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Author's Review

Potassium Permanganate in Liquid Ammonia. An Effective Reagent in the Chichibabin Amination of Azines

Henk C. van der Plas

Laboratory of Organic Chemistry, Agricultural University, De Dreijen 5, 6703 BC Wageningen, The Netherlands

and

Marian Wozniak

Institute of Organic Chemistry and Technology, Polytechnical University, Kraków, Poland

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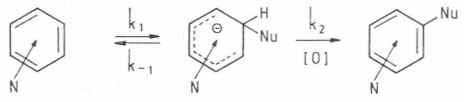
A special section of the S_NH reaction, notably Chichibabin aminations has been reviewed involving $KNH_2/NH_3/KMnO_4$ system as an reagent for amino-dehydrogenation.

A. *Introduction*

The replacement of hydrogen in azaromatics by a nucleophilic anionic or neutral reagent has been a subject of continuing interest for synthetic as well as physical-organic chemists.[1] These replacement reactions, designated by Russian authors as the symbol S_NH[1], can be described to occur according to an addition-elimination mechanism involving the intermediary Meisenheimer type σ-adduct *2*.[2] It is generally accepted that the elimination of hydrogen, attached to the sp^3-carbon atom, as a hydride ion, is difficult, since the hydride ion shows no tendency towards anionic stabilisation; consequently, severe conditions are required for elimination. An oxidising agent may be deliberately introduced in the reaction mixture and its effectiveness (expressed in k_2) depends on the ratio of the oxidation-reduction potential of intermediate *2* and the oxidant.



1 2 3

If $k_1 \gg k_{-1}$ and k_2 is large, product *3* can be obtained very easily. When $k_1 \gg k_{-1}$ but k_2 is small the reaction stops at the intermediate stage *2*. If $k_1 \ll k_{-1}$ and k_2 is large, intermediate *2* is present in a small steady-state concentration and the process only develops in the presence of an appropriate, selected oxidant.

In this review we only deal with a special section of the S_NH reaction i. e. the Chichibabin aminations.[3] The Chichibabin amination refers to a

reaction in which by action of sodamide or potassium amide in an aprotic solvent (dimethylaniline or aromatic hydrocarbons) the hydrogen in an heteroaromatic system, being attached to a ring carbon, is displaced by an amino group. This amino-dehydrogenation reaction takes place at elevated temperatures and has been successfully applied for aminating pyridines, quinolines and isoquinolines. Sodamide in liquid ammonia at low temperature has also been used as an aminating agent. It appeared that in this homogeneous system addition of potassium nitrate to the reaction mixture promoted the formation of amino products.[4,5] The introduction of an amino group in highly electron deficient systems, such as the diazines pyrazine[6] and pyridazine,[7] and triazine,[8] using sodamide in the aprotic solvent at elevated temperature could not be successfully achieved. The substrates decompose under the applied reaction conditions and, consequently, the yields of amino product are low, if any. No report is available on the amination of pyrimidine.

In the course of our ongoing studies on covalent amination of azaheteroaromatics we found that phenyl-1,2,4,5-tetrazine can be almost quantitatively converted into 3-amino-6-phenyl-1,2,4,5-tetrazine by potassium permanganate in liquid ammonia.[9,10,11] This surprisingly easy way of preparing amino--1,2,4,5-tetrazines by $NH_3/KMnO_4$ induced us to study the efficiency of this reagent, whether in combination with KNH_2 or not, to aminate azaheteroaromatics. Potassium permanganate in acetone has been used in reaction of CH-active compounds with azinium cations[12] but application of $KMnO_4$ in liquid ammonia has not been described earlier. The discussion of the results of this study on the Chichibabin amination using $NH_3/KMnO_4$ is the subject of this review.

In our studies the ^1H- and ^{13}C NMR spectroscopy proved to be an excellent tool for establishing the structures of the intermediary Meisenheimer σ-complexes *2* (Nu = NH_2). By these techniques the change of hybridisation (sp^2 sp^3) of the carbon atom which undergoes the addition of the amino group can easily be detected. Two spectroscopic parameters are of special interest: *i*) a considerable upfield shift for that specific carbon atom (about 80—90 ppm) and hydrogen (about 4—5 ppm) attached to that carbon and *ii*) change of the $J^{13}C—H$ from about 180 Hz (sp^2) to about 150 Hz (sp^3). It is beyond the scope of this report to discuss the structure of the intermediary σ-adducts in detail; we have to refer to the original literature. HMO calculations have shown[13] that the electron density is the most suitable parameter for predicting the orientation of the addition of the amide ion or ammonia. From our own studies we have to conclude that this prediction is only correct when the addition is kinetically controlled. In many cases, however, the amination is temperature dependent; we found that especially at higher temperatures the position of the addition is not determined by the electron density but by the thermodynamic stability of the σ-adduct formed. For a more detailed explanation see examples in several sections of this report.

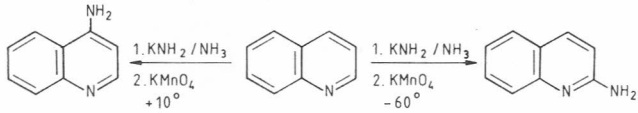
The procedure for carrying out the amination depends on the substrate. For electron-deficient systems, which require the strong nucleophilic amide ion for addition, one adds first the substrate to a solution of potassium amide in liquid ammonia, usually at —35 °C, and after some time solid $KMnO_4$. For highly electron-deficient systems, in which the weaker nucleophile liquid ammonia is able to form a σ-complex, two procedures were applied *i*) addition of solid $KMnO_4$ to a solution of the substrate in a great

excess of liquid ammonia or *ii*) addition of the substrate to a solution of $KMnO_4$ in excess of liquid ammonia. For each of the specific cases the reader has to consult the original literature.

B. *Amination of Monoazines*

B.1. Quinolines

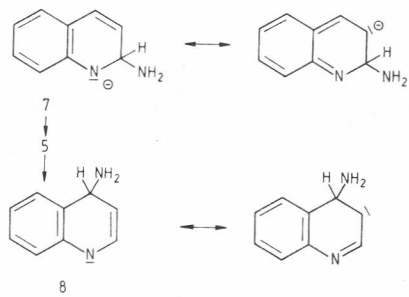
Treatment of quinoline (*5*) with $KNH_2/NH_3/KMnO_4$ at —60 °C gives 2-aminoquinoline (*6*, 55%). The amination is found to be strongly temperature dependent.[14] When quinoline is dissolved in KNH_2/NH_3 at —40 °C this solution is heated to about +10 °C, subsequently cooled and then treated with solid potassium permanganate nearly exclusively 4-aminoquinoline (*4*, 65%) is obtained; only a small amount of 2-aminoquinoline (*6*) is present in the reaction mixture.



4 5 6

This temperature dependency of the amination is supported by the result of a ^{1}H-NMR study. In a solution, obtained by dissolving *5* in KNH_2/NH_3 (thus without the presence of potassium permanganate) at —40 °C nearly exclusively the anionic σ-adduct *7* is present,[14,15] while in the solution being heated *to* +10 °C and then cooled to —40 °C only the C-4 adduct *8* can be detected. Apparently, at —40 °C species *7* is formed, which irreversibly converts into *8* (propably via *5*) at +10 °C. The formation of *7* is in agreement with calculations, showing that in *5* position 2 has the lowest electron density. The addition at C-2 is apparently a kinetically charged controlled reaction, the addition at C-4, leading to *8* is thermodynamically controlled.

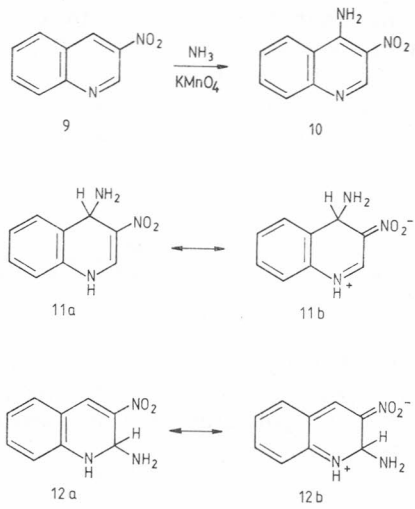
The reason why the anionic σ-adduct *8* is more stable than *7* has been explained by azaallylic resonance contribution being more important in *8* than in *7*. This contribution leads in *8* to a partial negative charge on C-3 and leaves one ring fully aromatic. This explanation is confirmed by the upfield shift value for C-3 in *8*. The parallel found in the temperature dependent addition pattern and product pattern leads to the unequivocal conclusion that the precursor of *6* is adduct *7* and that of *4* adduct *8*.



8

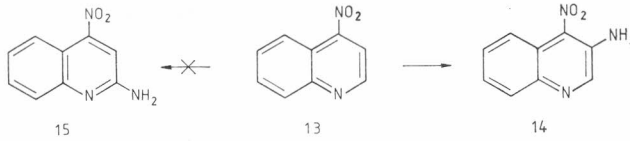
Due to the presence of an electron-withdrawing nitro group, enhancing the electrophilicity of the pyridine ring, the amination of 3-nitroquinoline (*9*)

only requires $NH_3/KMnO_4$.[14] In a yield of 65% 4-amino-3-nitroquinoline (*10*) is obtained when the amination is carried out at —40 °C. Temperature dependency is not observed. The formation of *10* is supported by ^{1}H-NMR spectroscopy, showing that in a solution of *9* in liquid NH_3 only the C-4 adduct *11* is formed. Adduct *11* is thermodynamically more stable than the C-2 adduct *12*, due to the important 6π-electron stabilisation in both resonance structures (*11a*—*11b*).



It is suggested that in the reaction of *m*-dinitrobenzene with the acetonide anion a biradical-dianion is involved,[16,17] and that in the amination of *9* a radical-anion may precede the formation of the Meisenheimer complex.[18] The occurrence of an electron transfer process certainly deserves further attention.

Treatment of 4-nitroquinoline (*13*) with $NH_3/KMnO_4$ did not give 2-amino-4-nitroquinoline (*15*), but 3-amino-4-nitroquinoline (*14*).[14] Apparently, the activating effect of the nitro group on its adjacent carbon surpasses that of the ring nitrogen on C-2. It is so far the sole example in our studies in which the amino group is introduced into a position *meta* towards the ring nitrogen.

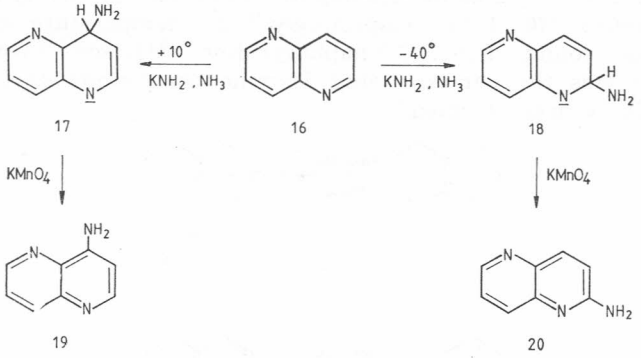


B.2 Naphthyridines

B.2.1 Parent Naphthyridines

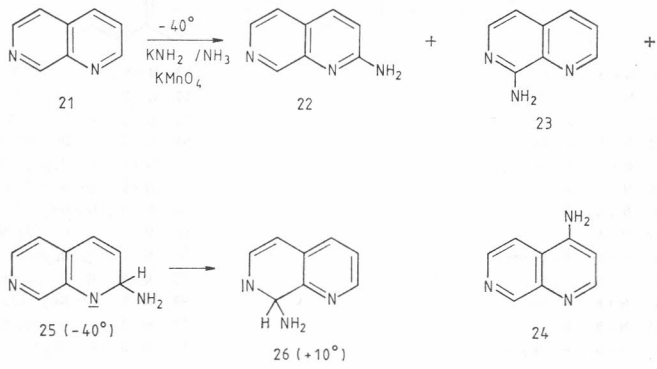
The amination of 1,X-naphthyridines (X = 5, 6, 7, 8) using $KNH_2/NH_3/KMnO_4$ has been extensively investigated.[19]

1,5-Naphthyridine (*16*) behaves quite similarly to quinoline. The amination is temperature dependent: at —40 °C the 2-amino compound (*20*, 36%) is obtained, but at +10 °C 4-amino-1,5-naphthyridine (*19*).[20]



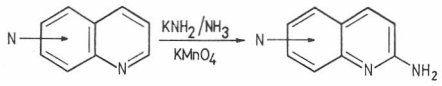
^{1}H- and ^{13}C-NMR spectroscopy convincingly shows that at —40 °C the kinetically favoured anionic Meisenheimer C-2 adduct *18* is formed,[20,21] and that at +10 °C the thermodynamically more favoured C-4 adduct *17* is present. It has been argued that the fast addition of the amide ion to *16* indicates that the electron distribution in the transition state of the addition is similar to that in the starting material. Consequently, the kinetically controlled addition takes place at the position with the lowest electron densitiy i. e. C-2. This result is in agreement with HMO calculations.[13] That the C-4 adduct *17* is more stable than the C-2 adduct *18* is due to the azaallylic contribution in *17*.[20] This contribution has indeed been confirmed by ^{13}C-NMR spectroscopy, showing the presence of a considerable charge on C-3.

The amination of 1,7-naphthyridine (*21*) was also found to be temperature dependent. At low temperature (—40 °C to —60 °C), a mixture of 2-amino--1,7-naphthyridine (*22*, 26%), 8-amino-1,7-naphthyridine (*23*, 19%) and 4--amino-1,7-naphthyridine (*24*, 10%) was obtained.[20] $KMnO_4$ treatment of a solution of *21* in KNH_2/NH_3 first being heated at +10 °C, gave only *23*. NMR spectroscopy confirms the presence of both C-2 adduct *25* and C-8 adduct *26* at —40 °, and the exclusive presence of *26* at +10 °C.[20] Apparently, by heating from —40 °C to +10 °C the C-2 adduct *25* irreversibly converts into the C-8 adduct *26* probably via *21*.



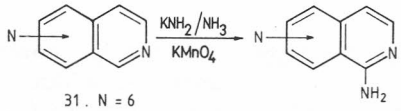
The formation of *24* suggests the intermediacy of a C-4 adduct; however, no indication of its existence has been found by NMR-spectroscopy.

1,6-Naphthyridine (*27*) and 1,8-naphthyridine (*28*) were converted with $KNH_2/NH_3/KMnO_4$ into 2-amino-1,6-naphthyridine (*29*, 35—40%) and 2-amino--1,8-naphthyridine (*30*, 10%), respectively.[20] No temperature effect on the amination was found. From 2,6-naphthyridine (*31*) and 2,7-naphthyridine (*32*) in low yields the corresponding 1-amino compounds *33* (18%) and *34* (8%), respectively, were formed.[22]



27. N = 6
28. N = 8

29. N = 6
30. N = 8

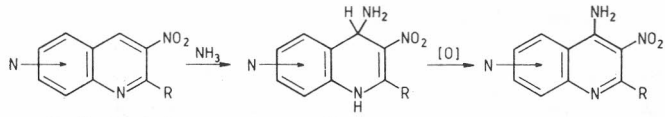


31. N = 6
32. N = 7

33. N = 6
34. N = 7

B.2.2 Nitronaphthyridines

Among the substituted naphthyridines the nitronaphthyridines are the most extensively studied. Due to high electrophilicity of the nitro-containing ring, the reaction can be carried out with the reagent $NH_3/KMnO_4$; thus, KNH_2 is not required. With this reagent 2-R-3-nitro-1,X-naphthyridine (X = 5, 6 and 8) (*35*—*47*) are successfully aminated to 4-amino-3-nitronaphthyridines (*48*—*60*).[23-25] It is important to note that in these systems the amino-dehydrogenation takes place *without* displacement of the chloro or ethoxy substituent, even when this substituent is present at an activated position. We refer to the 2-chloro compounds *37*, *42* and *46* and the 2-ethoxy compounds *39*, *43* and *47*, both series giving the 4-amino compounds. Although not always in excellent yields, compounds which are otherwise not easily accessible by this method become available. The interesting property of $NH_3/KMnO_4$ acting



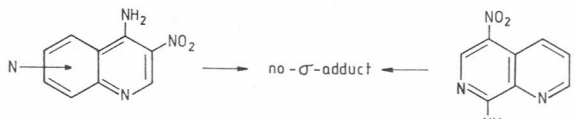
35. N = 5, R = H
36. N = 5, R = NH_2
37. N = 5, R = Cl
38. N = 5, R = OH
39. N = 5, R = OC_2H_5
40. N = 6, R = H
41. N = 6, R = NH_2
42. N = 6, R = Cl
43. N = 6, R = OC_2H_5
44. N = 8, R = H
45. N = 8, R = NH_2
46. N = 8, R = Cl
47. N = 8, R = OC_2H_5

61

48. N = 5, R = H (74%)
49. N = 5, R = NH_2 (33%)
50. N = 5, R = Cl (32%)
51. N = 5, R = OH (51%)
52. N = 5, R = OC_2H_5 (70%)
53. N = 6, R = H (55%)
54. N = 6, R = NH_2 (61%)
55. N = 6, R = Cl (33%)
56. N = 6, R = OC_2H_5 (70%)
57. N = 8, R = H (45%)
58. N = 8, R = NH_2 (25%)
59. N = 8, R = Cl (22%)
60. N = 8, R = OC_2H_5 (40%)

as aminating agent without attacking nucleophugic groups makes this reagent attractive for aminating systems with labile groups. Examples of reactions in which amination by hydrogen displacement is preferred to halogen displacement were very rare till now. An instance of substitution of hydrogen rather than halogen has been reported in the reaction of cyclohexylamine with s-chloroanthraquinone thiadiazole.[26]

In all the above-mentioned reactions no indication of the formation of 2-amino-3-nitronaphthyridines was obtained. Apparently, the addition to position 4, yielding *61* is more favourable than addition at position 2, due to the thermodynamic stability argument that the C-4 adduct is more resonance--stabilized than the C-2 adduct (see discussion in section B.1). In the presence of the oxidant, the loss of the hydrogen at C-4 in *61* takes place fast. Also, in the amination of the 2-R-3-nitronaphthyridines, in which R=Cl or OEt, no indication of the formation of 2,4-diamino-3-nitronaphthyridine was observed. This is apparently due to the fact that in the 2-R-4-amino-3-nitronaphthyridines, the C-2 substituents are deactivated for nucleophilic attack as a result of the presence of the amino group at C-4. The fact that the 2-R-3-nitronaphthyridines do not require KNH_2 as aminating agent, but only the weaker nucleophile NH_3 has made it possible to aminate the 2-hydroxy and 2-amino compound (*38*, *41* and *45* respectively). In the presence of KNH_2 deprotonation of the hydroxy and amino group takes place, preventing further nucleophilic attack in the anions formed. With NH_3, on the contrary, the hydroxy or amino group are not, or only partly, deprotonated. Thus, $NH_3/KMnO_4$ is a more useful reagent for aminating these systems.



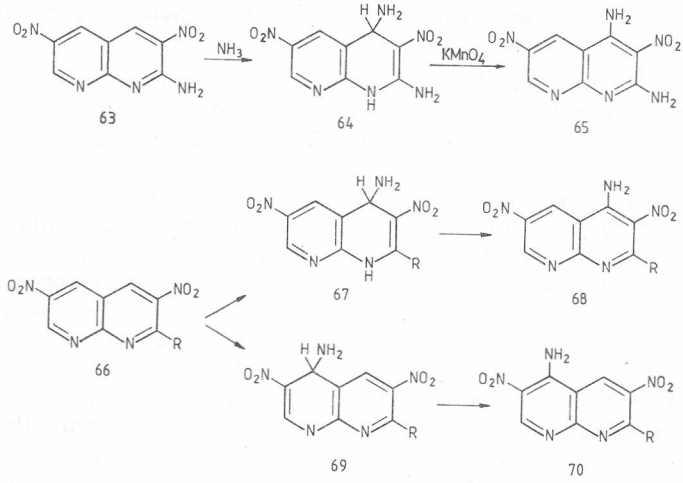
48 N = 5
53 N = 6
57 N = 8

62

In all the aminations described in this section the intermediary C-4 adducts are identified by NMR spectroscopy. It is interesting to mention that the 4-amino-3-nitro-1,X-naphthyridines [X = 5 (*48*), X = 6 (*53*), and X = 8 (*57*)] do not undergo addition at the unsubstituted C-2 position.[23–25] 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 (*62*) does not give addition at C-6 on treatment with NH_3.[27]

In order to explore further the potentiality of the $NH_3/KMnO_4$ reagent of preparing compounds, which by alternative routes are difficult to obtain or not accessible, we studied the amination of the highly activated 3,6-dinitro-1,8-naphthyridine system.[28,29] It was found that with $NH_3/KMnO_4$ at —40 °C 2-amino-3,6-dinitro-1,8-naphthyridine (*63*) can be converted into 2,4-diamino-3,6-dinitro-1,8-naphthyridine (*65* 11%), that 2-ethoxy-3,6-dinitro--1,8-naphthyridine (*66*, R=OC_2H_5) yields a mixture of 4-amino- (*68*, R=OC_2H_5, 20%) and 5-amino-2-ethoxy-3,6-dinitro-1,8-naphthyridine (*70*, R=OC_2H_5, 14%) and that 2-chloro-3,6-dinitro-1,8-naphthyridine (*66*, R=Cl) gives a highly com-

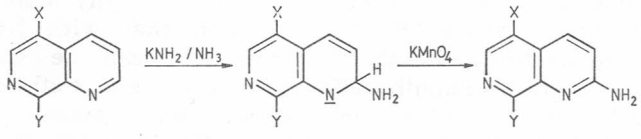
plicated reaction mixture, containing mainly the 5-amino compound *70* (R=Cl, 16%) together with 2,4-diamino-3,6-dinitro- (*68*, R=NH_2) and 2,5-diamino--3,6-dinitronaphthyridines (*70*, R=NH_2) (yield *68* + *70* = 30%).[28]



The formation of the intermediary neutral σ-adduct *64*, obtained when dissolving *63* in liquid ammonia, was unequivocally established by NMR--spectroscopy.[29] Dissolving *66* (R=Cl) or *66* (R=OC_2H_5) in liquid ammonia leads to the formation of both the C-4 adduct (*67*, R=Cl, OC_2H_5) and the C-5 adduct (*69*, R=Cl, OC_2H_5), as observed by NMR spectroscopic techniques. The ratio *67* (R=Cl)/*69* (R=Cl) = 50 : 50 (at —45 °C) but changes to 85 : 15 (at room temperature); the ratio *67* (R=OC_2H_5)/*69* (R=OC_2H_5) is less dependent on the temperature.[29]

B.2.3 Halogenonaphthyridines

As already mentioned in section B.2.2, the solution of $KMnO_4$ in NH_3 is a very effective reagent in aminating chloronitronaphthyridines while avoiding an amino-dechlorination displacement reaction. We have observed that halogenonaphthyridines, containing no nitro group(s), require $KNH_2/NH_3/KMnO_4$ to be aminated. However, despite the presence of the strong nucleophilic potassium amide, no amino-dehalogenation is observed; only aminodehydrogenation takes place. Examples of these amination reactions are the conversion of 5,8-dichloro- (*71*, X=Y=Cl), 5,8-dibromo (*71*, X=Y=Br) and 8-chloro-1,7-naphthyridine (*72*) into the corresponding 2-amino-1,7-naphthyridines *74* and *75* respectively[23,28] (yields 40—50%).



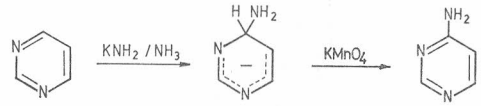
The displacement of the halogeno atom at C-5 in *71* and *72* by an amino group under these conditions is very unlikely since an $S_N(AE)$ process at C-5 does not occur at such a low temperature and an $S_N(EA)$ process involving a 5,6-didehydro-1,7-naphthyridine can also be excluded.

NMR-spectra of solutions of the compounds *71*—*72* in liquid ammonia clearly feature the presence of the C-2 σ-adducts *73* being the precursors of the 2-amino compounds *74*—*75*.[23,31,32]

C. *Amination of Diazines*

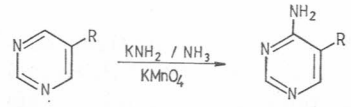
C.1. Pyrimidines

Pyrimidine (*76*) was the first heterocycle that was shown by ^{1}H-NMR spectroscopy to give a σ-adduct with KNH_2/NH_3 at —40 °C.[15,33] The anionic σ-adduct formed was proved to have the structure of 4-aminodihydropyrimidinide (*77*). Applying $KMnO_4$ as oxidant we could convert *77* successfully into 4-aminopyrimidine (*78*) in a reasonable yield (72%); a small amount of 2-aminopyrimidine was also formed.[34]



76 *77* *78*

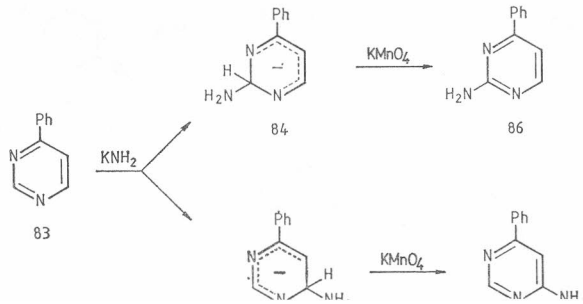
In a very similar way 5-phenyl- (*79*) and 5-bromopyrimidine (*80*) are converted into the corresponding 4-amino compounds *81* (70%) and *82* (37%), respectively; in the amination of *79*, besides *81*, a small amount of 2-amino-5-phenylpyrimidine was formed.



79, R = Ph
80. R = Br

81. R = Ph
82. R = Br

A more extensive amination study was carried out with 4-phenylpyrimidine (*83*).[35] It appeared in this study that the period of time, between dissolving *83* in the KNH_2/NH_3 and addition of $KMnO_4$ considerably deter-



83 *84* *86*

mined the course of the reaction. If $KMnO_4$ is added after one minute, the reaction mixture consists of 55% of 2-amino-4-phenylpyirimidine (*86*) and 45% of 6-amino-4-phenylpyrimidine (*87*). Addition of $KMnO_4$ two hours after the dissolving of *83* in KNH_2/NH_3 gave a reaction mixture containing 19% of *86* and 81% of *87*. This result indicates that *i*) in *83* two sites are susceptible to nucleophilic attack i. e. position 2, yielding *84* and position 6, yielding *85* and *ii*) σ-adduct *84* over an extended period of time can rearrange into σ-adduct *85* (via *83*).

^{1}H-NMR spectroscopy confirms the presence of both anionic σ-adducts *84* and *85*.[36] After resting of the reaction mixture the amount of *84* diminished and finally disappeared. Apparently, we are dealing with the kinetically favoured formation of *84* which slowly converts via *83* into the more stable adduct *85*.[36a]

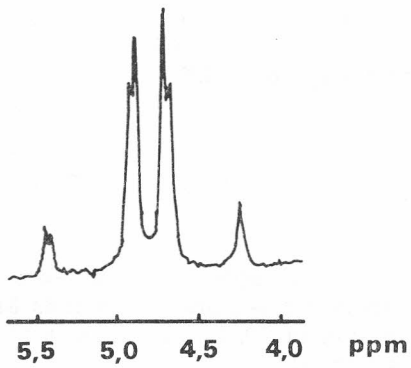
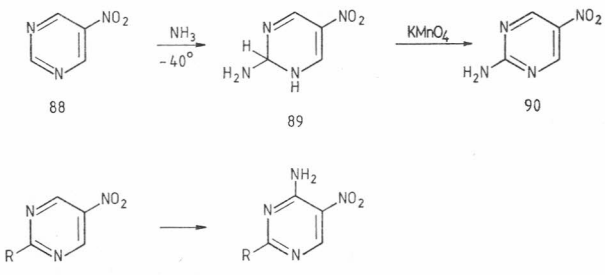
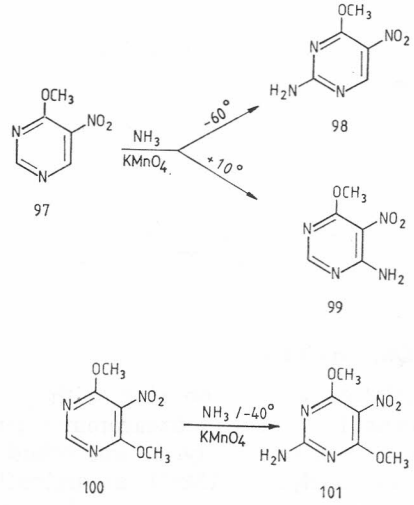


Figure 1. The signals for H-2 in *85* and H-6 in *84* lie under the phenyl multiplet.

5-Nitropyrimidine (*88*) and its derivatives *91*—*93* can be successfully aminated using the very mild reagent $NH_3/KMnO_4$ at low temperature.[37] In a yield of 45% 2-amino-5-nitropyrimidine (*90*) is obtained. There is convincing NMR-evidence for the intermediary existence of the C-2 adduct (*89*). HMO calculations on the electron density (*qr*) in 5-nitropyrimidine shows that *qr* of position 2 is the lowest. Thus, this result is in agreement with the discussion mentioned in the introduction that the kinetically controlled addition takes place at the position with the lowest electron density.

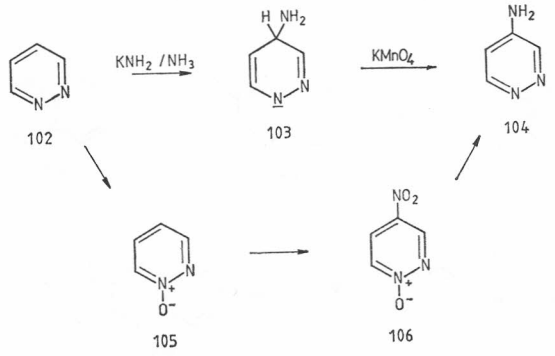


We observed that when position 2 is blocked, the position of amination changes from C-2 to C-4. 2-Methyl- (*91*), 2-methylthio (*92*) and 2-phenyl-5--nitropyrimidine (*93*) are conveniently converted into the 4-amino compounds *94* (53%), *95* (72%) and *96* (50%).[37] Especially worth mentioning is the fact that in compound *92* no replacement of the nucleophugal methylthio group takes place during amination, again showing the unique character of the reagent. Temperature dependency of the amination has also been found in the amination of 4-methoxy 5-nitropyrimidine (*97*). Treatment of *97* with $NH_3/KMnO_4$ at —60 °C to —70 °C gave 2-amino-4-methoxy-5-nitropyrimidine (*98*, 50%), while 6-amino-4-methoxy-5-nitropyrimidine (*99*) was obtained (yield 65%) when a solution of *97* in liquid NH_3 was allowed to stand for 5 minutes at room temperature, cooled to —40 °C and then treated with $KMnO_4$. 4,6--Dimethoxy-5-nitropyrimidine (*100*) gives the 2-amino compound (*101*, 53%).[37]



C.2 Pyridazines and Pyrazine

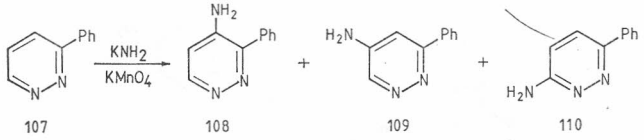
Although pyridazine was reported to resist Chichibabin amination[7] $KNH_2/NH_3/KMnO_4$ appeared to be a very effective reagent for aminating pyridazine (*102*) into 4-aminopyridazine (*104*) with an excellent yield (91%).[34] The method is far superior to the one involving oxidation of *102* into its

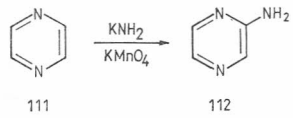


N-oxide (*105*), nitration of the pyridazine N-oxide into 4-nitropyridazine 1-oxide (*106*), followed by reduction of the 4-nitro compound.[38,39] The overall yield *102* → *105* → *106* → *104* is much lower than in our amination-oxidation procedure. The intermediary 4-aminodihydropyridazinide (*103*) has been identified by ^{1}H-NMR spectroscopy.[15,33]

3-Phenylpyridazine (*107*), when treated with $KNH_2/NH_3/KMnO_4$ gives a mixture of 4-amino- (*108*, 49%), 5-amino- (*109*, 18%) and 6-amino-3-phenylpyridazine (*110*, 5%).[34] This mixture could be separated by thin layer chromatography; however, the working-up procedure is tedious and, therefore, the method is not appropriate for the preparation of *108*, *109* or *110*.[34]

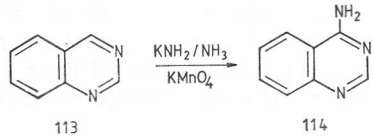
Amination of pyrazine (*111*) by $KNH_2/NH_3/KMnO_4$ at —40 °C has been reported to give 2-aminopyrazine (*112*, 65%).[34] This method for the preparation of *98* is much better than the one using only sodamide (yield of *112*, 3%).[6]

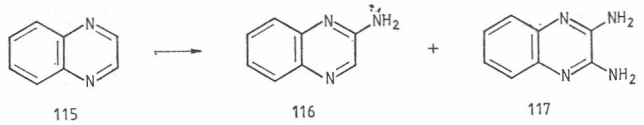


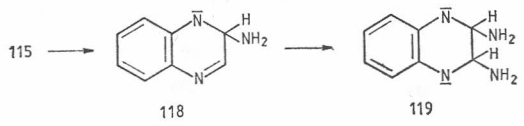


C.3 Quinazolines and Quinoxalines

The effect of annelating a benzene ring with pyrimidine and pyrazine on the electrophilic behaviour of the azaaromatic ring towards aminating agents has been the subject of our study. It was found that quinazoline (*113*), like pyrimidine, requires $KNH_2/NH_3/KMnO_4$ as aminating agent; substitution of hydrogen at C-4 by an amino group takes place, yielding 4-aminoquinazoline (*114*).[34]



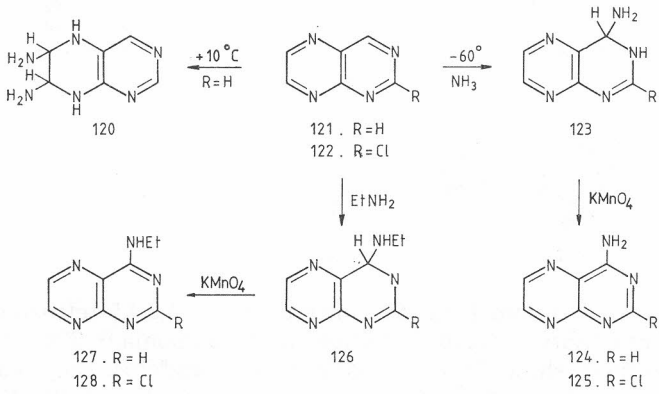




An increased electrophilic character was observed with quinoxaline (*115*).[34] On amination with $KNH_2/NH_3/KMnO_4$, besides the 2-amino compound (*116*, 53%), 2,3-diaminoquinoxaline (*117*, 23%) was formed. Compound *117* could be obtained as nearly the sole product when $KMnO_4$ was added 20 min after dissolving *115* in KNH_2/NH_3. Yield *116*, 4%, *117*, 57%. Undoubtedly, the 2,3-diamino σ-adduct *119* is slowly formed and it requires some time to shift the equilibrium *115* ⇆ *118* ⇄ *119* to the right.

C.4 Pteridines

Pteridine (*121*) exhibits addition with liquid ammonia at —60 °C at C-4, forming the neutral species 4-aminodihydropteridine (*123*, R=H).[40] When this solution is held at +10 °C the stable and isolable 6,7-diamino-5,6,7,8--dihydropteridine (*120*) is obtained. The σ-adduct (*123*, R=H) can easily be oxidised with $KMnO_4$ into 4-aminopteridine (*124*, 49%).[41] So far, all attempts to oxidise *120* into 6,7-diaminopteridine have failed. Also 2-chloropteridine (*122*), having a labile chloro atom at the C-2 position, can conveniently be converted into 4-amino-2-chloropteridine (*125*, 94%) on treatment with $NH_3/KMnO_4$.[41] The intermediacy of *123* (R=Cl) could be proved by NMR spectroscopy.



A similar procedure was applied to introduce an ethylamino group in position 4 of the pteridine ring. When *121* or *122* was added to a solution of $KMnO_4$ in ethylamine at —75 °C, the 4-ethylaminopteridines (*127*, 35%) and (*128*, 58%), respectively, are obtained.[41] Intermediates in these amination reactions are very probably the neutral σ-adducts *126*. By NMR spectroscopy species *126* (R=H) could be detected at —75 °C; σ-adduct *126* (R=Cl) could not be trapped by NMR techniques due to its instability. In the presence of the oxidant this unstable σ-adduct *126* (R=Cl) is quickly converted into *128* before decomposition takes place.

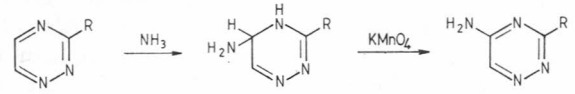
D. *Amination of Triazines and Tetrazines*

The enhanced electrophilicity of the triazine and tetrazine ring, in comparison with the diazines, makes 1,2,4-triazine (*129*) and even its C-3 derivatives, having in that position electron donating substituents (*130—134*), very suitable substrates for addition with ammonia.[42] The neutral intermediary

species 5-aminodihydro-1,2,4-triazines (*135*) are formed; these structures are proved by ^{1}H-NMR spectroscopy. The adducts *135* can be easily converted into the corresponding 5-amino-1,2,4-triazines by treatment with $KMnO_4$.[43] The yields obtained are for *136* (95%), *137* (63%), *138* (89%), *139* (30%), *140* (80%) and for *141* (87%). These yields are generally higher than the ones, reported for the majority of the compounds, mentioned in previous sections.

In the 1,3,5-triazine series amination of 2,4-diphenyl-1,3,5-triazine (*142*) by $NH_3/KMnO_4$ has been reported to give 6-amino-2,4-diphenyl-1,3-5-triazine (*143*, 83%) in a good yield.[34]

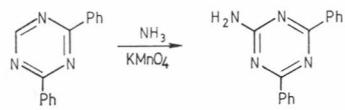
The effectiveness of this amination method is illustrated by the fact that in earlier reports the amination of *142* into *143* was mentioned to occur when using a great excess of potassium amide in liquid ammonia and a reaction time of 72 hrs![44]



129. R = H
130. R = CH_3
131. R = C_6H_5
132. R = NH_2
133. R = OCH_3
134. R = SCH_3

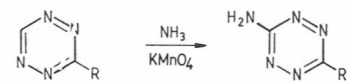
135

136. R = H
137. R = CH_3
138. R = C_6H_5
139. R = NH_2
140. R = OCH_3
141. R = SCH_3



142 143

As already mentioned in the introduction, 1,2,4,5-tetrazines exhibit a pronounced reactivity towards addition with ammonia.[11] The aminodihydrotetrazines formed show homoaromatic properties;[9,10,45] they can be easily reconverted into their 6π-electron system by oxidation with $KMnO_4$. Thus, from the 3-alkyl(aryl)-1,2,4,5-tetrazines (*144—147*) the corresponding 6-aminotetrazines [*148* (80%); *149* (72%); *150* (74%); *151* (81%)] are formed.[11]

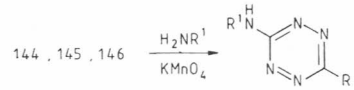


144. R = CH_3
145. R = t-C_4H_9
146. R = C_6H_5
147. R = p-Br-C_6H_4

148. R = CH_3
149. R = t-C_4H_9
150. R = C_6H_5
151. R = p-Br-C_6H_4

This easy procedure for obtaining aminotetrazines can also be applied to the preparation of (alkylamino)tetrazines. This is illustrated by the conversion of *144* into the 6-alkylaminotetrazines *152a* (76%), *152b* (35%), *152c* (35%), *153a* (81%), *153b* (47%), *153c* (58%), *154a* (59%), *154b* (44%), *154c* (38%), *154d* (18%) using the appropriate alkylamine with potassium perman-

ganate.[11] Attempts at using this method to introduce the arylamino group failed. The low nucleophilic character of the aromatic amine prohibits addition to the tetrazine ring.



144 , 145 , 146 → (H_2NR^1, $KMnO_4$) → 152 , 153 , 154

a , $R^1 = C_2H_5$
b , $R^1 = n\text{-}C_4H_9$
c , $R^1 = n\text{-}C_8H_{17}$
d , $R^1 = i\text{-}C_3H_7$

152. $R = CH_3$, R^1 = a, b, c
153. $R = t\text{-}C_4H_9$, R^1 = a, b, c
154. $R = C_6H_5$, R^1 = a, b, c, d

Conclusion

The report shows the potential application of $KNH_2/NH_3/KMnO_4$ as a useful reagent for amino-dehydrogenation. This oxidative-amination method can be carried out with $NH_3/KMnO_4$ in highly electron deficient systems, like nitronaphthyridines, nitropyrimidines, triazines, tetrazines and pteridines. This method can also be applied with substrates, which have substituents with a highly nucleophugic character. The procedure can be considered a useful extension of the Chichibabin amination.

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36a. The referee suggested that the conversion *84*—*85* may involve a 1,5[H]-shift. Although in this particular case this shift may possibly occur, there are reasons to believe that in general the isomerisation of amino σ-adducts does not involve a sigmatropic shift, since a) the amino group probably has a lower migratory aptitude than hydrogen and sigmatropic [H]-shifts have, however, never been observed in these adducts, b) the isomerisation of the 2-amino-dihydroquinolinide *7* into the C-4 adduct *8* would involve an antarafacial 1,3-[NH_2] shift, which is very unlikely. Also, the isomerisation of the 4-aminodihydropteridine (*123*) into the 6,7-diaminotetrahydropteridine *120* can hardly be explained by a sigmatropic [NH_2]-shift.
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POVZETEK

Kalijev permanganat v tekočem amoniaku. Učinkovit reagent pri Čičibanovem aminiranju azinov

Henk C. van der Plas in Marian Wozniak

Ta pregledni članek obravnava potencialno uporabnost sistema $KNH_2/NH_3/KMnO_4$ kot uporabnega reagenta za aminodehidrogeniranje. Metodo oksidativnega aminiranja z $NH_3/KMnO_4$ lahko uporabljamo pri sistemih s primanjkljajem elektronov, kot so npr. nitronaftiridini, nitropirimidini, triazini, tetrazini in pteridini. Prav tako lahko uporabljamo to metodo pri sistemih s substituenti z močno nukleofilnim značajem. Reakcija predstavlja uporabno razširitev Čičibanovega aminiranja.