazatricyclo[3.3.1.1^{3,7}]decan derivatives **9**–**11**, the 9-unsubstituted diamine **11** shows both antiplasmodial activity and low cytotoxicity; and therefore promising selectivity.

Conclusion

Several new 2,7-diaryl substituted, 1,5-diazabicyclo[3.2.1]octanes have been synthesized from 1,4-diazepanes. The structure of bicyclic compounds was established by NOE experiments and single crystal structure analysis. The formation of the bicyclic ring system was optimized via microwave irradiation and the course of the reaction compared with that of a conventional method. All new products were investigated for their in vitro

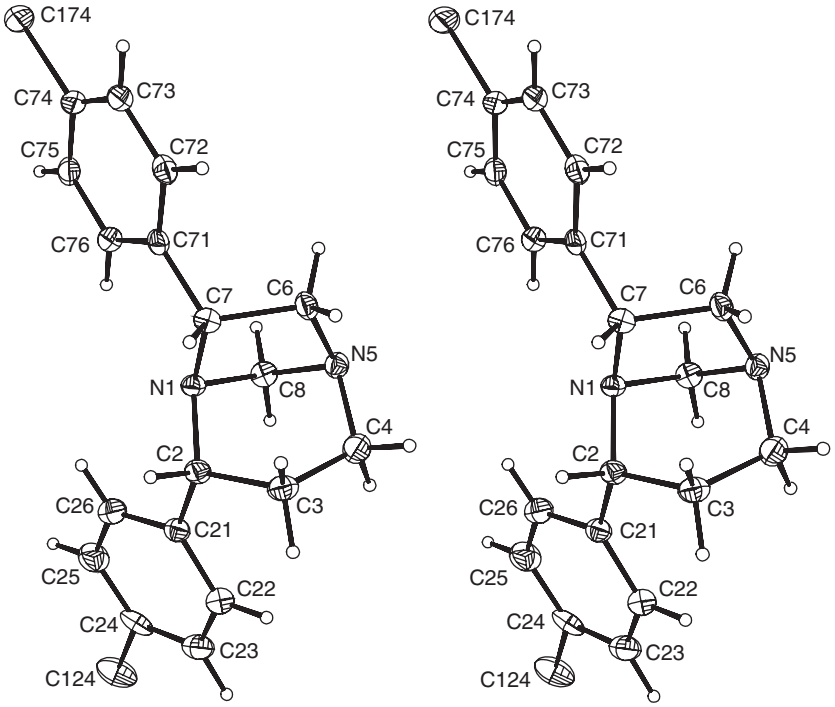


Fig. 3. Stereoscopic *ORTEP*[10] plot of **8c** showing the atomic numbering scheme. The probability ellipsoids are drawn at the 50% probability level. Selected distances and angles: N1-C2 1.500(3) Å, N1-C7 1.484(3) Å, N1-C8 1.474(3) Å, N5-C4 1.479(3) Å, N5-C6 1.468(3) Å, N5-C8 1.467(3) Å, C24-Cl24 1.755(3) Å, C74-Cl74 1.752(3) Å; C2-N1-C7 110.56(19)°, C2-N1-C8 108.2(2)°, C7-N1-C8 101.6(2)°, C4-N5-C6 112.0(2)°, C4-N5-C8 107.0(2)°, C6-N5-C8 101.0(2)°; C3-C2-C21-C22 9.2(4)°, N1-C7-C71-C76 0.7(3)°.

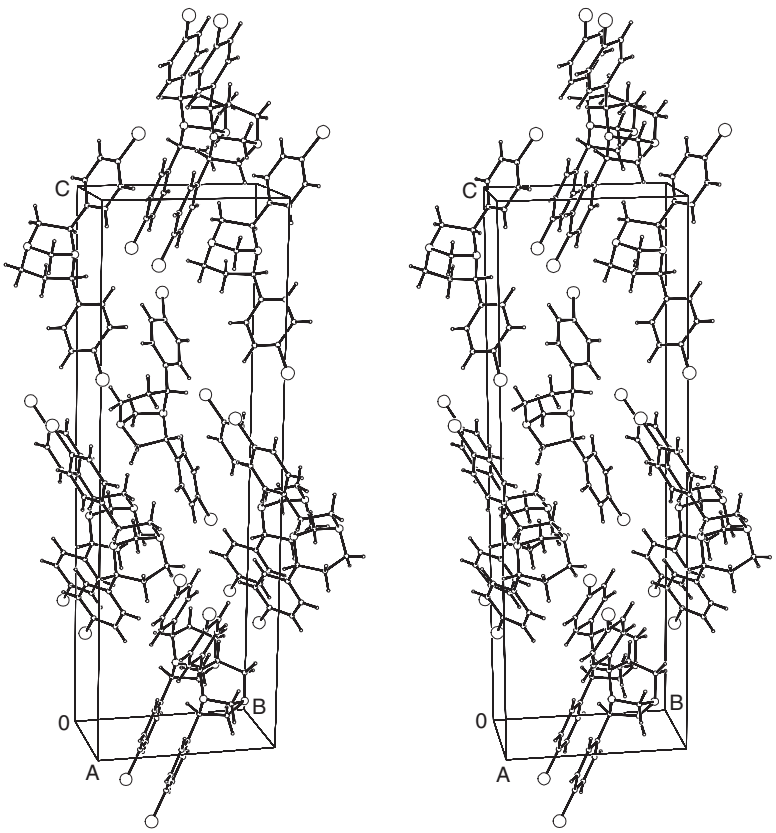


Fig. 4. Stereoscopic *ORTEP*[10] plot of the packing of **8c**. The atoms are drawn with arbitrary radii.

Table 2. Yields of compound 8a at different temperatures

Temp. [°C]	% Compound **8a**	
	After 5 min	After 10 min
70	71	90
80	85	89
90	32	86
100	35	55
120	16	42

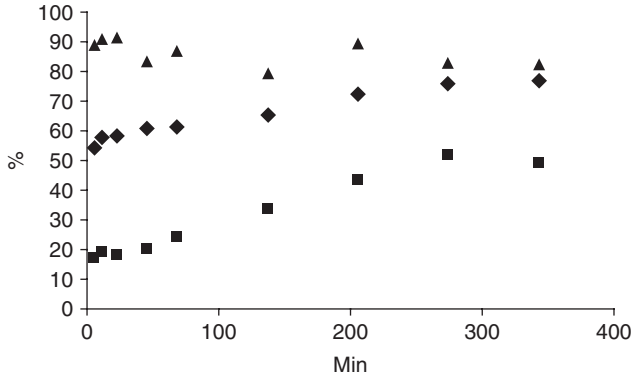
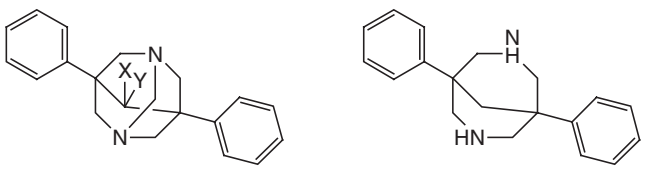


Fig. 5. Course of the reaction of **7a** to **8a**: under conventional conditions (■) and microwave assisted at 100°C (♦) and at 80°C (▲).



9 X + Y = O
10 X = H, Y = OH
11 X = H, Y = H

12

Fig. 6. Structures of compounds **9**–**12**.

activities against *P. falciparum K1* and *T. b. rhodesiense* as well as for their cytotoxicity using microplate assays. The 2,7-bis(4-chlorophenyl)-[1,4]diazepan showed sub-micromolar antitrypanosomal activity and will serve as a lead for further investigations.

Experimental

Materials and Methods

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. IR spectra were conducted with an infrared spectrometer system 2000 FT (Perkin–Elmer). UV/VIS spectra were recorded on a Lambda 17 UV/VIS-spectrometer (Perkin–Elmer), as either CH_2Cl_2 solutions (bases) or CH_3OH solutions (hydrochlorides). NMR spectra were recorded on a Varian Inova 400 (300 K) with 5 mm tubes in $CDCl_3$ containing 0.03% TMS. Chemical shifts were recorded in parts per million (ppm). For ^1H spectra, TMS (0.00) was used an internal standard, for ^{13}C spectra the central peak

Table 3. Antiprotozoal activities[A] of compounds 6–12

Comp.	*T. b. rhodesiense* IC_{50} [μM]	*P. falciparum K1* IC_{50} [μM]	Cytotoxicity L-6 cells IC_{50} [μM]
6a	190.8	16.22	>337.9
6b	171.5	>16.98	111.7
6c	40.99	>14.92	60.76
6d	26.60	5.47	23.48
7a	13.93	1.24	231.7
7b	3.09	4.64	40.64
7c	0.46	1.35	10.15
7d	1.30	1.67	8.27
8a	7.26	1.05	88.89
8b	2.19	4.41	36.59
8c	1.09	1.82	12.63
8d	1.63	3.06	12.68
9	136.1	>16.43	>295.7
10	>293.7	13.15	>293.7
11	88.60	1.55	>309.9
12	15.48	2.10	72.70
mel	0.0039		7.78
chl		0.12	188.5

[A]Values represent the average of four determinations (two determinations of two independent experiments). chl = chloroquine, mel = melarsoprol.

of the $CDCl_3$ peak was used as the internal reference (77.0). Abbreviations are as follows: aromatic H (ArH); aromatic C (ArC); quaternary aromatic C (ArC_q). Signal multiplicities are abbreviated as follows: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; m, multiplet; br, broad. Coupling constants (*J*) are reported in Hertz (Hz). ^1H and ^{13}C resonances were assigned using COSY, HSQC, and HMBC spectra. ^1H and ^{13}C resonances are numbered as given in the formulae. HRMS was performed on a Micromass tofspec 3E spectrometer (MALDI), GCT-Premier, Waters (EI, 70 eV). Crystal structure analysis was performed on a STOE four circle diffractometer. Microwave assisted reactions were carried out using a CEM Discover/Explorer system, in sealed 10 mL standard vessels with temperature control. For column-chromatography (CC), silica gel 60 (Merck 70–230 mesh, pore-diameter 60 Å) was used; TLC was completed using TLC plates (Merck, silica gel 60 F_{254} 0.2 mm, 200 × 200 mm); with compounds detected using a UV lamp at 254 nm. Solvents and reagents were obtained from commercial sources, arylketones **4** from Aldrich and Fluka. 2,6-Diphenylpiperidin-4-one **5a** was prepared according to a reported procedure.[12] Compounds **5b**–**5d** were prepared in a similar way and used directly for further reactions. 2,7-Diphenyl-[1,4]diazepan-5-one **6a** was prepared as reported.[13]

General Procedure for the Preparation of 2,7-Diaryl-1,4-diazepan-5-ones *6* via 2,6-Diarylpiperidin-4-ones *5*

Ammonium acetate, acetone, and the corresponding aryl aldehyde were dissolved in ethanol and the mixture refluxed until the colour changed to orange. The mixture was cooled to room temperature and poured into 100 mL of ether. The formed precipitate was filtered off and conc. HCl was added to the filtrate. The formed 2,6-diarylpiperidin-4-one hydrochloride (**5**·HCl) was filtered off, recrystallized repeatedly from ethanol/ether (1:10) and subsequently dried over phosphorous pentoxide. Cold conc. H_2SO_4 was poured into an Erlenmeyer flask and the **5**·HCl was added in portions. When the dissolution was complete, NaN_3 was

Table 4. Crystal data and structure refinement for 8c

CDC deposition no.	716833
Empirical formula	$C_{18}H_{18}Cl_2N_2$
Formula weight	333.24
Crystal description	Needle, colourless
Crystal size [mm^3]	$0.32 \times 0.20 \times 0.10$
Crystal system	Orthorhombic
Space group	P $2_12_12_1$
Unit cell dimensions	
a [Å]	5.9357(9)
b [Å]	9.3627(11)
c [Å]	28.503(3)
Volume [Å^3]	1584.0(3)
Z	4
Calc. density [mg m^{-3}]	1.397
Abs. coeff. μ [mm^{-1}]	0.407
Temperature [K]	95
Radiation source	Fine-focus sealed tube
Wavelength [Å]	0.71069
Scan type	ω scans
Standard reflections	3 every 100 reflections
Intensity decay [%]	0.0
θ range [°]	2.60 to 27.50
Reflections collected	3043
Reflections unique	2663
Sign. unique reflections	2313 with $I > 2\sigma(I)$
R(int)	0.0216
R(sigma)	0.0583
Compl. to $\Theta = 27.5°$	99.8%
Final *R* ind. [$I > 2\sigma(I)$]	
R_1	0.0394
wR_2	0.0787
R indices (all data)	
R_1	0.0494
wR_2	0.0835
Goodness-of-fit on F^2	1.036

added in portions of 0.1 g with vigorous stirring. The mixture was then poured over crushed ice and basified cautiously with cold 2 M NaOH to pH 8. A white solid separated. After the mixture was kept over night at room temperature, it was filtered, washed with water, and dried. It was dissolved in toluene, filtered, and the solution concentrated for crystallization. The precipitate was filtered and recrystallized.

2,7-Bis(4-methylphenyl)-1,4-diazepan-5-one ***6b***

Reaction of ammonium acetate (7.7 g, 0.1 mol), acetone (11.6 g, 0.2 mol), and 4-methylbenzaldehyde (24.0 g, 0.2 mol) in ethanol (20 mL) yielded **5b**·HCl (6.24 g, 20%). **5b**·HCl (2.95 g, 9.34 mmol) reacted in conc. H_2SO_4 (13 mL) with NaN_3 (745 mg, 11.5 mmol) giving a precipitate which was recrystallized from methanol yielding **6b** (2.20 g, 80%), mp 177°C. ν_{max} (KBr)/cm^{-1} 3212, 3088, 2920, 1674, 1511, 1486, 1456, 1430, 1406, 1351, 1320, 1108, 817, 771. λ_{max}/nm (log ε) 229 (3.550), 264 (2.960). δ_H 2.05 (1H, br s, NH), 2.32 (6H, s, $2CH_3$), 2.65 (1H, d, $J = 14.3$, H6), 3.08–3.14 (2H, m, H3, H6), 3.62 (1H, ddd, $J = 14.1$, 9.2, 4.2, H3), 3.99 (1H, d, $J = 8.8$, H2), 4.10 (1H, d, $J = 10.3$, H7), 6.02 (1H, br s, NH), 7.12–7.32 (8H, complex m, ArH). δ_C 21.03 ($2CH_3$), 47.77 (C6), 50.75 (C3), 59.11 (C7), 65.01 (C2), 126.24, 126.57, 129.22 (ArC), 137.19, 137.49, 139.42, 141.97 (ArC_q), 176.85 (C5). HRMS (MALDI): Found: 295.1805. $C_{19}H_{23}N_2O$ requires $[M + H]^+$ 295.1810.

2,7-Bis(4-chlorophenyl)-1,4-diazepan-5-one ***6c***

Reaction of ammonium acetate (7.7 g, 0.1 mol), acetone (11.62 g, 0.2 mol), and 4-chlorobenzaldehyde (28.11 g, 0.2 mol) in ethanol (20 mL) yielded **5c**·HCl (6.44 g, 18%). **5c**·HCl (2.7 g, 7.57 mmol) reacted in conc. H_2SO_4 (10 mL) with NaN_3 (605 mg, 9.3 mmol) to give a precipitate which was subsequently recrystallized from methanol yielding **6c** (2.36 g, 93%), mp 175°C. ν_{max} (KBr)/cm^{-1} 3398, 3222, 3083, 1665, 1491, 1464, 1437, 1409, 1362, 1333, 1317, 1176, 1091, 1015, 832, 805, 778, 730. λ_{max}/nm (log ε) 230 (3.996). δ_H 2.03 (1H, br s, NH), 2.62 (1H d, $J = 14.3$, H6), 3.05–3.13 (2H, m, H3, H6), 3.60 (1H, ddd, $J = 14.1$, 9.2, 4.0, H3), 4.01 (1H, d, $J = 8.8$, H2), 4.12 (1H, d, $J = 10.3$, H7), 6.09 (1H, br s, NH), 7.26–7.38 (8H, complex m, ArH). δ_C 47.54 (C6), 50.44 (C3), 58.63 (C7), 64.52 (C2), 127.73, 128.05, 128.86 (ArC), 133.42, 133.70, 140.47, 143.04 (ArC_q), 176.31 (C5). HRMS (MALDI): Found: 335.0735. $C_{17}H_{17}N_2Cl_2O$ requires $[M + H]^+$ 335.0718.

2,7-Bis(3,4-dichlorophenyl)-1,4-diazepan-5-one ***6d***

Reaction of ammonium acetate (4.63 g, 60 mmol), acetone (6.97 g, 120 mmol), and 3,4-dichlorobenzaldehyde (21.06 g, 120 mmol) in ethanol (12 mL) yielded **5d**·HCl (5.25 g, 21%). **5d**·HCl (1.50 g, 3.52 mmol) reacted in conc. H_2SO_4 (10 mL) with NaN_3 (0.308 g, 4.74 mmol) to give a precipitate which was recrystallized from toluene and subsequently from ethanol yielding **6d** (1.10 g, 77%). For analytical purposes, the crude product was purified by CC using CH_2Cl_2/methanol (9:1) as an eluent. ν_{max} (KBr)/cm^{-1} 3410, 1671, 1467, 1401, 1353, 1324, 1131, 1030, 820. λ_{max}/nm (log ε) 230 (4.460). δ_H 2.05 (1H, br s, NH), 2.61 (1H, d, $J = 14.7$, H6), 3.04–3.14 (2H, m, H3, H6), 3.59 (1H, ddd, $J = 14.1$, 9.2, 4.0, H3), 4.00 (1H, d, $J = 8.8$, H2), 4.10 (1H, d, $J = 10.6$, H7), 6.14 (1H, br s, NH), 7.25–7.57 (6H, complex m, ArH). δ_C 47.26 (C6), 50.14 (C3), 58.15 (C7), 64.03 (C2), 125.82, 126.11, 128.36, 128.69, 130.74 (ArC), 131.80, 132.07, 132.78, 132.84, 141.76, 144.33 (ArC_q), 175.93 (C5). HRMS (MALDI): Found: 400.9796. $C_{17}H_{13}N_2Cl_4O$ requires $[M - H]^-$ 400.9782.

General Procedure for the Preparation of 2,7-Diaryl-1,4-diazepanes ***7***

The powdered 2,7-diaryl-1,4-diazepan-5-ones **6** were suspended in stirred, ice cooled dry ether and $LiAlH_4$ added portion wise. The mixture was refluxed over night in an oil bath, cooled to room temperature and cautiously quenched with ice water while cooled and stirred in an ice bath. Then 2 M NaOH was added and the mixture was extracted 5 times with ether. The organic layers were combined, washed with water, dried over sodium sulfate, filtered and solvent evaporated under vacuum, to give yellow oils. The dihydrochlorides were prepared from a solution of the base in CH_2Cl_2 by repeated treatment with an excess of a 2 M ether solution of HCl. Solvents were evaporated and the residues recrystallized.

2,7-Diphenyl-1,4-diazepane ***7a***

Reaction of **6a** (1.64 g, 5.48 mmol) with $LiAlH_4$ (836 mg, 22 mmol) in dry ether (70 mL) yielded **7a** (1.304 g, 94%) as a yellow oil which crystallized spontaneously. The dihydrochloride was recrystallized from ethanol giving colourless crystals, mp (HCl) 297°C. ν_{max} (KBr)/cm^{-1} 3341, 3026, 2931, 2827, 1600, 1492, 1452, 1337, 1148, 1134, 1028, 915, 757, 700. λ_{max}/nm (log ε) 207 (4.270). δ_H 1.91–2.01 (1H, m, H6), 2.03–2.11 (1H, m, H6), 2.92 (1H, dd, $J = 13.2$, 9.9, H3), 3.04–3.20 (3H, m, H3, H5), 3.97 (1H, dd, $J = 9.9$, 3.7, H2), 4.07 (1H, dd,

$J = 10.3, 4.4$, H7), 7.18–7.41 (10H, complex m, ArH). δ_C 41.76 (C6), 46.67 (C5), 59.45 (C3), 64.17 (C7), 67.21 (C2), 126.44, 126.79, 126.93, 127.17, 128.40, 128.45 (ArC), 143.65, 146.35 (ArC_q). HRMS (MALDI): Found: 253.1644. $C_{17}H_{21}N_2$ requires $[M + H]^+$ 253.1705.

2,7-Bis(4-methylphenyl)-1,4-diazepane ***7b***

Reaction of **6b** (1.62 g, 5.48 mmol) with $LiAlH_4$ (836 mg, 22 mmol) in dry ether (70 mL) yielded **7b** (1.13 g, 70%). The dihydrochloride was recrystallized from EtOH giving colourless crystals, mp (HCl) 259°C. ν_{max} (KBr)/cm^{-1} 3417, 2923, 2734, 1616, 1561, 1518, 1456, 1437, 1191, 1055, 811. λ_{max}/nm ($\log \varepsilon$) 210 (4.378). δ_H 1.76 (2H, br s, NH), 1.89–1.98 (1H, m, H6), 2.01–2.08 (1H, m, H6), 2.30 (6H, s, $2CH_3$), 2.90 (1H, dd, $J = 13.4, 9.9$, H3), 3.03–3.18 (3H, m, H3, H5), 3.93 (1H, dd, $J = 9.9, 4.0$, H2), 4.02 (1H, dd, $J = 10.4, 4.2$, H7), 7.08–7.29 (8H, complex m, ArH). δ_C 20.95 (CH_3), 20.96 (CH_3), 41.75 (C6), 46.65 (C5), 59.48 (C3), 63.99 (C7), 66.97 (C2), 126.35, 126.68, 129.03, 129.07 (ArC), 136.46, 136.72, 140.71, 143.42 (ArC_q). HRMS (MALDI): Found: 281.2001. $C_{19}H_{25}N_2$ requires $[M + H]^+$ 281.2018.

2,7-Bis(4-chlorophenyl)-1,4-diazepane ***7c***

Reaction of **6c** (1.62 g, 4.8 mmol) with $LiAlH_4$ (836 mg, 22 mmol) in dry ether (70 mL) yielded **7c** (1.33 g, 86%). The dihydrochloride was recrystallized from MeOH giving colourless crystals, mp (HCl) 298°C. ν_{max} (KBr)/cm^{-1} 3424, 2963, 2736, 2684, 2646, 1598, 1550, 1495, 1462, 1426, 1088, 1054, 1016, 997, 824, 722, 691. λ_{max}/nm ($\log \varepsilon$) 220 (4.425). δ_H 1.73 (2H, br s, NH), 1.86–1.95 (1H, m, H6), 2.01–2.08 (1H, m, H6), 2.86 (1H, dd, $J = 13.2, 9.5$, H3), 3.03–3.17 (3H, m, H3, H5), 3.95 (1H, dd, $J = 9.5, 3.8$, H2), 4.06 (1H, dd, $J = 10.3, 4.0$, H7), 7.25–7.34 (8H, complex m, ArH). δ_C 41.64 (C6), 46.67 (C5), 59.36 (C3), 62.95 (C7), 66.23 (C2), 127.81, 128.17, 128.59, 128.64 (ArC), 132.59, 132.89, 142.05, 144.80 (ArC_q). HRMS (EI+): Found: 318.0633. $C_{17}H_{16}N_2Cl_2$ requires $[M - 2H]^+$ 318.0691. Found: 262.0193. $C_{14}H_{10}NCl_2$ requires $[M]^+$ 262.0190.

2,7-Bis(3,4-dichlorophenyl)-1,4-diazepane ***7d***

Reaction of **6d** (0.608 g, 1.50 mmol) with $LiAlH_4$ (257 mg, 6.77 mmol) in dry ether (22 mL) yielded **7d** (450 mg, 77%). The dihydrochloride was recrystallized from ethanol giving colourless crystals, mp (HCl, decomp.) 275°C. ν_{max} (KBr)/cm^{-1} 3426, 2962, 2712, 2679, 1549, 1468, 1435, 1412, 1137, 1032, 916, 834, 823, 778. λ_{max}/nm ($\log \varepsilon$) 205 (4.787). δ_H 1.76 (2H, br s, NH), 1.85–1.94 (1H, m, H6), 2.01–2.09 (1H, m, H6), 2.85 (1H, dd, $J = 13.4, 9.3$, H3), 3.04–3.16 (3H, m, H3, H5), 3.94 (1H, dd, $J = 9.2, 3.7$, H2), 4.05 (1H, dd, $J = 10.1, 3.8$, H7), 7.20–7.50 (6H, complex m, ArH). δ_C 41.36 (C6), 46.64 (C5), 59.04 (C3), 62.07 (C7), 66.49 (C2), 125.86, 126.26, 128.44, 128.80, 130.41, 130.47 (ArC), 130.81, 131.12, 132.45, 143.61, 146.34 (ArC_q). HRMS (MALDI): Found: 389.0119. $C_{17}H_{17}N_2Cl_4$ requires $[M + H]^+$ 389.0146.

General Procedure for the Preparation of 2,7-Diaryl-1,5-diazabicyclo[3.2.1]octanes ***8***

2,7-diaryl-1,4-diazepanes **7** and paraformaldehyde were suspended in dry ethanol and a catalytic amount of potassium carbonate was added. The mixture was refluxed over night at 100°C in an oil bath and the solvent was evaporated. The remaining residue was repeatedly extracted with ether. The combined organic phases were washed twice with water, dried over Na_2SO_4, and filtered. The solvents were evaporated under vacuum and the remaining residue was purified using CC on basic aluminum oxide with CH_2Cl_2 as eluent. Fractions containing compounds **8** were collected and the solvent was removed under vacuum. The oily residue was recrystallized.

2,7-Diphenyl-1,5-diazabicyclo[3.2.1]octane ***8a***

Reaction of **7a** (460 mg, 1.8 mmol) and paraformaldehyde (200 mg, 6.4 mmol) in dry ethanol (10 mL) in the presence of potassium carbonate (10 mg) yielded **8a** (467 mg, 98%).

Microwave-Assisted Reaction for Formation of 2,7-Diphenyl-1,5-diazabicyclo[3.2.1]octane ***8a***

Reaction of **7a** (137 mg, 0.54 mmol) and paraformaldehyde (40 mg, 1.3 mmol) in dry ethanol (4 mL) in the presence of potassium carbonate (4 mg), 1 h irradiation at 250 W at 120°C yielded **8a** (148 mg, 94%), mp (hexane) 60°C. ν_{max} (KBr)/cm^{-1} 3432, 3058, 3024, 2943, 2878, 1600, 1493, 1447, 1295, 1260, 1079, 1025, 900, 949, 825, 811, 775, 753, 730, 699. λ_{max}/nm ($\log \varepsilon$) 230 (3.433). δ_H 1.87 (1H, dd, $J = 15.2, 4.6$, $H3_{up}$), 2.25–2.36 (1H, m, $H3_{dn}$), 2.86–2.96 (2H, m, $H4_{dn}$, $H6_{up}$), 3.08 (1H, d, $J = 11.0$, $H8_r$), 3.28 (1H, ddd, $J = 18.3, 13.6, 4.8$, $H4_{up}$), 3.72 (1H, ddd, $J = 11.9, 7.9, 1.6$, $H6_{dn}$), 3.88 (1H, d, $J = 11.0$, $H8_l$), 4.10 (1H, d, $J = 7.0$, H2), 4.61 (1H, br t, $J = 6.4$, H7), 7.17–7.65 (10H, complex m, ArH). δ_C 19.86 (C3), 51.07 (C4), 60.92 (C6), 62.11 (C2), 65.62 (C7), 70.20 (C8), 125.70, 126.11, 126.53, 127.74, 128.11, 128.19 (ArC), 141.48, 143.99 (ArC_q). HRMS (MALDI): Found: 265.1706. $C_{18}H_{21}N_2$ requires $[M + H]^+$ 265.1705.

For the determination of reaction progress, the same reaction batch as above was used and 0.2 mL samples were taken at different times. The solvent was evaporated and the residue dried in a drying pistol. The residue was dissolved in $CDCl_3$ and the ratios of educt to product were determined using ^1H NMR integration.

2,7-Bis(4-methylphenyl)-1,5-diazabicyclo[3.2.1]octane ***8b***

Reaction of **7b** (446 mg, 1.59 mmol) with paraformaldehyde (177 mg, 5.90 mmol) in dry ethanol (10 mL) in the presence of potassium carbonate (10 mg) yielded **8b** (353 mg, 76%), mp (acetone) 116°C. ν_{max} (KBr)/cm^{-1} 3442, 2975, 2946, 2875, 1510, 1461, 1448, 1293, 1259, 1081, 1032, 1018, 989, 951, 936, 838, 798, 723. λ_{max}/nm ($\log \varepsilon$) 230 (3.758), 266 (3.024). δ_H 1.90 (1H, dd, $J = 15.0, 4.4$, H3), 2.31–2.40 (1H, m, H3), 2.34 (3H, s, CH_3), 2.38 (3H, s, CH_3), 2.88–2.95 (2H, m, H4, H6), 3.08 (1H, d, $J = 11.0$, H8), 3.31 (1H, ddd, $J = 18.3, 13.6, 4.8$, H4), 3.75 (1H, ddd, $J = 12.8, 7.7, 1.8$, H6), 3.90 (1H, d, $J = 11.0$, H8), 4.12 (1H, d, $J = 7.0$, H2), 4.63 (1H, br t, $J = 6.2$, H7), 7.14–7.57 (8H, m, ArH). δ_C 20.25 (C3), 20.99 (CH_3), 21.03 (CH_3), 51.40 (C4), 61.31 (C6), 62.19 (C2), 65.67 (C7), 70.32 (C8), 125.89, 127.91, 128.97, 129.04 (ArC), 135.77, 136.25, 138.89, 141.48 (ArC_q). HRMS (MALDI): Found: 293.2037. $C_{20}H_{25}N_2$ requires $[M + H]^+$ 293.2018.

2,7-Bis(4-chlorophenyl)-1,5-diazabicyclo[3.2.1]octane ***8c***

Reaction of **7c** (578 mg, 1.8 mmol) and paraformaldehyde (200 mg, 6.66 mmol) in dry ethanol (10 mL) in the presence of potassium carbonate (10 mg) yielded **8c** (472 mg, 79%), mp (ethanol) 126°C. ν_{max} (KBr)/cm^{-1} 3433, 2967, 2948, 2921, 2875, 1488, 1461, 1398, 1295, 1101, 1082, 1031, 1008, 991, 939, 844, 810, 776, 710. λ_{max}/nm ($\log \varepsilon$) 231 (4.031). δ_H 1.88 (1H, dd, $J = 15.4, 4.4$, H3), 2.31–2.41 (1H, m, H3), 2.87–2.93

(2H, m, H4, H6), 3.03 (1H, d, $J = 11.0$, H8), 3.25 (1H, ddd, $J = 18.3$, 13.6, 4.6, H4), 3.76 (1H, ddd, $J = 11.9$, 7.7, 2.2, H6), 3.83 (1H, d, $J = 11.0$, H8), 4.10 (1H, d, $J = 7.0$, H2), 4.60 (1H, br t, $J = 6.4$, H7), 7.29–7.60 (8H, m, ArH). δ_C 20.04 (C3), 51.06 (C4), 61.19 (C6), 61.78 (C2), 65.26 (C7), 70.34 (C8), 127.30, 128.45, 128.46, 129.32 (ArC), 131.99, 132.56, 140.04, 142.53 (ArC_q). HRMS (MALDI): Found: 333.0946. $C_{18}H_{19}N_2Cl_2$ requires $[M + H]^+$ 333.0925.

X-Ray Diffraction Data of ***8c***

All the measurements were performed using graphite-monochromatized Mo K_α radiation. The structure was solved by direct methods (*SHELXS-97*)[14] and refined by full-matrix least-squares techniques against F^2 (*SHELXL-97*).[15] The crystal was a racemic twin. The refinement was performed using a twin matrix (−1 0 0 / 0 −1 0 / 0 0 1). No scale factor between the two twin components was refined in the final refinements because it did not significantly deviate from 0.5. The non-hydrogen atoms were refined with anisotropic displacement parameters without any constraints. The H atoms of the CH_2 groups were refined with common isotropic displacement parameters for the H atoms of the same group and idealized geometry with approximately tetrahedral angles and C–H distances of 0.99 Å. The H atoms of the tertiary C–H groups were included with all X–C–H angles equal at a C–H distance of 1.00 Å\%A with their isotropic displacement parameters fixed to 1.2 times U_{eq} of the C atom they are bonded to. The H atoms of the phenyl rings were put at the external bisector of the C–C–C angle at a C–H distance of 0.95 Å and common isotropic displacement parameters were refined for the H atoms of the same phenyl group. For 205 parameters final R indices of $R_1 = 0.0394$ and $wR_2 = 0.0835$ ($GOF = 1.036$) were obtained (Table 4). The largest peak in a difference Fourier map was 0.240 e $Å^{-3}$.

2,7-Bis(3,4-dichlorophenyl)-1,5-diazabicyclo [3.2.1]octane ***8d***

Reaction of **7d** (215 mg, 0.55 mmol) and paraformaldehyde (61 mg, 2.0 mmol) in dry ethanol (5 mL) in the presence of potassium carbonate (10 mg) yielded **8d** (182 mg, 82%), mp (ethanol) 144°C. ν_{max} (KBr)/cm^{-1} 2947, 2884, 1470, 1383, 1293, 1263, 1202, 1127, 1084, 1027, 990, 945, 888, 867, 837, 806, 798, 736, 710. λ_{max}/nm (log ε) 231 (4.149), 274 (3.171), 283 (3.116). δ_H 1.86 (1H, dd, $J = 15.4$, 4.0, H3), 2.30–2.41 (1H, m, H3), 2.86–2.93 (2H, m, H4, H6), 3.03 (1H, d, $J = 11.4$, H8), 3.23 (1H, ddd, $J = 18.1$, 13.7, 4.6, H4), 3.76 (1H, dd, $J = 12.1$, 8.1, H6), 3.83 (1H, d, $J = 11.4$, H8), 4.08 (1H, d, $J = 6.6$, H2), 4.56 (1H, br t, $J = 6.2$, H7), 7.21–7.72 (6H, m, ArH). δ_C 20.02 (C3), 50.86 (C4), 61.12 (C6), 61.53 (C2), 64.92 (C7), 70.55 (C8), 125.39, 127.32, 127.87, 129.91, 130.34, 130.41 (ArC), 130.26, 132.43, 132.54, 141.69, 144.14 (ArC_q). HRMS (MALDI): Found: 401.0112. $C_{18}H_{17}N_2Cl_4$ requires $[M + H]^+$ 401.0146.

Biological Activities

In vitro Assay Against Trypanosoma b. rhodesiense*, Cytotoxicity*

Minimum Essential Medium (50 μL) supplemented according to Baltz et al.[16] with 2-mercaptoethanol and 15% heat-inactivated horse serum was added to each well of a 96-well microtiter plate. Serial drug dilutions were added to the wells. Then 50 μL of trypanosome suspension (*T. b. rhodesiense* STIB 900) was added to each well and the plate incubated at 37°C under a 5% CO_2 atmosphere for 72 h. Alamar Blue (10 μL) was then added to each well and incubation continued for a further 2–4 h. The plate was then read with a Millipore Cytofluor 2300 using an excitation wavelength of 530 nm and emission wavelength of 590 nm.[17] Fluorescence development was expressed as percentage of the control, and IC_{50} values determined. Cytotoxicity was assessed using the same assay and L-6 cells.

In vitro Assay Against Plasmodium falciparum

Antiplasmodial activity was determined using the K_1 strain of *P. falciparum* (resistant to chloroquine and pyrimethamine). A modification of the [^{3}H]-hypoxanthine incorporation assay was used.[18] Briefly, infected human red blood cells in RPMI 1640 medium with 5% Albumax were exposed to serial drug dilutions in microtiter plates for 48 h. Viability was assessed by measuring the incorporation of [^{3}H]-hypoxanthine by liquid scintillation counting 24 h after the addition of the radiolabel. The counts were expressed as percentage of the control cultures, sigmoidal inhibition curves were drawn and IC_{50} values calculated.

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