Synthesis and Structure of Bis-Urea Phenazines

Tom Fricke[a], Anton Dickmans[b], Umasish Jana[b], Manfred Zabel[c], Peter G. Jones[d], Ina Dix[d], Burkhard König[*,a] and Rainer Herges[*,b]

[a] Institut für Organische Chemie, Universität Regensburg, D-93040 Regensburg, Germany. Fax: 49 941 943 1717. Tel: 49 941 943 4576
E-mail: burkhard.koenig@chemie.uni-regensburg.de
[b] Institut für Organische Chemie, Universität Kiel, D-24098 Kiel, Germany. Fax: 49 431-880-1558. E-mail: rherges@oc.uni-kiel.de
[c] Zentrale Analytik der NWF IV, Universität Regensburg, D-93040 Regensburg, Germany.
[d] Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, D-38053 Braunschweig, Germany

[*] Reprint requests to Prof. Dr. B. König or Prof. Dr. R. Herges

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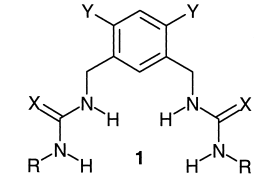
Phenazine, Urea, Anion Binding

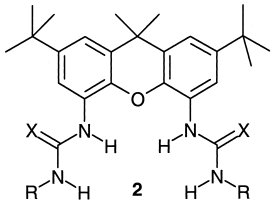
Substituted phenazines **7** and **15** with two urea units have been prepared and characterized. X-ray structure analyses are reported for intermediates **5**, **9**, **11b** and **12**. According to theoretical calculations the geometry of the two urea moieties in phenazines **7** and **15** should be well suited for the binding of trigonal planar anions, such as nitrate. NMR titration revealed that compound **15** indeed shows a weak interaction with nitrate ions in DMSO.

Introduction

The development of host-guest systems for ionic species has always played an important role in the chemistry of reversible intermolecular interactions [1]. A large number of selective neutral cation receptors, such as crown ethers or cryptants [2], is known. The number of neutral [3] anion receptors is far more limited, because the distinct geometry, larger size and weaker electrostatic forces of anions make their recognition more difficult [4,5]. Neutral acyclic anion receptors based on bridged bis-urea or thiourea structures have been reported by Umezawa [6,7] and Reinhoudt [8] (Fig. 1: **1a**: X = O, R = Bu, Y = H; **1b**: X = S, R = Bu, Y = H; **1c**: X = S, R = Ph, Y = H) (**2a**: X = S, R = Bu; **2b**: X = S, R = Ph) and others [9]. The bis-thiourea hosts show stronger binding by at least one order of magnitude if compared with their bis-urea analogous. This can be rationalized by the p*K*a of the donating thiourea groups, which is roughly 6 units smaller than the p*K*a of urea, making thioureas much stronger hydrogen bond donors [10]. Table 1 summarizes some reported association constants of compounds **1** and **2** with tetrabutyl ammonium salts in DMSO [6,7]. Basic anions, such as dihydrogen phosphate and acetate, are bound tightly, while less basic anions, such as nitrate, show only weak or non-detectable interaction. Deviations from a basicity ruled selectivity are explained by different solvation energies [7].



X = O, S; Y = H, ^{i}Pr; R = Bu, Ph



X = O, S; R = Bu, Ph

Fig. 1. Acyclic neutral anion receptors of Umezawa and Reinhoudt.

Using a rational approach, we aimed at optimizing these aryl bridged bis-urea systems for binding the weakly basic nitrate ion and finally to develop a macrocyclic ionophore [11] including three urea and three spacer units. We report here the design principles, the synthesis of substituted phenazines and the X-ray structure analyses of some interme-

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Anions[a]	**$H_2PO_4^-$**	**AcO^-**	**Cl^-**	**HSO_4^-**	**NO_3^-**	**ClO_4^-**
p*Ka*[b]	*2.16*	*4.76*	*–6.1*	*–3.1*	*–1.4*	*–7.3*
1a	110	43	4	1	< 1	no binding
1b	820	470	9	2	< 1	no binding
1c	4600	2300	10	n.d.[c]	n.d.	n.d.
2a	55,000	38,000	840	n.d.	n.d.	n.d.
2b	195,000	n.d.	1000	n.d.	n.d.	n.d.

Table 1. Reported association constants for anion binding of acyclic bisurea hosts in DMSO.

[a] Counter ion: NBu_4^+; [b] in water at 25 °C, I = 0, *Pure Appl. Chem.* **1969**, *20*, 133; [c] not determined.

diates, as well as a preliminary investigation of the nitrate binding ability in DMSO.

Results and Discussion

Rational design of a receptor structure

Basic strategy of designing the receptor geometry was to "cut" the molecular frame out of a graphite sheet [12] and to fine tune the geometry by selecting suitable spacer groups X and Y (Fig. 2). Urea groups were chosen as hydrogen bond donor sites because the nitrate/urea coordination is a frequent binding motif found in X-ray structures of nitrate containing compounds and because urea fits the chicken wire pattern with an optimal location and direction of H-bond donor groups (Fig. 2). The size of the cavity and the bite angle of the urea groups can be varied by introducing N/NH, O, S and CH/CH_2 in position X and Y. In principle, by considering these 4 elements, there are $4 \times 4 = 16$ permutations possible. However, those systems with NH and CH in position X were discarded, because the H-atom of these groups sterically interferes with the neighboring urea H-atoms and with an eventually bound nitrate. Thus the xanthene, acridine, thioxanthene, dibenzodioxine, phenoxathiin, phenoxazine, phenazine, phenothiazine and thianthrene systems are remaining as suitable aryl spacer groups. Inspection of the geometry by the semiempirical PM3 method (C_{2v} symmetry imposed) revealed, that the size of the binding site varies largely upon changing the aryl spacer. The phenazine (X,Y = N) and thianthrene system (X,Y = S) provide an arrangement of the two urea units which is closest to the arrangement of a nitrate anion complexed with three unrestrained urea molecules. With a distance $d_1 = 3.15$ Å, $d_2 = 5.28$ Å between the urea hydrogen atoms and a bite angle $\alpha = 52.4°$ (Table 2, Fig. 2) the cavity of the phenazine ligand is slightly too small and the thianthrene system ($d_1 = 3.80$ Å, $d_2 = 6.02$ Å, $\alpha = 55.1°$) is somewhat too large compared to the free urea nitrate 3:1 complex ($d_1 = 3.43$ Å, $d_2 = 6.02$ Å, $\alpha = 60°$). Thus both ligands provide a suitable preorientation for binding nitrate. For synthetic reasons we chose the phenazine system as the aryl spacer of our ligand.

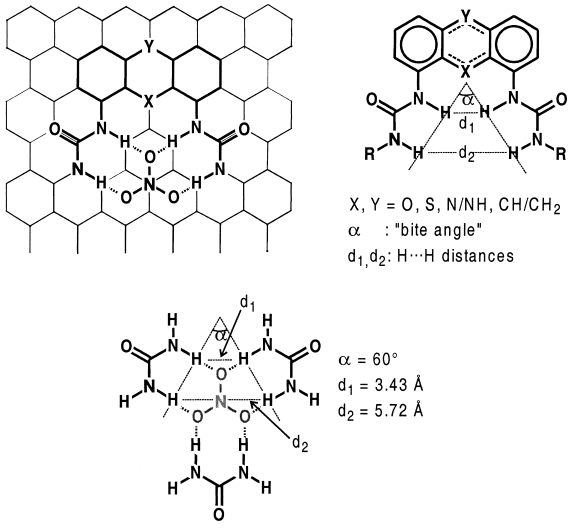

Fig. 2. Design of an anion receptor. The geometry parameters d_1, d_2 and α of the urea/nitrate 3:1 complex (D_{3h} symmetry imposed) (bottom) are calculated at the B3LYP/6–31G* level and have to be matched by variation of X and Y in the bis-urea system (top).

Synthesis

1,9-Bis(*N*-butyl urea) phenazine (**7**) was synthesized from the parent heterocycle phenazine (**3**) by nitration using standard conditions [13]. The reaction gave equal amounts of the two regioisomers 1,6- (**7**) and 1,9-dinitrophenazine (**4**). Compound **5** was characterised by X-ray analysis, which showed all bond lengths and angles of the compound with inversion symmetry as expected (Fig. 4). Reduction of **4** and **5** with hydrogen and

Table 2. Selected, PM3 calculated (C_{2v} symmetry imposed) geometry parameters of different tricyclic aryl spacer molecules (H···H distances d_1 and d_2 in Å, bite angle α in ° see Fig. 2). Parameters for the phenoxazine and phenothiazine ligand and for systems with X = CH/CH_2 are calculated (see text).

X		O			N/NH			S	
Y	d_1	d_2	α	D_1	d_2	α	d_1	D_2	α
CH/CH_2	2.86	4.75	46.5°	3.04	5.05	49.4°	3.98	6.42	60.1°
O	3.11	5.26	53.1°	–	–	–	4.19	6.84	67.2°
N/NH	2.98	4.95	49.0°	3.15	5.28	52.4°	4.07	6.58	63.2°
S	2.61	4.26	40.2°	–	–	–	3.80	6.02	55.1°

Pd/C gave the corresponding diaminophenazines. Several attempts were made to prepare a macrocyclic structure containing three phenanzine and three urea units in a trigonal fashion, but the reaction of 1,9-diaminophenazine with oxalyl chloride or thiophosgene under high dilution conditions gave only insoluble materials, which could neither be characterized nor their binding properties investigated. However, the reaction of the phenazine diamines with butyl isocyanate gave the acyclic compounds **7** in satisfactory yields. The reactivity of both phenazinediamines in the reaction with isocyanates is surprisingly low. To achieve conversion the reaction had to be performed in refluxing neat butyl isocyanate. The low reactivity of structurally related aminochinolines in reactions with isocyanates was previously reported [14]. Although compound **7** bears two butyl groups the solubility in organic solvents, such as chloroform or DMSO is still low.

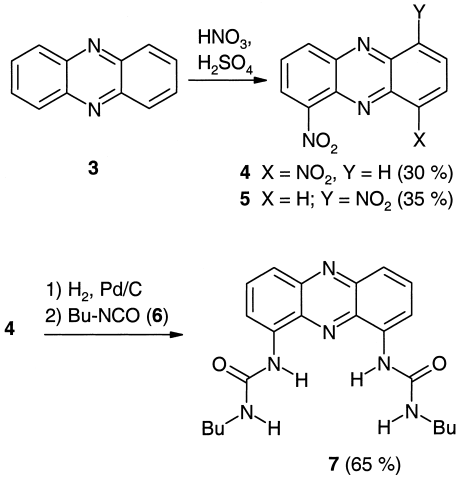

Fig. 3. Synthesis of bis-*N*-butyl urea phenazines from phenazine.

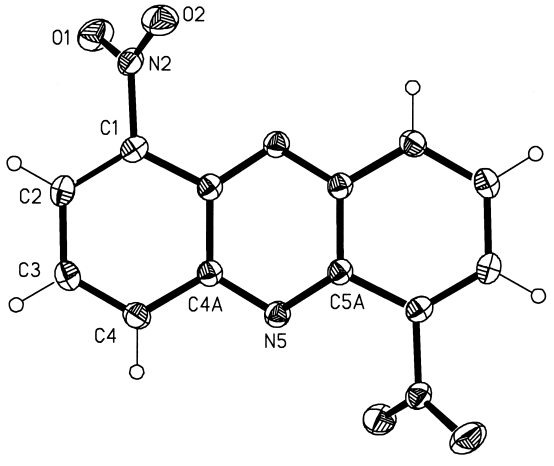

Fig. 4. Structure of compound **5** in the crystal.

To increase the solubility of the compounds substituted phenazine derivatives were prepared. The introduction of one *tert*-butyl and one methyl group into the phenazine is possible starting from **8** and **9** [15]. Copper-mediated nucleophilic aromatic substitution gave **10**, although in very low yield [16]. All attempts to improve the yield of this reaction, *e.g.* by the use of palladium-catalyzed coupling procedures and variation of reaction conditions, were unsuccessful [17]. Reductive ring closure of **10a** gave the non-symmetric 1,9-disubstituted phenazine **11a** in 60% yield along with 20% not-cyclized diamine **10b** and 10% of **11b**. Compound **11b** was characterised by X-ray structure analysis, which confirmed the proposed structure (Fig. 6).

Nitration of **11a** under standard conditions gave a 1:1 mixture of two isomeric dinitro compounds **12** and **13** in 35% and 30% yield, respectively. Single crystals were obtained of **12** and analyzed by X-ray structure analysis, which confirmed the ex-

pected connectivity of the compound (Fig. 7). Reduction of **13** in ethyl acetate with hydrogen and Pd/C gave **12** in nearly quantitative yield. Compound **14** was reacted with *N*-butyl isocyanate at room temperature to give **15** [18]. The proton NMR spectrum of **15** is well resolved in DMSO-D_6 solution, while a significant broadening of peaks is observed in $CDCl_3$. This may indicate self-aggregation of the compound in the less polar solvent.

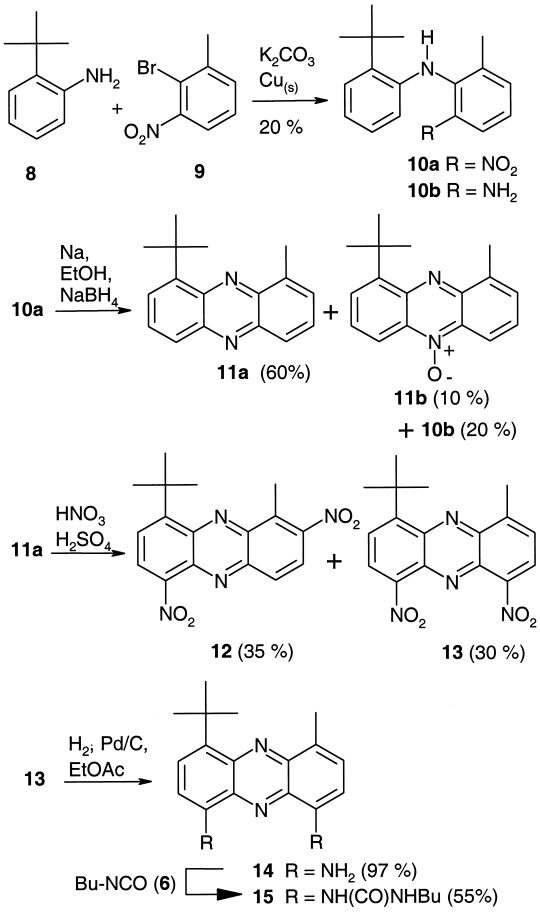

Fig. 5. Synthesis of substituted bis-urea-phenazine **15**.

The structurally related compound **17** was synthesized from pyridine-1,6-dinitrile (**16**) by reduction [19] and reaction with isocyanate **6** in 25% overall yield [20].

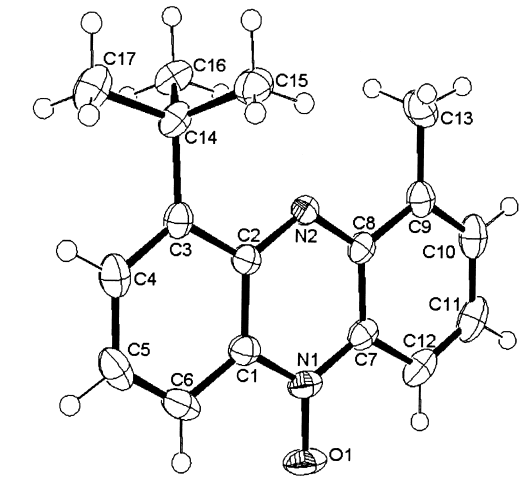

Fig. 6. Structure of compound **11b** in the crystal.

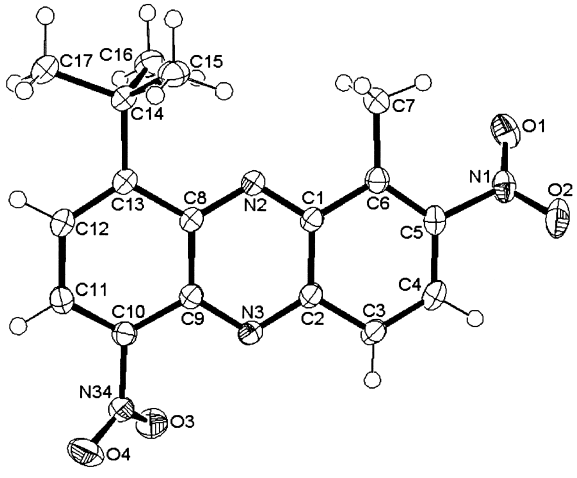

Fig. 7. Structure of compound **12** in the crystal.

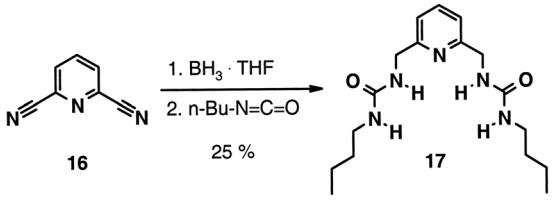

Fig. 8. Synthesis of bis-*N*-butyl urea pyridine **17** from 2,6-dicyanopyridine **18**.

Investigation of nitrate ion binding properties

The poor solubility of compound **7** did not allow to investigate its binding properties. The nitrate ion binding of compound **15** was investigated by NMR titration experiments in deuterated DMSO [21]. Table 3 summarizes the results. The 1:1 stoi-

chiometry of the binding motif was confirmed by the linearity of Scatchard plots. Compound **15** shows a weak, but significant interaction with nitrate anions in DMSO with defined 1:1 stoichiometry. For comparison the more flexible and structurally related compound **17** was tested for nitrate anion affinity. Only very small chemically induced shifts are observed in the titration and data analysis suggest no significant interaction [22]. The acetate anion, which is more basic by several orders of magnitude and therefore a much better hydrogen bond acceptor, binds to compound **17**. Although the association constant of **15** with nitrate ions is still low, the measurements support the proposed binding motif.

Table 3: Determined binding affinities of **15** and **17** in D_6-DMSO.

Compound	Anion	K_{11} [L mol^{-1}]	R	$\Delta\delta_{max}$ (obs.)
15	NO_3^-	2.2 ± 0.1	0.9999	0.7251 (47 eq.)
17	NO_3^-	< 1	0.9996	0.1486 (42 eq.)
17	OAc^-	21.9 ± 1.8	0.9968	2.1305 (42 eq.)

The model study shows that phenazine bis-urea compounds provide a suitable geometry for nitrate ion binding which may lead to higher affinity and selectivity if assembled to macrocyclic ionophores. However, the model study also shows, that the low solubility of urea phenazines and the difficult synthesis of substituted compounds hampers the synthetic realization and the use of such compounds in analytical applications markedly.

Experimental Section

General

Melting points were taken on a Hot-plate microscope apparatus and are not corrected. – NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ solutions unless otherwise stated. The multiplicity of the ^{13}C signals was determined with the DEPT technique and quoted as: (+) for CH_3 or CH, (–) for CH_2 and (C_{quat}) for quaternary carbons. CC means column chromatography on SiO_2. Compound **4** and **5** were synthesized according to known procedures [23].

Determination of binding properties by ^{1}H NMR-titration.

All titrations were performed at room temp. in D_6-DMSO on a 400 MHz NMR spectrometer. Bis-urea compounds were used in a concentration of 20 mmol·l^{-1} and anions were added as their tetrabutyl ammonium salts from a stock solution (0.9 mol·l^{-1}). Association constants were derived from the titration curves with the program HYPNMR 2000 [24]. To exclude a possible self association of the ionophores in DMSO solution, dilution experiments were performed and ^{1}H NMR spectra were recorded over a wide concentration range. The observed shifts of the resonance of the urea protons with varying concentrations are very small and can be neglected.

X-ray structure analyses

The intensity data for the crystals of the compounds **9**, **11b** and **12** were collected on a Stoe Imaging Plate Diffraction System [25], a crystal of compound **5** was used to record intensities on a Stoe STADI-4 diffractometer. The crystal structures were solved by direct methods using SIR-97 [26] or SHELXS-97 [27]. Non-hydrogen atoms were refined with anisotropic temperature factors. For compound **9** the hydrogen atoms were located from the electron-density difference map and refined as free atoms with isotropic thermal parameters. In all other cases the H atoms were treated as riding using SHELXL-97 defaults with U_{iso} (H) = 1.2 U_{eq} for attached atom. The structure of compound **9** and the crystallographic data for compounds **5**, **9**, **11b** and **12** are given in the supporting information to this article.

1-Butyl-3-[9-(3-butyl-ureido)-phenazine-1-yl]-urea (**7**)

1,9-Di-amino-phenazine (200 mg, 0.95 mmol, **4**) and *n*-butyl isocyanate (1.0 ml, 8.9 mmol, **6**) were refluxed for 16 h. Excess of *n*-butyl isocyanate was removed *in vacuo* and the residue was recrystallized from 60 ml of ethanol to give **7** (250 mg, 65%, R_f = 0.5 in toluene/EtOAc 3:2), as an orange solid, m.p. 265 °C (dec). – IR (KBr): $\tilde{\nu}$ = 3336 cm^{-1}, 2958, 1651, 1543. – UV/vis (MeOH): λ_{max} (lg ε) = 208 nm (4.507), 246 (4.368), 282 (4.829). – ^{1}H NMR (400 MHz, DMSO-d6): δ = 0.94 (t, ^3J = 7.3 Hz, 6 H), 1.41 (m, 4 H), 1.54 (m, 4 H), 3.25 (m, 4 H), 6.81 (t, ^3J = 5.6 Hz, 2 H), 7.71 (dd, ^3J = 8.8 Hz, ^4J = 0.8 Hz, 2 H), 7.85 (dd, ^3J = 8.8 Hz, ^3J = 7.7 Hz, 2 H), 8.52 (dd, ^3J = 7.7 Hz, ^4J = 0.8 Hz, 2 H), 9.56 (s, 2 H). – ^{13}C NMR (100 MHz, DMSO-

d6): δ = 13.7 (+), 19.7 (−), 31.9 (−), 38.9 (−), 112.7 (+), 119.6 (+), 131.7 (C_{quat}), 132.2 (+), 136.4 (C_{quat}), 143.2 (C_{quat}), 154.6 (C_{quat}). – MS (EI); *m/z* (%): 408 (12) $[M]^+$, 335 (8) $[M-n\text{-BuNHCO} + H]^+$, 236 (84) $[M-n\text{-BuNHCO}-n\text{-BuNH}]^+$, 210 (100) $[M-2\cdot n\text{-BuNHCO}]^+$. – HRMS: $C_{22}H_{28}N_6O_2$ (408.2274); $[M]^+$ = 408.2278 ± 0.3 ppm.

(2-tert-Butyl-phenyl)-(2-methyl-6-nitro-phenyl)-amine (**10a**)

A mixture of 2-bromo-3-nitro-toluene (**9**, 500 mg, 2.3 mmol), K_2CO_3 (3.2 g, 23 mmol), copper powder (150 mg, 2.3 mmol) and 2-*tert*-butyl-aniline (**8**, 3.4 ml, 23 mmol) was heated under dinitrogen for 4 h and evaporated in vacuo. The solid residue was purified by CC (CH_2Cl_2/Hexan; 1:1) to give 120 mg (20%) of **10a** (R_f = 0.6) as a red solid, m.p. 58 °C. – IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 1598, 1465, 1261 – UV/vis (CH_3CN): λ_{max} (lg ε) = 258 nm (6.537), 282 (6.306), 364 (6.015). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.57 (s, 9 H), 1.95 (s, 3 H), 6.54 (m, 1 H), 7.00 (m, 3 H), 7.35 (d, ^3J = 7.4 Hz, 1 H), 7.42 (m, 1 H), 8.01 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 1 H), 8.82 (bs, 1 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.4 (+), 30.1 (+), 34.9 (C_{quat}), 120.6 (+), 121.1 (+), 123.3 (+), 124.1 (+), 126.4 (+), 127.1 (+), 132.8 (C_{quat}), 137.6 (+), 139.3 (C_{quat}), 140.0 (C_{quat}), 140.9 (C_{quat}), 141.2 (C_{quat}). – MS (EI); *m/z* (%): 284 (81) $[M]^+$, 269 (12) $[M - CH_3]^+$, 208 (100).

1-tert-Butyl-9-methyl-phenazine (**11a**)

To a solution of sodium (160 mg, 7.0 mmol) in 15 ml of ethanol was added under nitrogen $NaBH_4$ (270 mg, 7.1 mmol) and the suspension was stirred for 15 min. Compound **10a** (100 mg, 0.35 mmol) was added, the red reaction mixture was refluxed for 4 h and the solvent was removed *in vacuo*. The crude product was dissolved in dichloromethane, the organic phase was washed with aqueous HCl (2 M), the organic phase was dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by CC (CH_2Cl_2), which gave three fractions: 1.) (R_f = 0.6, CH_2Cl_2) 55 mg (60%) of **11a** as a yellow solid, m.p. 108 °C. – IR (KBr): $\tilde{\nu}$ = 2950 cm^{-1}, 1532, 975, 755. – UV/vis (CH_3CN): λ_{max} (lg ε) = 264 nm (6.146), 355 (5.000), 373 (5.243). – ^{1}H NMR: δ = 1.78 (s, 9 H), 2.95 (s, 3 H), 7.62 (d, ^3J = 6.7 Hz, 1 H), 7.69 (dd, ^3J = 8.7 Hz, ^3J = 6.7 Hz, 1 H), 7.73 (m, 2 H), 8.03 (d, ^3J = 8.7 Hz, 1 H), 8.08 (dd, ^3J = 7.2 Hz, ^4J = 2.8 Hz, 1 H). – ^{13}C NMR: δ = 18.2 (+), 31.0 (+), 36.8 (C_{quat}), 126.1 (+), 126.9 (+), 128.1 (+), 128.9 (+), 130.1 (+), 130.2 (+), 138.3 (C_{quat}), 140.9 (C_{quat}), 141.9 (C_{quat}), 142.2 (C_{quat}), 143.9 (C_{quat}), 148.9 (C_{quat}). – MS (EI); *m/z* (%): 250 (69) $[M]^+$, 235 (100) $[M-CH_3]^+$, 208 (84). – $C_{17}H_{18}N_2$ (250.34): calcd. C 81.55, H 7.25, N 11.20; found C 80.61, H 7.21, N 10.94. – 2.) (R_f = 0.7, CH_2Cl_2) 20 mg (20%) of N^2-(2-tert-butyl-phenyl)-3-methyl-benzene-1,2-diamine (**10b**). White solid, m.p. 126 °C. – IR (KBr): $\tilde{\nu}$ = 3379 cm^{-1}, 2967, 1606, 1493. – UV/vis (CH_3CN): λ_{max} (lg ε) = 210 nm (6.490), 258 (5.789), 326 (5.662). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.59 (s, 9 H), 2.19 (s, 3 H), 3.73 (bs, 2 H), 5.21 (bs, 1 H), 6.34 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1 H), 6.72 (m, 3 H), 7.02 (m, 2 H), 7.36 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1 H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 18.4 (+), 30.0 (+), 34.5 (C_{quat}), 113.0 (+), 113.5 (+), 118.5 (+), 120.6 (+), 125.9 (C_{quat}), 126.6 (+), 126.8 (+), 127.3 (+), 133.6 (C_{quat}), 136.7 (C_{quat}), 143.5 (C_{quat}), 144.4 (C_{quat}). – MS (EI); *m/z* (%): 254 (100) $[M]^+$, 239 (12) $[M-CH_3]^+$, 222 (32) $[M-CH_3-NH_2 + H]^+$, 197 (22) $[M-t\text{-Bu}]^+$. – $C_{17}H_{22}N_2$ (254.18): calcd. C 80.26, H 8.72, N 11.02; found C 80.00, H 8.60, N 10.95. – 3.) (R_f = 0.4, CH_2Cl_2) 10 mg (10 %) of *1-tert-Butyl-9-methyl-phenazine-5-ol* (**11b**), as a yellow solid, m.p. 217 °C. – IR (KBr): $\tilde{\nu}$ = 2958 cm^{-1}, 1482, 1336, 763. – UV/vis (CH_3CN): λ_{max} (lg ε) = 272 nm (5.342), 330 (4.435), 382 (4.343), 428 (4.374). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.76 (s, 9 H), 2.92 (s, 3 H), 7.69 (m, 4 H), 8.52 (m, 1 H), 8.62 (dd, ^3J = 8.7 Hz, ^4J = 1.6 Hz, 1 H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 18.5 (+), 31.1 (+), 37.1 (C_{quat}), 116.7 (+), 117.5 (+), 127.2 (+), 129.9 (+), 130.0 (+), 130.1 (+), 133.9 (C_{quat}), 135.4 (C_{quat}), 139.3 (C_{quat}), 142.8 (C_{quat}), 143.7 (C_{quat}), 149.8 (C_{quat}). – MS (EI); *m/z* (%): 266 (29) $[M]^+$, 251 (100) $[M-CH_3]^+$, 235 (26) $[M-CH_3-O]^+$.

4-tert-Butyl-5-methyl-1,6(9)-dinitro-phenazine (**12**, **13**)

Compound **11a** (150 mg, 0.60 mmol) was dissolved in 1.5 ml of conc. sulfuric acid, 0.7 ml of fuming sulfuric acid and 1.5 ml of fuming nitric acid were added with ice cooling. The reaction mixture was stirred for 2 h at 100 °C, cooled to r. t., poured into ice water and the yellow precipitate was collected by filtration. The crude product was purified by CC (toluene) to give two fractions: 1.) (R_f = 0.4, toluene) 75 mg (35%) of *1-tert-Butyl-9-methyl-4,6-dinitro-phenazine* (**13**), as a yellow solid, m.p. 163 °C. – IR (KBr): $\tilde{\nu}$ = 2921 cm^{-1}, 1521, 1344, 806. – UV/vis (CH_3CN): λ_{max} (lg ε) = 254 nm (6.813), 348 (5.942), 364 (6.141). – ^{1}H NMR (250 MHz, DMSO-d_6): δ = 1.72 (s, 9 H), 2.94

(s, 3 H), 8.00 (m, 2 H), 8.56 (m, 2 H). – ^{13}C NMR (62 MHz, DMSO-d_6): δ = 18.0 (+), 30.6 (+), 37.2 (C_{quat}), 126.4 (+), 126.7 (+), 127.6 (+), 128.8 (+), 133.5 (C_{quart}), 134.9 (C_{quat}), 139.4 (C_{quat}), 140.3 (C_{quat}), 143.8 (C_{quat}), 144.3 (C_{quat}), 145.5 (C_{quat}), 153.5 (C_{quat}). – MS (EI); *m/z* (%): 340 (100) $[M]^+$, 325 (96) $[M-CH_3]^+$, 208 (28) $[M-NO_2 + H]^+$. – $C_{17}H_{16}N_4O_4$ (340.34): calcd. C 60.00, H 4.74, N 16.46; found C 59.81, H 4.96, N 16.20. – 2.) (R_f = 0.7, toluene) 60 mg (30%) of *9-tert-butyl-1-methyl-2,6-dinitro-phenazine (***12**), as a yellow solid, m.p. 224 °C. – IR (KBr): $\tilde{\nu}$ = 2961 cm^{-1}, 1532, 1357, 806. – UV/vis (CH_3CN): λ_{max} (lg ε) = 202 nm (5.747), 252 (5.648), 366 (4.996). – ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.75 (s, 9 H), 3.08 (s, 3 H), 8.00 (d, ^3J = 7.9 Hz, 1 H), 8.26 (dd, ^3J = 9.5 Hz, ^4J = 0.7 Hz, 1 H), 8.39 (d, ^3J = 9.5 Hz, 1 H), 8.56 (d, ^3J = 7.9 Hz, 1 H). – ^{13}C NMR (100 MHz, DMSO-d_6): δ = 13.5 (+), 30.7 (+), 37.3 (C_{quat}), 126.2 (+), 126.6 (+), 126.7 (+), 128.4 (+), 133.8 (C_{quat}), 135.8 (C_{quat}), 140.0 (C_{quat}), 140.7 (C_{quat}), 142.2 (C_{quat}), 145.7 (C_{quat}), 149.4 (C_{quat}), 153.4 (C_{quat}). – MS (EI); *m/z* (%): 340 (100) $[M]^+$, 325 (88) $[M-CH_3]^+$, 295 (14) $[M-NO_2 + H]^+$. – HRMS: $C_{17}H_{16}N_4O_4$ (340.1172); $[M]^+$ = 340.1169 +/- 0.8 ppm.

4-tert-Butyl-6-methyl-phenazine-1,9-diamine (**14**)

To a solution of **13** (50 mg, 0.15 mmol) in EtOAc (10 ml) was added Pd/C (10%, 30 mg, 0.03 mmol) and hydrogen pressure of 10^6 Pa was applied for 16 h. The catalyst was filtered off, the filtrate evaporated *in vacuo* and the red solid residue was purified by CC (R_f = 0.9, EtOAc) to yield 40 mg (97%) of **14** as a red solid, m.p. 59 °C. – IR (KBr): $\tilde{\nu}$ = 3446 cm^{-1}, 2926, 1625, 1494. – UV/vis (CH_3CN): λ_{max} (lg ε) = 237 nm (4.765), 291 (5.441), 514 (4.145). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.73 (s, 9 H), 2.80 (s, 3 H), 4.93 (bs, 4 H), 6.79 (d, ^3J = 7.5 Hz, 1 H), 6.82 (d, ^3J = 7.8 Hz, 1 H), 7.38 (d, ^3J = 7.5 Hz, 1 H), 7.49 (d, ^3J = 7.8 Hz, 1 H). – ^{13}C NMR (62 MHz, $CDCl_3$): δ = 17.5 (+), 31.1 (+), 36.0 (C_{quat}), 107.6 (+), 108.0 (+), 126.0 (C_{quat}), 127.0 (+), 129.7 (+), 131.7 (C_{quat}), 133.1 (C_{quat}), 137.0 (C_{quat}), 141.3 (C_{quat}), 141.5 (C_{quat}), 141.9 (C_{quat}), 142.4 (C_{quat}). – MS (EI); *m/z* (%): 280 (38) $[M]^+$, 265 (60) $[M-CH_3]^+$, 237 (100). – HRMS: $C_{17}H_{20}N_4$ (280.1688); $[M]^+$ = 280.1686 ± 0.6 ppm.

1-Butyl-3-[6-tert-butyl-9-(3-butyl-ureido)-4-methyl-phenazine-1-yl]-urea (**15**)

To a solution of 4-*tert*-butyl-6-methyl-phenazine-1,9-diamine (**14**) (40 mg, 0.14 mmol) in toluene (10 ml) were added 0.1 ml (0.9 mmol) of *n*-butyl isocyanate (**6**) and 0.1 ml (1.2 mmol) of pyridine. The reaction mixture was refluxed for 16 h and evaporated *in vacuo* to dryness. CC (R_f = 0.3; toluene/ethyl acetate 4:1) gave **15** (37 mg, 55%), as an orange solid, m.p. 147 °C. – IR (KBr): $\tilde{\nu}$ = 3328 cm^{-1}, 2925, 1646, 1573. – UV/vis (CH_3CN): λ_{max} (lg ε) = 353 nm (6.313), 370 (6.471), 476 (6.601). – ^{1}H NMR (400 MHz, D_6-DMSO): δ = 0.93 (t, ^3J = 7.3 Hz, 6 H), 1.38 (m, 4 H), 1.51 (m, 4 H), 1.68 (s, 9 H), 2.75 (s, 3 H), 3.22 (m, 4 H), 6.75 (m, 2 H), 7.68 (m, 2 H), 8.39 (m, 2 H), 9.40 (s, 1 H), 9.45 (s, 1 H). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.63 (bs, 6 H), 0.85 (m, 4 H), 1.33 (s, 9 H), 1.68 (s, 3 H), 2.35 (bs, 4 H), 3.17 (bs, 4 H), 6.86 (bs, 3 H), 7.19 (bs, 1 H), 8.04 (bs, 1 H), 8.24 (bs, 1 H), 9.32 (s, 1 H), 9.48 (bs, 1 H). – ^{13}C NMR (100 MHz, D_6-DMSO): δ = 13.7 (+), 16.9 (+), 19.6 (–), 30.8 (+), 31.8 (–), 35.7 (C_{quat}), 38.8 (–), 112.5 (+), 112.8 (+), 127.2 (C_{quat}), 127.7 (+), 130.5 (+), 130.6 (C_{quat}), 132.0 (C_{quat}), 134.1 (C_{quat}), 134.7 (C_{quat}), 138.2 (C_{quat}), 140.1 (C_{quat}), 141.0 (C_{quat}), 154.6 (C_{quat}), 154.7 (C_{quat}). – MS (CI); *m/z* (%): 957 (50) $[2\cdot M + H]^+$, 479 (100) $[M + H]^+$, 335 (24) $[M-n\text{-BuNH} + H]^+$, 380 (41) $[M-n\text{-BuNHCO} + H]^+$. – HRMS: $C_{27}H_{38}N_6O_2$ (478.3056); $[M]^+$ = 478.3058 ± 0.8 ppm.

1-Butyl-3-{6-[(3-butyl-ureido)-methyl]pyridine-2-ylmethyl}-urea (**17**)

To a solution of pyridine-2,6-dinitrile (**16**) (260 mg, 2.0 mmol) in 10 ml of THF were added 25 ml (25 mmol, 1 M) of $BH_3\cdot$THF. The reaction mixture was stirred for 16 h at r.t., excess of borane was destroyed by careful addition of methanol and the mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from 30 ml of HCl saturated ethanol, filtered and dried to yield 340 mg (1.4 mmol) pyridine-1,6-methylene-diamine. The compound was allowed to react with 0.3 ml (3.2 mmol) of *n*-butyl isocyanate (**6**) and 1.0 ml (7.0 mmol) of NEt_3 in 30 ml of THF for 16 h under reflux. The reaction mixture was evaporated to dryness and recrystallization from ethanol gave **17** (170 mg, 25%; R_f = 0.2, CH_2Cl_2/MeOH, 20:2), as a white solid, m.p. 183 °C. – IR (KBr): $\tilde{\nu}$ = 3326 cm^{-1}, 2927, 1627, 1459. – UV/vis (MeOH): λ_{max} (lg ε) = 264 nm (4.107). – ^{1}H NMR (400 MHz, D_6-DMSO): δ = 0.87 (t, ^3J = 7.2 Hz, 6 H), 1.27 (m, 4 H), 1.35 (m, 4 H), 3.00 (m, 4 H), 4.26 (d, ^3J = 5.9 Hz, 4 H), 6.09 (t, ^3J = 5.7 Hz, 2 H), 6.38 (t, ^3J = 5.9 Hz, 2 H), 7.10 (d, ^3J = 7.7 Hz, 2 H), 7.71 (t, ^3J = 7.7 Hz, 1 H). – ^{13}C NMR (62 MHz, D_6-DMSO): δ = 13.7 (+), 19.5 (–), 32.1 (–), 32.1

(–), 44.9 (–), 118.6 (+), 137.1 (+), 158.0 (C_{quat}), 159.2 (C_{quat}). – MS (EI); *m/z* (%): 335 (2) $[M]^+$, 262 (12) $[M-n\text{-BuNH}-H]^+$, 190 (28) $[M-2\cdot n\text{-BuNH}-H]^+$, 30 (100). – HRMS: $C_{17}H_{29}N_5O_2$ (335.2321); $[M]^+$ = 335.2320 +/- 0.9 ppm.

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