Cyclic Guanidines; IV.[1] Intramolecular Nucleophilic Aromatic Substitution of Hydrogen in (3-Nitrophenyl)guanidines

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Received 1 July 1991; revised 22 August 1991

Cyclization of substituted (3-nitrophenyl)guanidines is achieved in basic medium by nucleophilic displacement of hydrogen. The reaction offers a new route to benzimidazoles as well as to tricyclic imidazo-, pyrimido- and diazepino-benzimidazoles with uncommon substitution patterns. The mechanism of the redox process is investigated and the regioselectivity is discussed in terms of substrate structure and reaction conditions. An outline is given on the scope of the ring closure.

The nucleophilic displacement of hydrogen in electron deficient aromatics is not a frequent but rather an "old" reaction. Wohl[2], in 1899, found that treatment of nitrobenzene with potassium hydroxide resulted in the formation of *o*-nitrophenol. Although Wohl could not see any concomitant reduction products of nitrobenzene, preceding investigators found azo and azoxy compounds in related reactions.[3] According to de Boer and Dirkx[4] the regioselectivity of amino-dehydrogenations "depends somewhat mysteriously on reaction conditions", and Huisgen[5] assumed that the involved metal ion plays a decisive role. Apart from the modern "Vicarious Nucleophilic Substitution" (VNS) of hydrogen,[6] this type of S_NAr reaction has rarely been used for the preparation of heterocyclic compounds.[7,8]

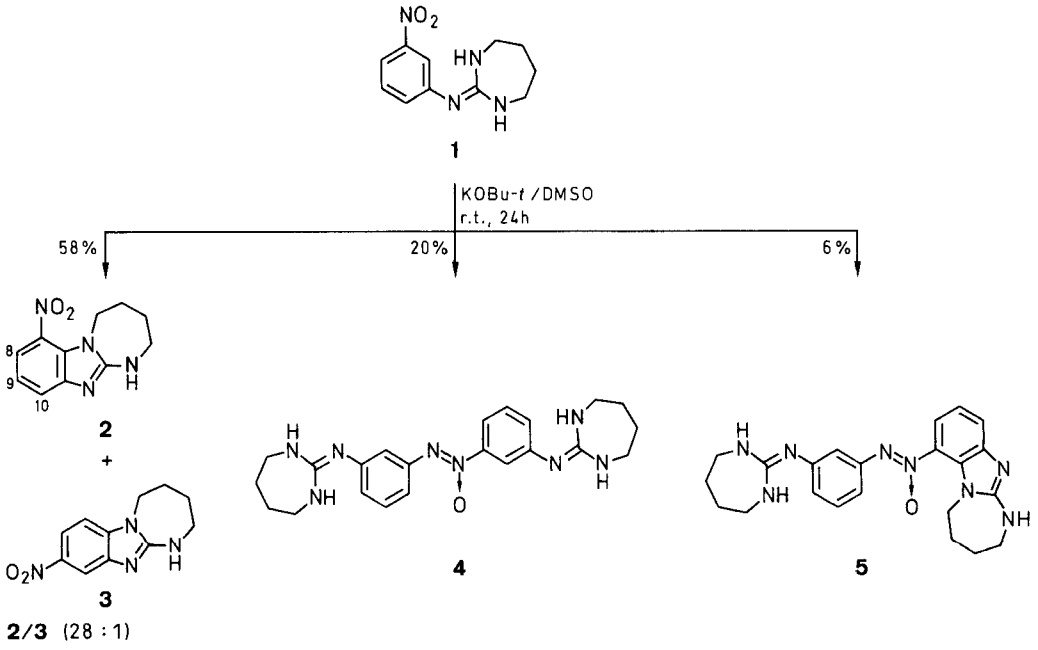
The present paper describes the intramolecular amino-dehydrogenation of (3-nitrophenyl)guanidines furnishing bi- and tricyclic 2-aminobenzimidazoles of special substitution pattern. If, for example, the diazepine **1** is treated with potassium *tert*-butoxide in dimethyl sulfoxide the ortho substitution product **2** constitutes the main product, while substitution para to the nitro group, leading to **3**, is almost completely suppressed (Scheme 1).

Structural proof of the isomeric substitution patterns on the aromatic rings of the products was easily established using chemical shifts and in particular coupling constants from ^1H NMR spectra. Even in those cases in which the minor isomer could not be isolated, separation of the aryl protons was sufficient for a clean analysis.

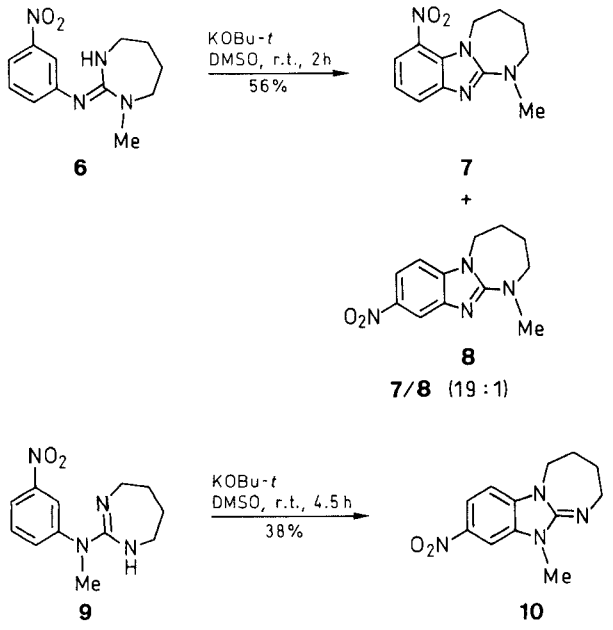
The formation of the azoxy compounds **4** and **5** as byproducts reveals the concomitant oxidizing quality of **1** and uncovers the mechanism of the redox process. Azoxy compounds were cogenerated in all following reactions using potassium *tert*-butoxide/dimethyl sulfoxide as medium (Table) but usually were not isolated. Due to the stoichiometry of the disproportionation reaction the yields of heterocyclic compounds generally could not exceed 60%.

In order to study structural features influencing the regioselectivity of the reaction, we investigated the conversion of methylated diazepines. 1-Methylated substrate **6** primarily gives the ortho substitution product **7** containing a minor amount of para product **8** (Scheme 2). If, however, *N*-methyl derivative **9** is reacted, para substitution affords the orange colored [1,3]diazepino[1,2-*a*]benzimidazole **10** as the only cyclization product.

Next we were curious to see, whether the ring size of the heterocyclic moiety influenced the regioselectivity. Surprisingly, cyclization of pyrimidine **11a** gives ortho product **12a** as the sole tricyclic compound in any sizable amount (Scheme 3; yield 22%). Only if one offers a good leaving group like chlorine in **11b** as a sort of bait to the



Scheme 1



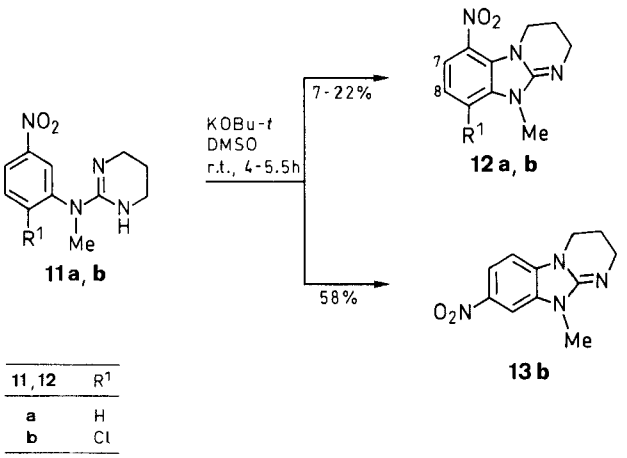
Scheme 2

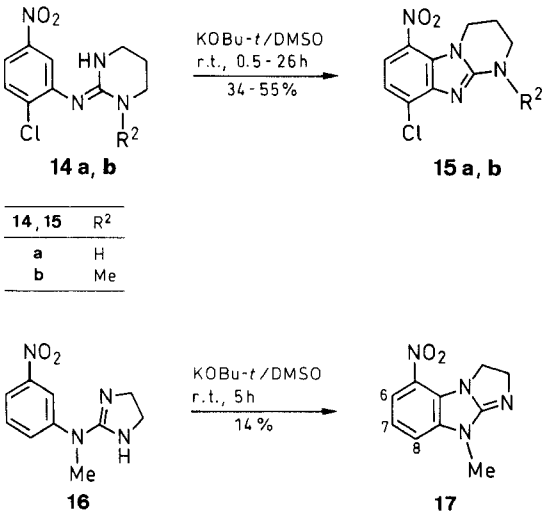
attacking nucleophile, para substitution leading to **13b** dominates over the ortho product **12b** by factor 10. As base is consumed in this reaction, more than a catalytic amount of potassium *tert*-butoxide is necessary. This type of ring closure has been observed previously as a side reaction of a rearrangement.[9]

If, on the other hand, the starting material is not methylated or 1-methylated as in **14a,b**, the amino-dehydrogenation is favored over the amino-dehalogenation (Scheme 3). This behavior seems unusual, however, examples about preferred nucleophilic displacement of hydrogen relative to chlorine exist in the literature,[10-12] appear to be the rule in VNS[13,14] and even show up in intramolecular VNS.[15]

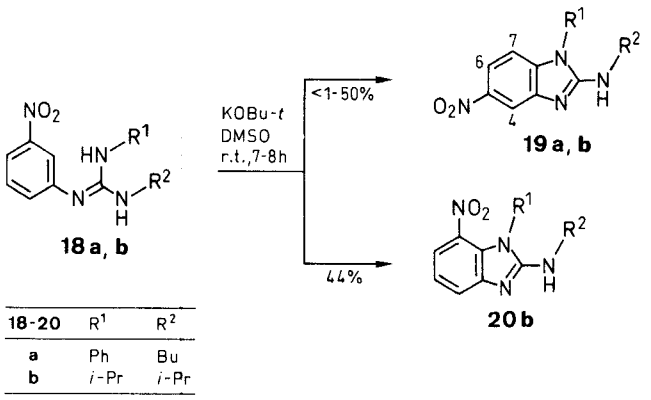
Turning to the imidazoline **16** as starting material, which corresponds to **11a**, we find the expected ortho cyclization (Scheme 3). The low yield of the brilliant red imidazo[1,2-*a*]benzimidazole **17** may have to do with ring strain, disfavoring its formation.

To test the scope of the reaction, differently substituted acyclic guanidines were used as reactants (Scheme 4). Starting compound **18a** displays a twofold regioselectivity as far as only the phenyl-N is attacking selectively para to the nitro group furnishing **19a** in 50% yield. In contrast, the bisisopropylguanidine **18b** affords, although its substitution pattern corresponds to **18a**, predominantly ortho product **20b** along with a trace of para product **19b**.





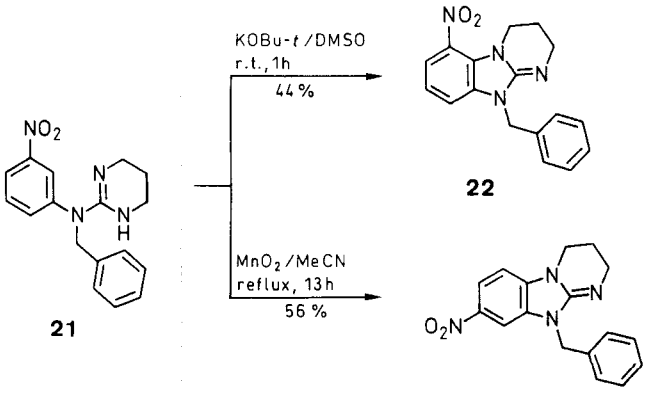
Scheme 3



Scheme 4

The limitation of the reaction is indicated by the fact that unsubstituted (3-nitrophenyl)guanidine does not react at all under standard conditions.

Regioselectivity may also depend on reaction conditions; this is demonstrated in the following example. If pyrimidine derivative **21** is treated with potassium *tert*-butoxi-



Scheme 5

Table. Preparation of Heterocycles According to the Typical Procedure

Substrate	Conditions: KOBu-*t* (equiv)	Conditions: Time (h)	Product	Yield (%)	mp (°C)	Molecular Formula[a]	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)	MS *m/z* (%)
1	0.13	24	**2**·HCl	56	238–241	$C_{11}H_{12}N_4O_2 \cdot HCl$ (268.7)	2.18 (m, 4H), 3.71 (m, 2H), 4.15 (m, 2H), 7.46 (t, 1H, J = 8, H-9), 7.71 (dd, 1H, J = 8, 2, H-10), 7.95 (dd, 1H, J = 8, 2, H-8)[b]	–
			4	20	239–240 (dec)	$C_{22}H_{28}N_8O$ (420.5)	1.63 (m, 8H), 3.12 (m, 8H), 4.72 (br s, 4H), 6.91, 7.03, 7.35, 7.60, 7.74, 7.76, 7.83 (m, 8H)	420 (10), 404 (6), 403 (7), 324 (18), 308 (35), 29 (100)
			5	6	265–266 (dec)	$C_{22}H_{26}N_8O$[c] (418.5)	1.55 (m, 4H), 1.92, 1.96 (2m, 4H), 3.02 (m, 4H), 3.17, 3.33 (2m, 4H), 4.43 (br s, 3H), 7.00 (dd, 1H, J = 8, 2, H-4), 7.07 (t, 1H, J = 8, H-9), 7.30 (dd, 1H, J = 8, 1, H-10), 7.38 (t, 1H, J = 8, H-5), 7.56 (t, 1H, J = 2, H-2), 7.66 (dd, 1H, J = 8, 2, H-6), 8.22 (dd, 1H, J = 8, 1, H-8)[d]	418 (5), 402 (4), 322 (25), 202 (80), 29 (100)
6	0.25	2	**7**	56	136–140	$C_{12}H_{14}N_4O_2$ (246.3)	2.04 (m, 4H), 3.21 (s, 3H), 3.37 (m, 2H), 3.89 (m, 2H), 7.15 (t, 1H, J = 8, H-9), 7.70 (dd, 1H, J = 8, 1, H-10), 7.73 (dd, 1H, J = 8, 1, H-8)[e]	–
9	0.13	4.5	**10**	38	173	$C_{12}H_{14}N_4O_2$ (246.3)	2.06 (m, 4H), 3.30 (s, 3H), 3.67, 3.86 (2m, 4H), 6.71 (d, 1H, J = 9, H-7), 7.51 (d, 1H, J = 2, H-10), 7.89 (dd, 1H, J = 9, 2, H-8)[f]	246 (100), 218 (65), 191 (48), 172 (30)
11a·HI	1.25	4	**12a**	22	130–132	$C_{11}H_{12}N_4O_2$[g] (232.2)	1.89 (m, 2H), 3.36 (s, 3H), 3.55 (m, 2H), 3.95 (m, 2H), 6.93 (dd, 1H, J = 8, 2, H-9), 6.99 (t, 1H, J = 8, H-8), 7.45 (dd, 1H, J = 8, 2, H-7)	–
11b	0.5	5.5	**13b**	58	173	$C_{11}H_{12}N_4O_2$[h] (232.2)	2.04 (m, 2H), 3.38 (s, 3H), 3.59 (t, 2H, J = 7), 3.88 (t, 2H, J = 7), 6.76 (d, 1H, J = 9, H-6), 7.62 (d, 1H, J = 2, H-8), 7.96 (dd, 1H, J = 9, 2, H-7)[i]	–
14a	0.13	26	**15a**	34	> 300	$C_{10}H_9ClN_4O_2$ (252.7)	2.00 (m, 2H), 3.39 (m, 2H), 4.15 (m, 2H), 7.14 (d, 1H, J = 9, H-8), 7.47 (d, 1H, J = 9, H-7)[j]	252, 254 (100, 33), 206, 208 (50, 18)
14b	0.13	0.5	**15b**	55	167–170	$C_{11}H_{11}ClN_4O_2$ (266.7)	2.18 (m, 2H), 3.33 (s, 3H), 3.45 (m, 2H), 4.21 (m, 2H), 7.09 (d, 1H, J = 9, H-8), 7.51 (d, 1H, J = 9, H-7)	266, 268 (100, 33), 220, 222 (42, 14)
16·HI	2	5	**17**	14	214–217	$C_{10}H_{10}N_4O_2$ (218.2)	3.28 (s, 3H), 4.15 (t, 2H, J = 7), 4.30 (t, 2H, J = 7), 6.94 (t, 1H, J = 8, H-7), 7.16 (dd, 1H, J = 8, 2, H-8), 7.92 (dd, 1H, J = 8, 2, H-6)[j]	–
18a	0.4	8	**19a**	50	120–123	$C_{17}H_{18}N_4O_2$ (310.4)	0.94, 1.39, 1.64 (3m, 7H), 3.55 (m, 2H), 4.45 (t, 1H, J = 4), 6.88 (d, 1H, J = 8, H-7), 7.34–7.59 (m, 5H), 7.90 (dd, 1H, J = 8, 2, H-6), 8.32 (d, 1H, J = 2, H-4)	–
18b	1.4	7	**20b**	44	82–84	$C_{13}H_{18}N_4O_2$ (262.3)	1.36, 1.56 (2d, 12H, J = 7), 4.20 (d, 1H, J = 7), 4.27 (m, 1H), 4.57 (q, 1H, J = 7), 7.09 (t, 1H, J = 8, H-5), 7.53 (dd, 1H, J = 8, 2, H-4), 7.62 (dd, 1H, J = 8, 2, H-6)	–
			19b	< 1	204–206	$C_{13}H_{18}N_4O_2$[c] (262.3)	1.36, 1.62 (2d, 12H, J = 7), 4.13 (br s, 1H), 4.26, 4.38 (2m, 2H), 7.21 (d, 1H, J = 10, H-7), 7.97 (dd, 1H, J = 3, 10, H-6), 8.33 (d, 1H, J = 3, H-4)	–
21	0.13	1	**22**	44	160	$C_{17}H_{16}N_4O_2$ (308.3)	1.95 (m, 2H), 3.59, 4.01 (2m, 4H), 5.11 (s, 2H), 6.83 (dd, 1H, J = 8, 2, H-9), 6.90 (t, 1H, J = 8, H-8), 7.27 (m, 5H), 7.49 (dd, 1H, J = 8, 2, H-7)	–

[a] Satisfactory microanalysis obtained: C ±0.42, H ±0.19, N ±0.54, Cl ±0.21, unless stated otherwise.
[b] NMR of base, recorded in CD_3OD.
[c] Microanalysis not available.
[d] Recorded in DMSO-d_6/$CDCl_3$ (1:1).
[e] Containing **8** (ca. 5%).
[f] Confirmed by NOE between CH_3 and H-10.
[g] Microanalysis: C −0.95, N −0.87.
[h] Microanalysis: C −0.92, N −0.70.
[i] Raw product contains **12b** (ca. 10%).
[j] Recorded in DMSO-d_6.

de/dimethyl sulfoxide at room temperature the ortho ring closure is the clearly dominating reaction affording carmine colored **22** (Scheme 5). Refluxing **21**, on the other hand, together with manganese(IV) oxide in acetonitrile leads to the formation of orange-red para product **23** in good yield with no concomitant azoxy compounds detectable. Since it is known, that manganese(IV) oxide in combination with amines triggers radical processes,[16] we suppose the reaction mechanism to differ from the general one.

In case of the basic reaction conditions the selectivity of the nucleophile can be explained by the argument of Mąkosza,[17] that chelation of K^+ between NO_2-group and N-anion favors ortho attack. A qualitative modelling study of geometrical prerequisites and charge distributions in SYBYL[18] supports the hypothesis that such a complex may be relevant.[19] Under neutral, oxidizing conditions repulsive forces between NO_2 and guanidino group may be active, directing the nucleophile towards the para position with the result of **23** being formed.

In general, the observed preferred substitution of hydrogen ortho to the nitro group is paralleled by literature findings,[5,11] especially in VNS.[13–15,17,20] However, the para products **10** (Scheme 2) and **19a** (Scheme 4) cannot be interpreted in terms of the above mentioned arguments. Additional experiments are necessary to fully elucidate the rules governing regioselectivity in these cyclizations.

Finally there remains the question, why we do not generally use external oxidizing agents, like in the synthesis of **23**. We would expect improved yields and could circumvent the trouble of separating the azoxy byproducts. The answer is simple: Preliminary experiments indicate, that in most cases the oxidative procedure does not work! It is, however, by no means precluded, that future investigations will identify more universally applicable oxidizing conditions, which in addition bear the potential of variant regioselectivity.

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on Bruker instruments, usually on the AM-250 unit, routinely using TMS as internal standard. Mass spectra were recorded on a Varian-MAT-CH7 mass spectrometer, operated on line with an Incos 2100 data system. Experimental conditions: electron energy 70 eV, ion source temperature 200 °C, emission current 300 μA; direct insertion probe with manual temperature control; scan range *m/z* 10–650 in 5 or 6 seconds. TLC used Merck silica gel plates of type 60 F_{254} and 0.25 mm layer thickness: Schlittler's Reagent was used as indicator.

2-(3-Nitrophenylimino)-2,3,4,5,6,7-hexahydro-1*H*-1,3-diazepine (1):
3-Nitroaniline (42.17 g, 305 mmol), HCl (32%, 29.5 mL, 300 mmol), H_2O (20.3 mL), ammonium thiocyanate (25.12 g, 330 mmol) and $NaHSO_3$ (40%, 3.5 mL) were combined and stirred at 80–90 °C for 4.5 h. After cooling to r.t. the crystals were separated by suction, washed with H_2O and dried in an oven at 50 °C. The obtained *N*-(3-nitrophenyl)thiourea (52 g) was used as raw material in the following reaction.

N-(3-Nitrophenyl)thiourea (51.5 g, 260 mmol) was combined with MeCN (400 mL) and MeI (24.6 mL, 390 mmol) and heated at 60–70 °C for 1 h. The mixture was concentrated under reduced pressure, the residue taken up in little MeCN, the crystals separated by suction and washed with MeCN and Et_2O. After drying at 50 °C crude *N*-(3-nitrophenyl)-*S*-methylisothiuronium iodide (67.75 g) was obtained. The crude iodide (67.5 g, 200 mmol), DMSO (310 mL) and 1,4-butanediamine (40 mL, 400 mmol) were combined and stirred at 110 °C for 3 h. The mixture was concentrated in vacuo and the residual oil was taken up in H_2O and NH_3. The crystalline precipitate was separated by suction, washed with H_2O and dried at 50 °C in an oven. The crude product **1** (33.3 g) was chromatographed on a silica gel column (230 g, 70–230 mesh) using THF/MeOH (4:1) as eluent. The collected pure fractions were combined, concentrated in vacuo and the residue was washed successively with EtOAc and Et_2O and dried at 50 °C yielding **1** as light orange colored crystals; yield: 25 g (36%); mp 176–178 °C.

$C_{11}H_{14}N_4O_2$	calc.	C 56.40	H 6.02	N 23.92
(234.3)	found	56.01	6.12	23.93

^{1}H NMR ($CDCl_3$): δ = 1.64 (m, 4H, CCH_2CH_2C), 3.12 (m, 4H, 2-NCH_2), 4.86 (br s, 2H, 2NH), 7.14–7.77 (m, 4 H_{arom}).

7-Nitro-2,3,4,5-tetrahydro-1*H*-[1,3]diazepino[1,2-*a*]benzimidazole (2), 3,3′-Bis(2,3,4,5,6,7-hexahydro-1*H*-1,3-diazepine-2-ylideneamino)azoxybenzene (4) and 7-{3-(2,3,4,5,6,7-hexahydro-1*H*-1,3-diazepine-2-ylideneamino)phenyl-*NNO*-azoxy}-2,3,4,5-tetrahydro-1*H*-[1,3]diazepino[1,2-*a*]benzimidazole (5); Typical Procedure:
Compound **1** (3.51 g, 15 mmol) and KOBu-*t* (0.21 g, 1.9 mmol) were dissolved in DMSO (15 mL) and stirred for 24 h at r.t. The mixture was poured into H_2O (100 mL) and the crystalline precipitate was separated by suction, washed with H_2O and dried at 50 °C in an oven. The crude material (3.18 g) consists, according to TLC, of at least 4 compounds. It was chromatographed on a silica gel column (12 × 3 cm, 70–230 mesh) using THF/MeOH (4:1) as eluent. The fastest moving material was collected, the solvent evaporated, the residue washed with Et_2O and dried at 50 °C. The obtained yellow crystals (2.05 g) consisted, according to NMR analysis, of **2** (96%) and 9-nitro-2,3,4,5-tetrahydro-1*H*-[1,3]diazepino[1,2-*a*]benzimidazole (**3**; 4%).

^{1}H NMR of **3** (CD_3OD): δ = 2.18 (m, 4H, CCH_2CH_2C), 3.67 (m, 2H, NCH_2), 4.36 (m, 2H, NCH_2), 7.69 (d, 1H, J = 8 Hz, H-7), 8.21 (d, 1H, J = 2 Hz, H-10), 8.22 (dd, 1H, J = 8, 2 Hz, H-8).

The crystals were dissolved in THF (50 mL), HCl/Et_2O was added and the precipitate was separated by suction, washed with THF and Et_2O, and dried at 50 °C, furnishing **2** · HCl (2.24 g, 56%) as light yellow crystals. For analytical data see Table.

The second substance eluting from the column was collected, the solvent evaporated in vacuo, giving **5** (0.18 g; 6%) as yellow crystals. For analytical data see Table.

The third substance was eluted from the column with THF/MeOH/NH_3 (16:4:1) yielding, after the usual work up, **4** (0.64 g; 20%) as yellow crystals. Analytical data given in the Table.

1-Methyl-2-(3-nitrophenylimino)-2,3,4,5,6,7-hexahydro-1*H*-1,3-diazepine (6):
Procedure in analogy to **1** using *N*-methyl-1,4-butanediamine instead of 1,4-butanediamine. Yield: 14%; yellow crystals; mp 87–92 °C.

^{1}H NMR ($CDCl_3$): δ = 1.63 (m, 4H, CCH_2CH_2C), 2.98 (s, 3H, NCH_3), 3.07, 3.23 (2 m, 4H, 2NCH_2), 4.13 (br s, 1H, NH), 7.13 (m, 1 H_{arom}), 7.35 (t, J = 9 Hz, 1 H_{arom}), 7.63 (t, J = 2 Hz, 1 H_{arom}), 7.74 (m, 1 H_{arom}).

2-[Methyl(3-nitrophenyl)amino]-2,3,4,5-tetrahydro-1*H*-1,3-diazepine (9):
Compound **1** (11.7 g; 50 mmol) was dissolved in MeCN (200 mL), MeI (4.7 mL; 75 mmol) was added and the mixture was refluxed for 5 h. The solvent was distilled off under reduced pressure and the residual oil was treated with H_2O, causing the precipitation of crystals. The solid was separated by suction, washed with H_2O and dried at 50 °C affording crude product as HI salt (9.9 g). The solid material was suspended in H_2O (50 mL), 10 N NaOH (20 mL) was added and the mixture extracted with CH_2Cl_2 (150 mL). The organic phase was extracted with 5 N NaOH (2 × 50 mL) and concentrated under reduced pressure, giving a residue which was taken up in Et_2O, filtered by suction, washed with Et_2O and dried at 50 °C. In this way **9** (5.8 g, 47%) was obtained as yellow crystals; mp 113–115 °C.

$C_{12}H_{16}N_4O_2$	calc.	C 58.05	H 6.50	N 22.57
(284.3)	found	57.82	6.46	22.71

^{1}H-NMR ($CDCl_3$): δ = 1.70 (m, 4H, CCH_2CH_2C), 3.25 (m, 4H, 2NCH_2), 3.34 (s, 3H, NCH_3), 4.15 (br s, 1H, NH), 7.36, 7.53, 7.90, 7.91 (4 m, 4 H_{arom}).

2-[Methyl(3-nitrophenyl)amino]-1,2,3,4-tetrahydropyrimidine (11a):
2-(3-Nitrophenylimino)-1,2,3,4,5,6-hexahydropyrimidine (32.4 g, 147 mmol; obtained analogous to **1**) was methylated as described for

9 in the preceding procedure, yielding **11a** · HI (38.3 g, 72%) as light yellow crystals; mp 195–198 °C.

2-[Methyl(2-chloro-5-nitrophenyl)amino]-1,2,3,4-tetrahydropyrimidine (11b):
Procedure as described for **11a** using the corresponding chloro compound as starting material yielded **11b** (59%) as yellow crystals; mp ca. 305 °C (dec).

2-(2-Chloro-5-nitrophenylimino)-1,2,3,4,5,6-hexahydropyrimidine (14a):
2-chloro-5-nitroaniline (43.1 g, 250 mmol), formic acid (96–100%, 500 mL) and Ac_2O (175 mL) were combined, stirred at r.t. for 5 h and the resulting solution was concentrated under reduced pressure. The solid residue was taken up in H_2O (350 mL), filtered by suction, washed with H_2O and dried at 50 °C yielding crude 2-chloro-5-nitroformanilide (50 g) as light grey crystals.

The crude formanilide (50 g), $SOCl_2$ (82 mL) and SO_2Cl_2 (29 mL) were combined and heated at 50–60 °C for 44 h. The mixture was concentrated under reduced pressure, the residue dissolved in light petroleum ether, decanted from a precipitate and the clear solution evaporated to constant weight. The remaining yellow liquid constituted 2-chloro-5-nitrophenylisocyano dichloride (35.5 g) and was used in the following reaction without further purification.

The crude isocyano dichloride (35.5 g, 140 mmol) was dissolved in THF (135 mL) and added dropwise within 30 min to a solution of 1,3-propanediamine (58 mL, 700 mmol) in THF (335 mmol) which was kept at 0–5 °C. The orange colored suspension was stirred for one more h at 0–5 °C another 5 h at r.t. The mixture was filtered, the filtrate concentrated in vacuo, the solid residue taken up in H_2O, separated by suction and washed with H_2O and Et_2O. After drying at 50 °C **14a** (28.1 g, 44%) was obtained as orange colored crystals; mp 189–191 °C.

$C_{10}H_{11}ClN_4O_2$	calc.	C 47.16	H 4.35	N 22.00	Cl 13.92
(254.7)	found	47.20	4.41	21.82	13.88

^{1}H NMR ($CDCl_3$): δ = 1.94 (m, 2H, CCH_2C), 3.31 (m, 4H, $2NCH_2$), 5.32 (br s, 2H, 2NH), 7.45 (d, J = 10 Hz, 1 H_{arom}), 7.64 (dd, J = 3, 10 Hz, 1 H_{arom}), 7.84 (d, J = 3 Hz), 1 H_{arom}).

1-Methyl-2-(2-chloro-5-nitrophenylimino)-1,2,3,4,5,6-hexahydropyrimidine (14b):
Preparation as described for **14a** using *N*-methylpropanediamine instead of 1,3-propanediamine as reactant. **14b** (41.6 g; 62%) was obtained as yellow crystals; mp 144–146 °C.

$C_{11}H_{13}ClN_4O_2$	calc.	C 49.17	H 4.88	Cl 13.19	N 20.85
(268.7)	found	49.23	5.00	13.31	20.72

^{1}H NMR ($CDCl_3$): δ = 2.00 (m, 2H, CCH_2C), 3.09 (s, 3H, NCH_3), 3.24, 3.33 (2 m, 4H, $2NCH_2$), 4.06 (br s, 1H, NH), 7.45 (d, J = 10 Hz, 1 H_{arom}), 7.65 (dd, J = 3, 10 Hz, 1 H_{arom}), 7.78 (d, J = 3 Hz, 1 H_{arom}).

2-[Methyl(3-nitrophenyl)amino]-4,5-dihydro-1*H*-imidazole (16):
2-(3-Nitrophenylimino)imidazolidine (5.5 g; 27 mmol) was methylated as described in the procedure for **11a**, affording **16** · HI (8.6 g, 92%) as yellow crystals; mp 181–187 °C. TLC: R_f = 0.2; mobile phase: toluene/dioxane/EtOH/25% NH_3 (10:8:3:1).

***N*-(Butyl)-*N'*-(3-nitrophenyl)-*N''*-phenylguanidine (18a):**
S-Methyl-*N*-(3-nitrophenyl)-*N'*-phenylisothiuronium iodide (26.4 g, 64 mmol), MeCN (320 mL) and 1-butanamine (25.1 mL, 127 mmol) were combined and refluxed for 5.5 h. The brown solution was concentrated under reduced pressure, the residual oil taken up in H_2O (200 mL) and 1 M aq Na_2CO_3 (100 mL) and the solution extracted with Et_2O (200 mL). The ether layer was washed with H_2O and extracted with 0.1 N HCl (850 mL).

The aqueous phase was washed with Et_2O (150 mL), made alkaline by addition of 1 M aq Na_2CO_3 (100 mL) and extracted with Et_2O (350 mL). The organic layer was concentrated under reduced pressure, the crystalline residue taken up in light petroleum ether, separated by suction, washed with light petroleum ether and dried at 40 °C yielding the raw product (13.5 g). This material was dissolved in Et_2O and chromatographed over a short column of silica gel (200 g) using Et_2O as eluent. The fractions containing the pure compound were combined, concentrated under vacuo, the residue treated with light petroleum ether, filtered by suction and dried at 50 °C giving **18a** (10.5 g, 53%) as yellow crystals; mp 94–97 °C.

$C_{17}H_{20}N_4O_2$	calc.	C 65.37	H 6.45	N 17.94
(312.4)	found	65.36	6.51	17.98

^{1}H NMR ($CDCl_3$): δ = 0.93 (m, 3H, CH_3), 1.36, 1.55 (2 m, 4H, CCH_2CH_2C), 3.32 (m, 2H, NCH_2), 3.63, 4.17 (2 br s, 2H, 2NH), 6.63–7.82 (m, 9 H_{arom}).

***N*-(3-Nitrophenyl)-*N'*,*N''*-diisopropylguanidine (18b):**
3-Nitroaniline (6.9 g, 50 mmol), DMF (100 mL), diisopropylcarbodiimide (7.8 mL, 50 mmol) and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene; 8.2 mL, 55 mmol) were combined and stirred for 17 h at 140 °C. The mixture was evaporated under reduced pressure and the black residue chromatographed over silica gel (250 g) using EtOAc as eluent. The fractions containing the pure compound were combined and evaporated to dryness yielding **18b** (3 g, 23%) as dark orange crystals; mp 91–93 °C.

^{1}H NMR ($CDCl_3$): δ = 1.13, 1.19 (2 d, 12H, J = 7 Hz, $4CH_3$), 3.65 (d, 1H, J = 6 Hz, NH), 3.80 (m, 2H, 2NCH), 4.15 (d, 1H, J = 6 Hz, NH), 7.13–7.81 (m, 4 H_{arom}).

3-Nitrophenylguanidine:
Preparation from 3-nitroaniline (27.1 g, 155 mmol) and cyanamide (20 g, 476 mmol) similar to Lit.[21], but using 2-methoxyethanol (155 mL) as solvent and refluxing for 12 h yielded 3-nitrophenylguanidine (3.2 g, 21%) as grey crystals; mp 140–143 °C (Lit.[21] mp 145 °C).

$C_7H_8N_4O_2$	calc.	C 46.67	H 4.48	N 31.10
(180.2)	found	46.33	4.59	30.92

2-[Benzyl(3-nitrophenyl)amino]-1,2,3,4-tetrahydropyrimidine (21):
2-(3-Nitrophenylimino)-1,2,3,4,5,6-hexahydropyrimidine (15.4 g; 70 mmol) was reacted as described for **11a**, using benzyl bromide as reactant, yielding **21** (3.4 g; 16%) as yellow crystals; mp 113–115 °C.

^{1}H NMR ($CDCl_3$): δ = 1.80 (m, 2H, CCH_2C), 3.42 (m, 4H, $2NCH_2$), 4.07 (br s, 1H, NH), 4.94 (s, 2H, $ArCH_2$), 7.14–7.89 (m, 9 H_{arom}).

10-Benzyl-8-nitro-2,3,4,10-tetrahydropyrimido[1,2-*a*]benzimidazole (23):
21 (1 g, 3.2 mmol), freshly prepared MnO_2 (0.56 g, 6.4 mmol) and MeCN were combined and refluxed for 13 h. The mixture was filtered over siliceous earth and the filtrate concentrated in vacuo yielding dark brown solid raw product (0.85 g). The crude material was dissolved in THF/MeOH (4:1) and chromatographed over a short column of silica gel. The eluent containing the pure compound was filtered, concentrated under reduced pressure, and the remaining substance suspended in a small amount of Et_2O, separated by suction, washed with Et_2O and dried at 50 °C in an oven, affording **23** (0.56 g, 56%) as orange-red crystals; mp 163–170 °C.

$C_{17}H_{16}N_4O_2$	calc.	C 66.22	H 5.23	N 18.17
(308.3)	found	66.28	5.24	18.44

^{1}H NMR ($CDCl_3$): δ = 2.02 (m, 2H, CCH_2C), 3.61, 3.88 (2 m, 4H, $2NCH_2$), 5.01 (s, 2H, $ArCH_2$), 6.70 (d, 1H, J = 8 Hz, H-6), 7.22–7.36 (m, 5H), 7.47 (d, 1H, J = 2 Hz, H-9), 7.93 (dd, 1H, J = 8, 2 Hz, H-7).

EI-MS: m/z (%) = 308 (M^+, 30), 91 (100).

UV (EtOH): λ_{max} (ε) = 275 (15754), 394.5 nm (7303).

UV (0.1 N HCl/EtOH): λ_{max} (ε) = 228 (16118), 249.5 (13399), 325 nm (7419).

The competent technical assistance by H.-P. Ignatow is gratefully appreciated.

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