On the Amination of Azaheterocycles. A New Procedure for the Introduction of an Amino Group (1)

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A new method of amination of diazines and triazines, using potassium amide, liquid ammonia and potassium permanganate, has been described.

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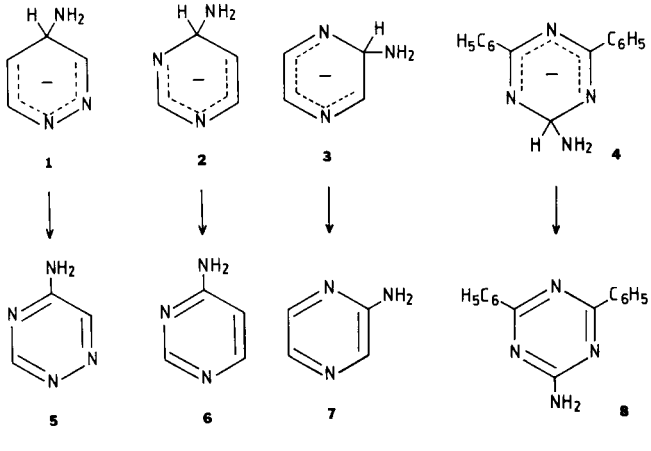
The Chichibabin amination of the three parent diazines has been reported to give the following results. Pyrazine undergoes amination on treatment by sodamide in inert solvents (or even without use of a solvent), yielding aminopyrazine in low yield (3). With potassium amide in liquid ammonia pyrazine forms an "Opaque dirty green" solution, from which no definitive product was isolated (4). No report is available on the amination of pyrimidine, and pyradizine was found to resist the Chichibabin amination (5).

It is interesting that the anionic σ-adducts **1-3** are easily formed, when pyrazine, pyrimidine and pyridazine are dissolved in liquid ammonia, containing potassium amide (potassium amide/liquid ammonia) (6). This addition reaction seems almost irreversible ($K \leq 10^{-5}$ *M*).

Scheme 1

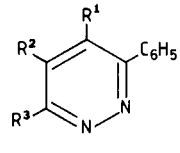


The highly electron-deficient 1,2,4,5-tetrazines and pteridines easily give neutral σ-adducts (7-9) when they are dissolved in liquid ammonia without containing potassium amide. We have discovered recently that these σ-adducts can easily be oxidized by potassium permanganate into the corresponding 3-amino-1,2,4,5-tetrazines (7) and 4-aminopteridines (10). These results induced us to try this oxidation method for conversion of the anionic σ-adducts **1-3** into the corresponding amino compounds **5-7**. This approach appeared to be highly successful. 4-Aminopyridazine (**5**), 4-aminopyrimidine (**6**) and aminopyrazine (**7**) are easily obtained and in good-to-excellent yields (see Table, entries 1,3,6), when the corresponding parent diazines are dissolved in potassium amide/liquid ammonia and potassium permanganate was added.

This method was also successfully applied to introducing an amino group into a few derivatives of pyridazine and pyrimidine. 3-Phenylpyridazine (**9a**) gives in 72% yield a mixture of 4-, 5- and 6-amino-3-phenylpyridazine (**9b-9d**) (see entry 2). The main compontents in the mixture are, as expected, the 4- and 5-amino compounds **9b** and **9c**. Both compounds **9b** and **9c** are new, and their structures could easily be established by taking into account the difference in coupling constants between the *ortho*-hydrogens in the pyridazine ring in **9b** ($J_{5,6} = 6$ Hz) and the *meta*-hydrogens in **9c** ($J_{4,6} = 2$ Hz) (11).

Similarly, when treating 5-bromopyridine (**10a**) and 5-phenylpyrimidine (**10b**) with potassium amide/liquid ammonia and potassium permanganate (see entries 4 and 5), the corresponding 4-aminopyrimidines **10c** and **10d** were obtained; in the reaction of **10a** also some debromination occurs, 4-aminopyrimidine (**6**) being formed.

Scheme 2



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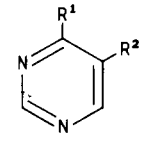
a) $R^1 = R^2 = R^3 = H$
b) $R^1 = NH_2$, $R^2 = R^3 = H$
c) $R^1 = H$, $R^2 = NH_2$, $R^3 = H$
d) $R^1 = R^2 = H$, $R^3 = NH_2$



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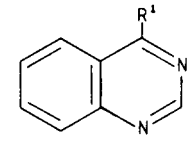
a) $R^1 = H$, $R^2 = Br$
b) $R^1 = H$, $R^2 = C_6H_5$
c) $R^1 = NH_2$, $R^2 = Br$
d) $R^1 = NH_2$, $R^2 = C_6H_5$



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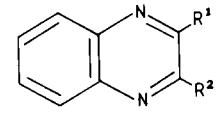
a) $R^1 = H$
b) $R^1 = NH_2$



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a) $R^1 = R^2 = H$
b) $R^1 = H$, $R^2 = NH_2$
c) $R^1 = R^2 = NH_2$

Table

Amination of Diazines and Triazines by Liquid Ammonia-Potassium Amide in the Presence of Potassium Permanganate

Entry	Substrate	Product(s)	Yield (%)
1	pyridazine	4-NH_2-pyridazine (**5**)	91
2	3-C_6H_5-pyridazine (**9a**)	4-NH_2-3-C_6H_5-pyridazine (**9b**)	49
		5-NH_2-3-C_6H_5-pyridazine (**9c**)	18
		6-NH_2-3-C_6H_5-pyridazine (**9d**)	5
3	pyrimidine	4-NH_2-pyrimidine (**6**)	72
4	5-Br-pyrimidine (**10a**)	4-NH_2-pyrimidine (**6**)	37
		4-NH_2-5-Br-pyrimidine (**10c**)	28
5	5-C_6H_5-pyrimidine (**10b**)	4-NH_2-5-C_6H_5-pyrimidine (**10d**)	70
6	pyrazine	NH_2-pyrazine (**7**)	65
7	di-C_6H_5-1,3,5-triazine	2-NH_2-4,6-di-C_6H_5-1,3,5-triazine (**8**)	83
8	quinazoline (**11a**)	4-NH_2-quinazoline (**11b**)	62
		4,4'-diquinazolylamine	2
9	quinoxaline (**12a**)	2-NH_2-quinoxaline (**12b**)	53 (a)
		2,3-di-NH_2-quinoxaline (**12c**)	23 (a)

(a) When the reaction was carried out in such a way that the potassium permanganate was added 30 minutes after dissolving of quinazoline instead of after 5-10 minutes (as is mentioned in the general procedure) then **12b** could be isolated in 4% yield and **12c** in 57% yield.

We extended this work also to the amination of 1,3,5-triazines. It has already been reported (12) that diphenyl-1,3,5-triazine gives with potassium amide/liquid ammonia 1:1 σ-adduct **4** and that after reaction for 72 hours with a *great* excess of potassium amide 2-amino-4,6-diphenyl-1,3,5-triazine (**8**) was isolated (72% yield). However, in this study we found that **8** could also be obtained, even in higher yield, when a solution of diphenyl-1,3,5-triazine in liquid ammonia, containing only a little excess of potassium amide was treated with potassium permanganate (see entry 7). Also this example shows the usefulness of the method for the introduction of amino groups in azines.

We also want to give some initial results obtained in the amination of the bicyclic compounds quinazoline (**11a**) and quinoxaline (**12a**). It has already been reported that with sodamide in dimethylaniline as solvent, **11a** is converted into 4-aminoquinazoline (**11b**) (13) and compound **12a** into 2,2'-biquinoxalinyl and 2,3-dihydroxyquinoxaline (14). With potassium amide/liquid ammonia **12a** yields dihydrohexaazapentacene (fluorubin) (4).

Using our mild amination-oxidation procedure **11a** was converted into 4-aminoquinazoline in 62% yield (see entry 8), together with a small yield (2%) of a compound, which by ^1H nmr spectroscopy and mass spectroscopy was assigned the structure of 4,4'-diquinazolylamine. On applying this procedure to aminate **12a**, adding, as usual, potassium permanganate 5-10 minutes after **12a** is dissolved in potassium amide/liquid ammonia, a mixture of 2-aminoquinoxaline (**12b**, 53%) and 2,3-diaminoquinoxaline (**12c**, 23%) is formed. However, when the potassium permanganate is added 30 minutes after dissolving **12a** in potassium amide/liquid ammonia the composition of the reaction product is completely different: **12b** (4%) and **12c** (57%).

In conclusion, we feel that the amination-oxidation procedure, using potassium amide/liquid ammonia as aminating agent and potassium permanganate as oxidant, is a very useful and attractive method for the introduction of an amino group in azaheteroarenes.

The generality and scope of this method is now under full investigation.

EXPERIMENTAL

General Procedure for the Amination.

To a stirred solution of liquid ammonia (15-20 ml), containing potassium amide (2.5 equivalents), the substrate (1-2 moles) was added. After 5-10 minutes, potassium permanganate (3.5 equivalents) was added portion by portion and stirring was continued for 10 minutes. The reaction mixture was then quenched with ammonium sulfate (5 equivalents) and after 10 minutes methanol (15-20 ml) was added through the condenser. The ammonia was evaporated and the whole mixture was filtered by suction. Silica gel (1-2 g) was added to the methanolic solution and this mixture was dried. The residue was subjected to column chromatography on silica gel (2-3 g) for purification (eluent: chloroform or chloroform-methanol). The physical data (mp, ^1H nmr spectrum) of the compounds obtained were compared with those of authentic specimens, if available.

Amination of Pyridazine.

Amination of pyridazine (160 mg, 2 mmoles) gave 4-aminopyridazine (**5**) in pale brown crystals (173 mg, 91%), melting range 107-114°; recrystallization from ethyl acetate afforded pale yellow needles, mp 127-129° (lit (15) 129-131°).

Amination of Pyrimidine.

Amination of pyrimidine (160 mg, 2 mmoles) gave 4-aminopyrimidine (**6**) in colorless crystals (137 mg 72%), melting range 143-148°; recrystallization from ethyl acetate gave colorless plates, mp 151-152° (lit (16) 151-152°).

Amination of Pyrazine.

Amination of pyrazine (160 mg, 2 mmoles) gave aminopyrazine (**7**) in pale yellow crystals (124 mg, 65%), melting range 107-111°; recrystalliza-

tion from benzene yielded pale yellow needles, mp 114-117° (lit (17) 115-118°).

Amination of 5-Phenylpyrimidine.

Amination of 5-phenylpyrimidine (156 mg, 1 mmole) gave 4-amino-5-phenylpyrimidine (**10d**) in colorless crystals (119 mg, 70%) mp 150-153°; recrystallization from benzene-methanol yielded colorless prisms, mp 157-158; ^{1}H nmr (deuteriochloroform): δ 7.45 (5H, s, phenyl H), 8.08, 8.45 (each 1H, s, 2- and 6-H).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30. Found: C, 70.25; H, 5.43.

Amination of 5-Bromopyrimidine.

Amination of 5-bromopyrimidine (159 mg, 1 mmole) gave a reaction mixture from which by column chromatography 4-amino-5-bromopyrimidine (**10c**) (49 mg, 28%), mp 211-212° (in closed tube) (lit (18) 208-210°) (from water) and 4-aminopyrimidine (**6**) (35 mg, 37%), mp 145-148° (ethyl acetate) (lit (16) 151-152°) were obtained.

Amination of 3-Phenylpyridazine.

Amination of 3-phenylpyridazine (156 mg, 1 mmole) gave after separation by column chromatography the following three products described below.

a) 6-Amino-3-phenylpyridazine (**9d**).

This compound was obtained in a yield of 5% as colorless scales (benzene), mp 154-156°, (lit (19) 152°); ^{1}H nmr (deuteriochloroform + perdeuteriomethanol): δ 6.9 (1H, d, J = 9 Hz, 4- or 5-H), 7.30-7.87 (6H, complex, phenyl H + 5- (or 4)-H).

b) 4-Amino-3-phenylpyridazine (**9b**).

This compound was obtained in a yield of 49% (84 mg) as colorless needles (benzene), mp 146.5-147.5°; ^{1}H nmr (perdeuteriomethanol): δ 6.77, 8.38 (each 1H, d, J = 6 Hz, 5- and 6-H), 7.44 (5H, s, phenyl H).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30. Found: C, 70.19; H, 5.15.

c) 5-Amino-3-phenylpyridazine (**9c**).

This compound was obtained in 18% yield (32 mg) as pale brown prisms (benzene-methanol), mp 149-150°; ^{1}H nmr (perdeuteriomethanol): δ 6.93, 8.38 (each 1H, d, J = 2 Hz, 4- and 6-H), 7.37 (3H, m, phenyl H), 7.75 (2H, m, phenyl H).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30. Found: C, 69.85; H, 5.30.

Amination of 4,6-Diphenyl-1,3,5-triazine.

Amination of diphenyl-1,3,5-triazine (233 mg, 1 mmole) gave 2-amino-4,6-diphenyl-1,3,5-triazine (**8**) as colorless scales (205 mg, 83%), mp 172-174°, (lit (12) 172-173°).

Amination of Quinazoline.

Amination of quinazoline (260 mg) gave the following two products.

a) 4,4'-Diquinazolylamine.

This compound was obtained in 2% yield (6 mg) as pale yellow needles (methanol), mp 241-242°; ms: m/e 273 (M^+), 144 (M^+ - quinazolyl), 129 ($C_8H_5N_2^+$, quinazolyl); ^{1}H nmr (deuteriochloroform + perdeuteriomethanol): δ 7.62 (6H, complex, aromatic H), 8.42 (2H, s, 2-and 2'-H), 8.60 (2H, d, J = 7 Hz, 5-and 5'-H or 8- and 8'-H).

b) 4-Aminoquinazoline (**11b**).

This compound was obtained in 62% yield (179 mg) as pale yellow prisms (methanol) mp 269-270° (in closed tube) (lit (20) 267-269°); ^{1}H nmr (DMSO-d_6): δ 7.63 (3H, complex, aromatic H), 8.23 (1H, d, J = 7 Hz, 5- or 8-H), 8.33 (1H, s, 2-H).

Amination of Quinoxaline.

Amination of quinoxaline (260 mg, 2 mmoles) gave the following products.

a) 2-Aminoquinoxaline.

This compound was obtained in a yield of 53% (155 mg) as brown needles (benzene), mp 155-157° (lit (21) 155-156°).

b) 2,3-Diaminoquinoxaline.

This compound was obtained in a yield of 23% (72 mg) as brown fine prisms (benzene-methanol) mp >350° (lit (22) >360°).

Acknowledgment.

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