Review Article

Amination of Nitroazaaromatics*

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The use of liquid ammonia/potassium permanganate as a new method for the introduction of an amino group into nitroazaaromatics is discussed. The high regioselectivity of amination as observed in some of these systems is supported by FMO calculations.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

A. Introduction

During recent years considerable efforts have been made to develop a new method for the substitution of hydrogen in aza- and carba-aromatics by an amino group[1] ($S_N H$ substitutions). These aminations involve in principle the oxidation of a σ-amino adduct obtained by dissolving the aromatic in liquid ammonia, or in the case of a less activated substrate by dissolving the substrate in liquid ammonia, containing potassium amide. Potassium permanganate has been found to be an effective agent for oxidizing the σ-adduct.
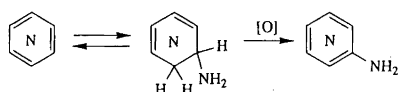
Scheme 1.

In this review we will limit ourselves to a description of our results obtained in the amination of nitroazaaromatics. These compounds are highly π-electron deficient, and therefore able to form with liquid ammonia, being less nucleophilic than the amide ion, a covalent σ-adduct.

B. Amination of monocyclic nitroazines

B.1. Amination of 3-nitropyridines. 3-Nitropyridine (1a), when dissolved in liquid ammonia, gives, after treatment with potassium permanganate, a mixture of 2-amino-3-nitro- (2a), 4-amino-3-nitro- (3a), 6-amino-3-nitro- (4a), and 2,6-diamino-3-nitro-pyridine (5a).[2] For the yields obtained, see Table 1. The ratio 2a:3a:4a, determined by ^{1}H NMR integration of the peak area of one of the aromatic hydrogen atoms was 1.7:1.1:1.0, respectively.
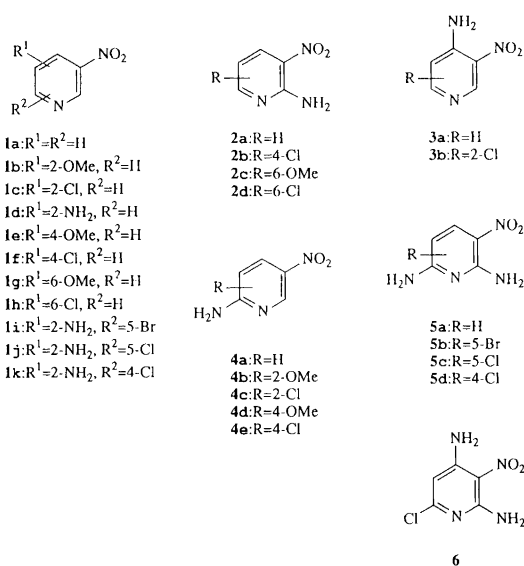
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Attempts to detect the intermediate σ-adduct by ^{1}H NMR spectroscopic measurement appeared to be unsuccessful. A solution of 1a in liquid ammonia (thus without the presence of potassium permanganate) did not give any evidence of the presence of high-field signals of one of the ring hydrogens, as expected for a change in the hybridization of ring hydrogens from $sp^2 \rightarrow sp^3$ on adduct formation. Apparently the equilibrium 1a ⇌ σ-amino adduct lies far to the left, so that by ^{1}H NMR spectroscopy no considerable concentration of σ-adduct can be detected. On addition of permanganate the reaction immediately is driven to adduct formation, as the adduct is oxidized to the amino product.

The results, summarized in Table 1,[2] clearly show that $S_N H$ amination of 3-nitropyridines easily takes place, and that, interestingly, those 3-nitropyridines that contain nucleofugal groups in α- and γ-positions of the ring nitrogen and the nitro-group, react under the applied reactions conditions usually *without* substitution of the nucleofugal group. Examples are the formation of 4b from 1b, of 4c from 1c, of 2c from 1g, and of 2d from 1h. These results show that the method can be highly effective in the preparation of amino-3-nitropyridine derivatives, which otherwise are sometimes difficult to obtain.

Quantum chemical calculations suggest that the experimentally observed regioselectivity of the amination of 3-nitropyridines is controlled by coulombic interactions[2] (see also the discussion in section C.2).

It is worth mentioning that 2-nitropyridine, 4-nitropyridine and their respective N-oxides are *not* aminated by liquid ammonia/potassium permanganate. Also the 2-, 4- and 6-hydroxy- and 4- and 6-amino-3-nitropyridines are not reactive; apparently the electron-donating properties of both hydroxy and amino groups decrease the π-deficiency of the system, preventing the addition of the ammonia.[2]
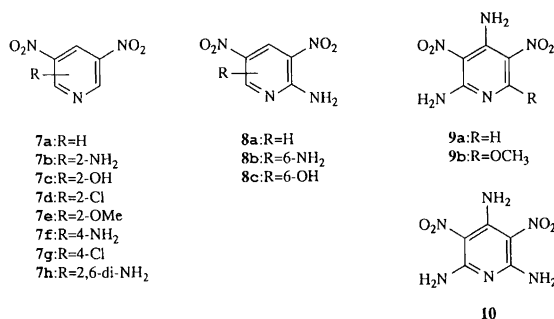
3,5-Dinitropyridines (7) have also been found to

1a:R^1=R^2=H
1b:R^1=2-OMe, R^2=H
1c:R^1=2-Cl, R^2=H
1d:R^1=2-NH$_2$, R^2=H
1e:R^1=4-OMe, R^2=H
1f:R^1=4-Cl, R^2=H
1g:R^1=6-OMe, R^2=H
1h:R^1=6-Cl, R^2=H
1i:R^1=2-NH$_2$, R^2=5-Br
1j:R^1=2-NH$_2$, R^2=5-Cl
1k:R^1=2-NH$_2$, R^2=4-Cl

2a:R=H
2b:R=4-Cl
2c:R=6-OMe
2d:R=6-Cl

3a:R=H
3b:R=2-Cl

4a:R=H
4b:R=2-OMe
4c:R=2-Cl
4d:R=4-OMe
4e:R=4-Cl

5a:R=H
5b:R=5-Br
5c:R=5-Cl
5d:R=4-Cl

6

Scheme 2.

undergo very smooth S$_N$H amino-dehydrogenation; the products and their yields are listed in Table 2.[3, 4]

An important difference between the amination of 3-nitropyridines and that of 3,5-dinitropyridines has been found. Owing to the strong activating power of two nitro groups, a chloro atom, when present in 3,5-dinitropyridines easily undergoes substitution under the conditions of the reaction (7d → 8a + 10). Therefore, in

7a:R=H
7b:R=2-NH$_2$
7c:R=2-OH
7d:R=2-Cl
7e:R=2-OMe
7f:R=4-NH$_2$
7g:R=4-Cl
7h:R=2,6-di-NH$_2$

8a:R=H
8b:R=6-NH$_2$
8c:R=6-OH

9a:R=H
9b:R=OCH$_3$

10

Scheme 3.

*Table 1.* Yields and products, obtained on treatment of 1a–k with liquid ammonia (−33°C)/potassium permanganate.[2]

Substrate	Product (yield, %)
1a	2a (33); 3a (24); 4a (19); 5a (2)
1b	4b (62)
1c	4c (40); 3b (8)
1d	5a (17)
1e	3a (8); 4d (4)
1f	4e (54); 2b (15); 5d (10); 3a (5)
1g	2c (75)
1h	2d (57); 6 (12)
1i	5b (85)
1j	5c (83)
1k	5d (25)

Table 2. Yields and products, obtained on treatment of 7 with liquid ammonia (−33°C)/potassium permanganate.[3, 4]

Substrate	Products (yield, %)
7a	8a (16); mixture 9a + 8b (10); 10 (7)
7b	mixture 9a + 8b (8); 10 (6)
7c	8c (5)
7d	8a (70); 10 (5)
7e	9b (36)
7f	10 (25)
7g	10 (20)
7h	10 (7)

addition to S$_N$H substitution, S$_N$(Ar) displacement also takes place, in contrast with the exclusive S$_N$H substitution, observed for 3-nitropyridines (see above). This behaviour is also supported by the experimental finding that compound 7d, when dissolved in liquid ammonia (−33°C, not containing potassium permanganate) exclusively gives amino-dehalogenation, to yield 8a.[3] The enhanced π-deficiency of compounds 7, compared with that of 1, usually results in mixtures of diamino- and triamino-2,5-dinitropyridines.

It is of interest to mention that the intermediacy of σ-amino 3,5-dinitropyridine adducts could very easily be established. Solutions of 7a–f when dissolved in liquid ammonia form adducts in high concentration, as detected by ^{1}H NMR spectroscopy.[3, 4] It was further shown by ^{1}H NMR spectroscopy that the position of addition of liquid ammonia is temperature dependent. 2-Chloro-3,5-dinitropyridine (7d), when dissolved in liquid ammonia at −60°C gives addition at C-4 (i.e. 11), while at −40°C, addition at C-6 is strongly favoured (i.e. 12).[3] At an intermediate temperature (−50°C) both adducts 11 and 12 are present.


11   12
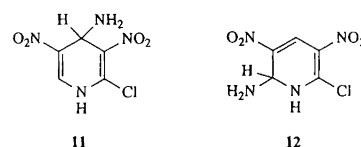
Scheme 4.

B.2. *Amination of 5-nitropyrimidines.* It has been reported that a solution of pyrimidine in liquid ammonia/potassium amide on treatment with potassium permanganate can be converted into 4-aminopyrimidine in high yield.[5] 5-Bromo- and 5-phenyl-pyrimidine react analogously.[5] However, the electron attracting character of the nitro group makes 5-nitropyrimidine (13) so highly π-electron deficient that it was possible to aminate 13 successfully with the mild reagent liquid ammonia/potassium permanganate. 2-Amino-5-nitropyrimidine (15) was obtained in 45% yield; NMR spectroscopy proves convincingly the intermediate existence of the σ-amino adduct 14.[6]

We observed that when position 2 is blocked, the position of amination changes from C-2 to C-4.

13   14   15

16   17

a:R=CH₃, b:R=SCH₃, c:R=C₆H₅
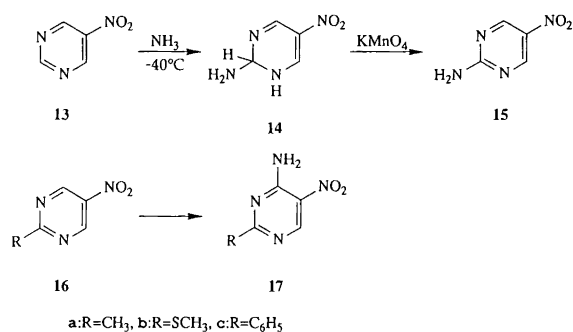
Scheme 5.

2-Methyl- (**16a**), 2-methylthio- (**16b**) and 2-phenyl-5-nitropyrimidine (**16c**) are conveniently converted into the 4-amino compounds **17a** (53%), **17b** (72%) and **17c** (50%).[6] Especially worth mentioning is the fact that in compound **16b** no nucleophilic replacement of the methylthio group takes place during amination, again showing the unique character of the reagent. Temperature dependence of the amination has also been found in the amination of 4-methoxy-5-nitropyrimidine (**18**). Treatment of **18** with liquid ammonia/potassium permanganate at −60°C to −70°C gave 2-amino-4-methoxy-5-nitropyrimidine (**19**, 50%), while 6-amino-4-methoxy-5-nitropyrimidine (**20**) was obtained (yield 65%) when a solution of **18** in liquid NH_3 was allowed to stand for 5 min at 10–20°C, cooled to −40°C and then treated with potassium permanganate.[6] 4,6-Dimethoxy-5-nitropyrimidine (**21**) gives the 2-amino compound **22** (53%).[6]
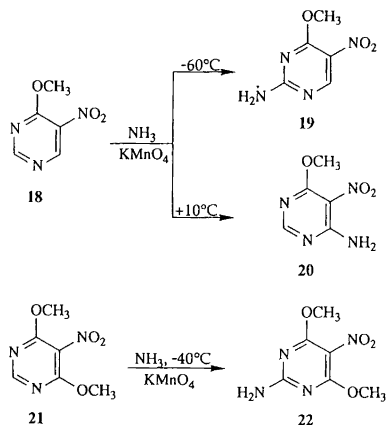
Scheme 6.

B.3. Amination of 4-nitropyridazines. Pyridazine has been found to be aminated by liquid ammonia/potassium amide/potassium permanganate to give 4-amino-pyridazine.[5] However, 4-nitropyridazine (**23a**) requires only liquid ammonia/potassium permanganate as the aminating reagent; the yield of 5-amino-4-nitropyridazine (**24a**) is low (18%).[7] However, the 3,6-di(2-pyridyl)- (**23b**), the 6-phenyl- (**23c**) and 6-(p-methoxyphenyl)-

(**23d**) derivatives give the 5-amino products **24b–d** in high yields (>90%).[7]

23   24   25

a:R¹=R²=H; b:R¹=R²=2-pyridyl; c:R¹=H, R²=C₆H₅; d:R¹=H, R²=p-CH₃O-C₆H₄
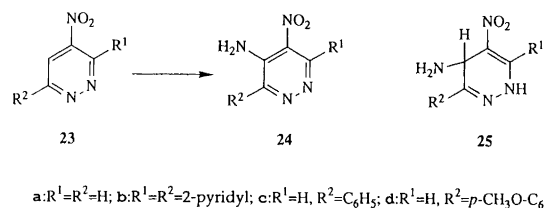
Scheme 7.

There is ample ¹H NMR spectroscopic evidence for the existence of the intermediate 4-amino-1,4-dihydropyridazine derivative **25b,c**.[7]

Treatment of 4-nitropyridazine 1-oxide (**26a**) and its derivatives **26b,c** with liquid ammonia/potassium permanganate gives in reasonable-to-good yields the corresponding 5-amino-4-nitropyridazine 1-oxides **27a** (75%), **27b** (54%) and **27c** (62%).[8] Until now, these reactions belong to the few examples of amination of nitroazine N-oxides (see also section C.2).

26   27

a:R¹=R²=H; b:R¹=OCH₃, R²=Cl; c:R¹=R²=OCH₃
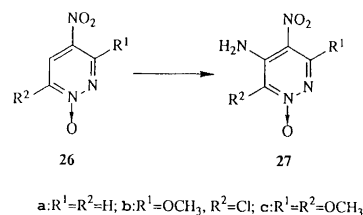
Scheme 8.

C. Amination of bicyclic nitroazines

C.1. Amination of nitroquinolines. The amination of all isomeric mononitroquinolines[9,10] and some of their derivatives,[9,11] using liquid ammonia/potassium permanganate, was studied; the results are summarized in Table 3.

28   29
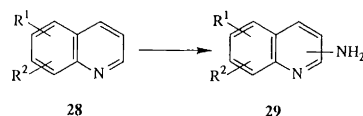
Scheme 9.

From the results in Table 3 it is evident that, in general, the mononitroquinolines are excellent substrates for $S_N H$ amination. The favoured position for attack by ammonia is always the one adjacent to the nitro group; when this position is blocked no product formation takes place. For example, 5-nitro-8(chloro, bromo, methyl)quinoline (**28d, 28e, 28f**) undergoes amination at C-6, but 5-nitro-6(chloro, bromo, methyl)quinoline does not yield an amino product.[11] Similarly, 8-nitro-6(chloro, bromo)-quinoline (**28j** and **28k**) gives amination at C-7, but

Table 3. Products and yields obtained in the animation of **28** with liquid ammonia/potassium permanganate.[9-11]

Substrate	R^1	R^2	Product	R^1	R^2	R^3	Yield (%)
Mononitroquinolines							
28a	3-NO$_2$	H	**29a**	3-NO$_2$	H	4-NH$_2$	65
28b	4-NO$_2$	H	**29b**	4-NO$_2$	H	3-NH$_2$	86
28c	5-NO$_2$	H	**29c**	5-NO$_2$	H	6-NH$_2$	33
28d	5-NO$_2$	8-Cl	**29d**	5-NO$_2$	8-Cl	6-NH$_2$	88
28e	5-NO$_2$	8-Br	**29e**	5-NO$_2$	8-Br	6-NH$_2$	85
28f	5-NO$_2$	8-CH$_3$	**29f**	5-NO$_2$	8-CH$_3$	6-NH$_2$	5
28g	6-NO$_2$	H	**29g**	6-NO$_2$	H	5-NH$_2$	10
28h	7-NO$_2$	H	**29h**	7-NO$_2$	H	8-NH$_2$	7
28i	8-NO$_2$	H	no product				
28j	8-NO$_2$	6-Cl	**29j**	8-NO$_2$	6-Cl	7-NH$_2$	30
28k	8-NO$_2$	6-Br	**29k**	8-NO$_2$	6-Br	7-NH$_2$	28
Dinitroquinolines							
28l	5-NO$_2$	7-NO$_2$	**29l**	5-NO$_2$	7-NO$_2$	8-NH$_2$	40
28m	5-NO$_2$	7-NO$_2$		no product			
28n	6-NO$_2$	8-NO$_2$	**29n**	6-NO$_2$	8-NO$_2$	5-NH$_2$	43

7-chloro-8-nitroquinoline is unreactive and starting material was recovered nearly quantitatively.[11] 2-Nitroquinoline does not undergo $S_N H$ amination, but does, to a small extent, undergo amino-denitration, to yield 2-aminoquinoline (5%).[9]

Based on yields of products and recovered material, the reactivity order in the series of unsubstituted nitroquinolines for the $S_N H$ substitution is 3-NO$_2$ ≃ 4-NO$_2$ > 5-NO$_2$ > 6-NO$_2$ > 7-NO$_2$ ≫ 8-NO$_2$.

FMO calculations were carried out using the MNDO-method on the regioselectivity of the amination of the parent nitroquinolines.[9] Both the LUMO and LUMO + 1 energy levels of the mononitroquinolines and the values of the coefficients at the carbons and ring nitrogen in the LUMO and LUMO + 1 orbitals were determined. Using $E_{HOMO} = -11.9$ eV for ammonia, the values of the stabilization energy (ΔE) for each position of the mononitroquinoline was calculated (see Table 4).[9]

The calculations confirm nicely the experimental results. In each of the parent compounds the highest contribution of stabilization energy is the position adjacent to the one occupied by the nitro group. Moreover, those calculations predict the order of reactivity, i.e.,

3-NO$_2$ ~ 4-NO$_2$ > 5-NO$_2$ ≃ 8-NO$_2$ > 6-NO$_2$ > 7-NO$_2$ > 2-NO$_2$. With the exception of the 8-NO$_2$ and 2-NO$_2$ compounds, this reactivity order is in agreement with the experiments. For comparison, calculations of the formal charges/electron densities on all annular carbon and nitrogen atoms (see Table 5) show that in general, these data do *not* confirm the results of experiments. Therefore, the conclusion that the electron density is not a suitable parameter for predicting the regiospecific $S_N H$ substitution in nitroquinolines seems justified. It should be noted at this point that similar reactions in some 3-nitropyridines are proposed to be controlled by coulombic interactions.[2] It has been suggested[2] that this is due to the lower charge differentiation on the atoms of both heterocyclic rings as compared with that in the 3-nitropyridines.

Extension of this work to the amination of dinitroquinolines shows that they exhibit behaviour similar to that of the mononitroquinolines: the amination always takes place at the position *ortho* to the nitro group and never at a position between two nitro groups. So, from 5,7-dinitroquinoline (**28l**) (and its 6-methyl derivative), the 8-amino compounds (**29l**) [and its methyl derivative (82%)] were obtained.[9,11] Similar behaviour is

Table 4. Values of ΔE/kcal mol^{-1} when a molecule of NH$_3$ attacks different positions in mononitroquinolines.

Mononitro-quinoline	N-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Position preference for NH$_3$ attack
3-NO$_2$	0.023	0.054	0.038	0.069	0.027	0.036	0.025	0.023	C-4 > C-2 > C-6
4-NO$_2$	0.029	0.043	0.067	0.046	0.012	0.032	0.028	0.014	C-3 > C-4 > C-2
5-NO$_2$	0.011	0.035	0.034	0.017	0.037	0.062	0.035	0.044	C-6 > C-8 > C-5
6-NO$_2$	0.017	0.030	0.040	0.036	0.056	0.036	0.047	0.031	C-5 > C-7 > C-3
7-NO$_2$	0.021	0.041	0.028	0.032	0.033	0.047	0.038	0.055	C-8 > C-6 > C-2
8-NO$_2$	0.011	0.041	0.032	0.023	0.046	0.036	0.060	0.038	C-7 > C-5 > C-2
2-NO$_2$	0.039	0.046	0.052	0.045	0.026	0.027	0.034	0.028	C-3 > C-2 > C-4

Table 5. Formal charge at the different atoms of mononitroquinolines.

Mono-nitro-quinoline	N-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	Position preference for NH_3 attack
2-NO$_2$	−0.1538	0.0575	−0.0608	0.0029	−0.0421	−0.0355	−0.0520	−0.0118	C-2 > C-4
3-NO$_2$	−0.2199	0.1250	−0.1577	0.1080	−0.0167	−0.0600	−0.0259	−0.0389	C-2 > C-4
4-NO$_2$	−0.1791	0.0508	−0.0405	−0.0093	−0.0331	−0.0456	−0.0468	−0.0230	C-2 > C-4
5-NO$_2$	−0.2160	0.0795	−0.1131	0.0119	−0.0598	0.0329	−0.0886	0.0306	C-2 > C-6 > C-8
6-NO$_2$	−0.2237	0.0990	−0.1263	0.0262	0.0634	−0.0869	−0.0055	−0.0344	C-2 > C-5 > C-4
7-NO$_2$	−0.2063	0.0779	−0.1028	0.0000	−0.0373	−0.0160	−0.0729	0.0639	C-2 > C-8 > C-4
8-NO$_2$	−0.2031	0.0980	−0.1205	0.0148	0.0210	−0.0937	0.0454	−0.0603	C-2 > C-7 > C-5 > C-4

observed with the 6,8-dinitroquinolines (see **28n**).[9] With 5,7-dinitro-8-methylquinoline no product is formed.[11]
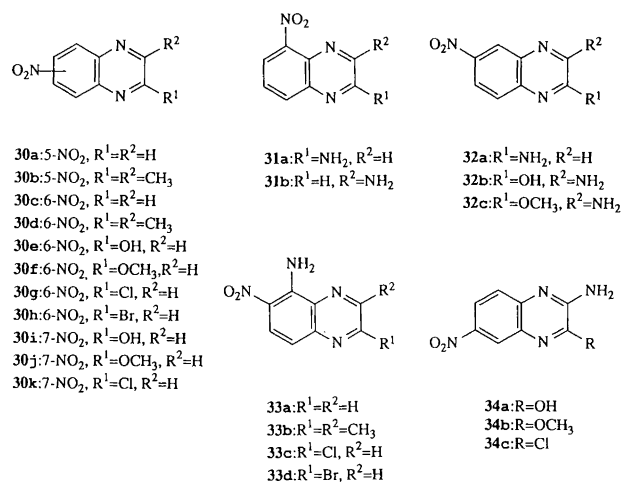
The mononitro compounds **28a** and **28b**, and the dinitroquinolines **28l** and **28n**, when dissolved in liquid ammonia, give easily detectable σ-amino adducts.[9, 10] This is exemplified by the 5,7-dinitro compound **28l** and 6,8-dinitro compound **28m** (see Table 6).[9] The upfield shift for H-8 in the σ adduct of **28l** and for H-5 in the σ-adduct of **28m** is clearly seen.

C.2. Amination of nitroisoquinolines. The amination of 1-, 5- and 8-nitroisoquinoline and some of their derivatives has also been investigated.[12] It was found that the pattern of reactivity of the $S_N H$ amination was very similar to that found for the nitroquinolines, with the exception of 1-nitroisoquinoline, which undergoes amino-derivation into 1-aminoisoquinoline only to a very small extent (2%). 5-Nitroisoquinoline gives 6-amino-5-nitro-isoquinoline in high yield (82%); as in the nitroquinolines the $S_N H$ substitution occurs at the position *ortho* to the nitro group and not at the position *ortho* to the ring nitrogen. In addition, 5-nitroisoquinoline *N*-oxide, when treated with liquid ammonia/potassium permanganate, is converted into the 6-amino compound. As observed before (see section A.1), 1-chloro-, 1-methoxy- and 1-bromo-5-nitroisoquinolines undergo the $S_N H$ substitution at C-6, without substitution of the nucleofugal group at position 1. For further details we refer to Ref. 12.

FMO calculations have been carried out concerning the regioselectivity of the amination of a few nitroiso-quinolines. These calculations show that the observed regioselectivity is *not* explained by considering the electron density at each carbon position, but is caused by

interaction of the HOMO orbital of ammonia with LUMO's of the nitroisoquinoline.[12] This result is in full agreement with those obtained in the nitroquinoline series.[3]

C.3. Amination of nitroquinoxalines. 5-, 6-, 7-Nitro-quinoxalines and several of their derivatives could be easily aminated with liquid ammonia/potassium permanganate.[13] The results are summarized in Table 7. Interesting differences in comparison with the amination of nitroquinolines and nitroisoquinolines are observed. Whereas, for example, in the amination of 5-nitro-quinoline the reaction takes place exclusively at C-6 (**28c → 29c**), 5-nitroquinoxaline aminates exclusively in the pyrazine ring (**30a → 31a** or **31b**). Somewhat similar

30a:5-NO$_2$, R^1=R^2=H
30b:5-NO$_2$, R^1=R^2=CH$_3$
30c:6-NO$_2$, R^1=R^2=H
30d:6-NO$_2$, R^1=R^2=CH$_3$
30e:6-NO$_2$, R^1=OH, R^2=H
30f:6-NO$_2$, R^1=OCH$_3$,R^2=H
30g:6-NO$_2$, R^1=Cl, R^2=H
30h:6-NO$_2$, R^1=Br, R^2=H
30i:7-NO$_2$, R^1=OH, R^2=H
30j:7-NO$_2$, R^1=OCH$_3$, R^2=H
30k:7-NO$_2$, R^1=Cl, R^2=H

31a:R^1=NH$_2$, R^2=H
31b:R^1=H, R^2=NH$_2$

32a:R^1=NH$_2$, R^2=H
32b:R^1=OH, R^2=NH$_2$
32c:R^1=OCH$_3$, R^2=NH$_2$

33a:R^1=R^2=H
33b:R^1=R^2=CH$_3$
33c:R^1=Cl, R^2=H
33d:R^1=Br, R^2=H

34a:R=OH
34b:R=OCH$_3$
34c:R=Cl

Scheme 10.

Table 6. Chemical shifts (δ) of ring hydrogens in compounds **28l** and **28m** in the solvents DMSO and NH$_3$(l).[a]

| Compd.	solvent	H-2	H-3	H-4	H-5	H-6	H-7	H-8
28l	DMSO-d_6	9.27	8.02	8.90		9.01		9.14
	NH$_3$	8.32	7.32	9.04		8.78		5.27
	Δδ	−0.95	−0.70	+0.14		−0.23		−3.87
28m	DMSO-d_6	9.23	7.90	8.89	9.07		9.36	
	NH$_3$	8.44	6.18	7.85	5.17		8.75	
	Δδ	−0.79	−1.72	−1.04	−3.90		−0.61	

[a] $J_{H_8-H_4}$ = 1.1 Hz; $J_{H_5-H_7}$ = 2.8 Hz.

Table 7. Products and yields (%) obtained in the amination of **30**, using liquid ammonia/potassium permanganate.[13]

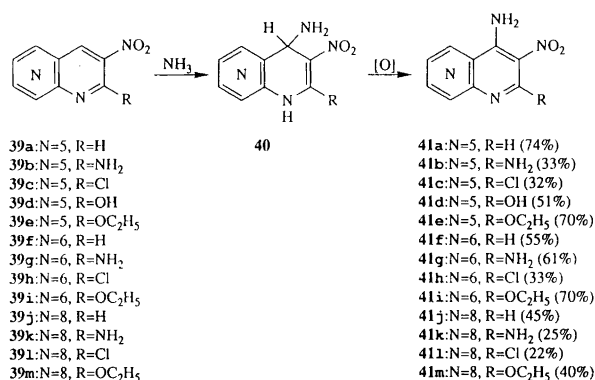| Substrate	Products (yield, %)
30a	31a or 31b (10)
30b	no products
30c	32a (51) + 33a (32)
30d	33b (18)
30e	32b (8)
30f	32c (5)
30g	33c (22) + 32a (15)
30h	33d (8) + 32a (18)
30i	34a (31)
30j	34b (28)
30k	34c (65)

behaviour is observed with 6-nitroquinoxaline (**30c**) which on amination yields as the main product the 2-amino compound (**32a**), along with the 5-amino compound (**33a**). It is evident as positions 2 and 3 are occupied by a methyl group, reaction cannot occur in the pyrazine ring (see **30b** and **30d**). In the case where a halogen atom is present at position 2 of the pyrazine ring in the nitroquinoxalines (see **30g** and **30h**) both $S_N H$ substitution at C-5 (**33c** and **33d**, respectively) and $S_N Ar$ replacement at C-2 to form **32a** take place.

C.4. Amination of nitroquinazolines. A number of compounds in this series have been investigated, i.e., 4-chloro-7-nitro- (**35**), 4-chloro-6-nitro-, 4-hydroxy-6-nitro-, 4-hydroxy-7-nitro, 4-amino-7-nitro- (**37**) and 4-amino-6-nitro-quinazoline.[14] Only 4-chloro-7-nitroquinazoline (**35**), on amination with liquid ammonia/potassium permanganate, gave, besides 4-amino-7-nitroquinazoline (**37**, 80%), 4,8-diamino-7-nitroquinazoline (**38**) in low yield (5%). The other compounds are unreactive. Since 4-amino-7-nitroquinazoline (**37**) is completely inert to amination by liquid ammonia/potassium permanganate, the conclusion that **36** is formed first by an initial $S_N H$ reaction at C-8, followed subsequently by amino-dehalogenation at C-4 seems justified. The low yield of **38** is due to the fact that the conversion of **37** → **38** does not take place, and that the rate of the competitive amino-dechlorination (**35** → **37**) is rather high. The reaction route for the formation of **38** is presented in Scheme 11 (**35** → **36** → **38**).
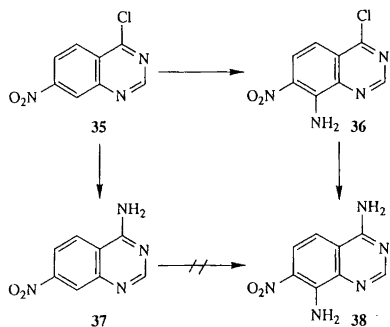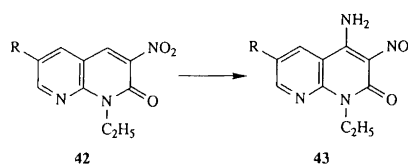

Scheme 11.

C.5. Amination of 3-nitronaphthyridines. The amination of the title compounds has been extensively studied.[15, 16, 17] Owing to the highly electrophilic character of the nitro-containing aza ring, the reaction can be easily achieved with liquid ammonia/potassium permanganate. Using this method the 2-R-3-nitro-1,X-naphthyridines ($X = 5$, 6, 8; **39a–m**) were successfully aminated to the 4-amino-3-nitronaphthyridines (**41a–m**) in reasonable-to-good yields (see Scheme 13). It is important to note that in these systems $S_N H$ substitution is also preferred to substitution of the nucleofugal group (chloro- or ethoxy-group) even when this group is present at an activated position.

|	
39a:N=5, R=H	41a:N=5, R=H (74%)
39b:N=5, R=NH₂	41b:N=5, R=NH₂ (33%)
39c:N=5, R=Cl	41c:N=5, R=Cl (32%)
39d:N=5, R=OH	41d:N=5, R=OH (51%)
39e:N=5, R=OC₂H₅	41e:N=5, R=OC₂H₅ (70%)
39f:N=6, R=H	41f:N=6, R=H (55%)
39g:N=6, R=NH₂	41g:N=6, R=NH₂ (61%)
39h:N=6, R=Cl	41h:N=6, R=Cl (33%)
39i:N=6, R=OC₂H₅	41i:N=6, R=OC₂H₅ (70%)
39j:N=8, R=H	41j:N=8, R=H (45%)
39k:N=8, R=NH₂	41k:N=8, R=NH₂ (25%)
39l:N=8, R=Cl	41l:N=8, R=Cl (22%)
39m:N=8, R=OC₂H₅	41m:N=8, R=OC₂H₅ (40%)

Scheme 12.

In all of the above-mentioned reactions there was no indication of the formation of 2-amino-3-nitronaphthyridines. Similarly in the amination of 2-R-3-nitronaphthyridines, in which R is a chloro- or ethoxy-group, no evidence for the formation of a 2,4-diamino compound was obtained. In the primarily formed 2-R-4-amino-3-nitronaphthyridines, the C-2 substituent is deactivated towards nucleophilic displacement by ammonia owing to the presence of the electron-donating amino group at C-4.

It is interesting to note that even 2-amino- and 2-hydroxy-3-nitronaphthyridines (3-nitro-1,2-dihydronaphthyridin-2-one) readily undergo $S_N H$ substitution. Apparently ammonia, being a weak base, is not able to deprotonate the hydroxy- or amino-group, which would then deactivate the system for an $S_N H$ substitution. Supporting evidence comes the fact that N-ethyl-3-nitro-1,2-dihydro-1,8-naphthyridin-2-one (**42**, R = H) can easily be aminated into the 4-amino compound (**43**, R = H).[14]
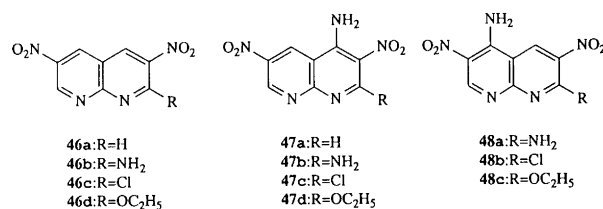

Scheme 13.

In all of the reactions described the intermediacy of the C-4 σ-adducts were identified by ^{1}H NMR spectroscopy (see **40**).[15-17] The 4-amino-3-nitro-1,X-naphthyridines (**44a–c**) do not give adducts at the unsubstituted C-2 position. These results show again that the position between the nitro group and the ring nitrogen is deactivated, as further illustrated by the fact that 8-amino-5-nitro-1,7-naphthyridine (**45**) does not undergo addition at C-6 on treatment with liquid ammonia.[14]

44a:N=5
44b:N=6
44c:N=8

45
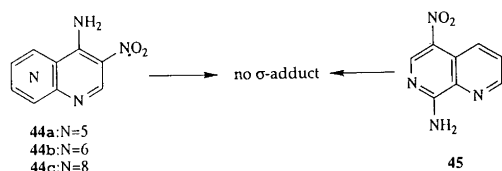
Scheme 14.

In order to explore further the potential of the liquid ammonia/potassium permanganate reagent for preparing amino compounds, which, by alternative routes, are difficult to obtain or not accessible, the amination of some relatively easily accessible 3,6-dinitro-1,8-naphthyridines (**46a–d**) was studied.[14, 18]

46a:R=H	**47a:**R=H	**48a:**R=NH$_2$
46b:R=NH$_2$	**47b:**R=NH$_2$	**48b:**R=Cl
46c:R=Cl	**47c:**R=Cl	**48c:**R=OC$_2$H$_5$
46d:R=OC$_2$H$_5$	**47d:**R=OC$_2$H$_5$	

Scheme 15.

It is reported that **46a** and **46b** are exclusively converted into the 4-amino compounds **47a** (40%) and **47b** (11%), respectively; **46d**, however, gives a mixture of the 4-amino compound **47d** (20%) and the 5-amino compound **48c** (14%), see Scheme 15. The 2-chloro compound **46c** yields a highly complicated mixture, from which the 5-amino compound (**48b**, 16%), the 2,4-diamino-1,8-naphthyridine (**47b**) and the 2,5-diamino derivative **48a** could be isolated.

There is ample NMR proof for the existence of intermediate C-4 σ-adducts.[19] In case of R = chloro or ethoxy both the C-4 adducts and the C-5 adducts were detected. The ratio between these adducts was found to be temperature dependent.

2-Nitro-1,X-naphthyridines ($X = 5$, 6 and 8) do not undergo an $S_N H$ substitution when treated with liquid ammonia/potassium permanganate.[13] Only to a very small extent does amino-denitration take place. In this respect 2-nitro-1,X-naphthyridines behave similarly to 2-nitroquinoline and 1-nitroisoquinoline.

D. Conclusions

The liquid ammonia/potassium permanganate system is found to be very effective and useful for the amination of the highly π-deficient nitro six-membered azaaromatics. The methodology is complementary to the previously reviewed amination procedure[1] using liquid ammonia/potassium amide/potassium permanganate.

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