On the Chichibabin Amination of Quinoline and some Nitroquinolines [1]

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Quinoline is aminated into 2-aminoquinoline (55-60%) when treated with potassium amide/liquid ammonia/potassium permanganate at -65°. When the amination is carried out by allowing the solution of quinoline in potassium amide/liquid ammonia to raise from -60° to +15° before addition of potassium permanganate, the main product is 4-aminoquinoline. Using as reagent liquid ammonia/potassium permanganate (thus without the presence of potassium amide) 3-nitroquinoline is exclusively aminated at -40° into 4-amino-3-nitroquinoline. Using the same conditions, from 4-nitroquinoline 3-amino-4-nitroquinoline is obtained. The mechanism of these amination reactions is discussed.

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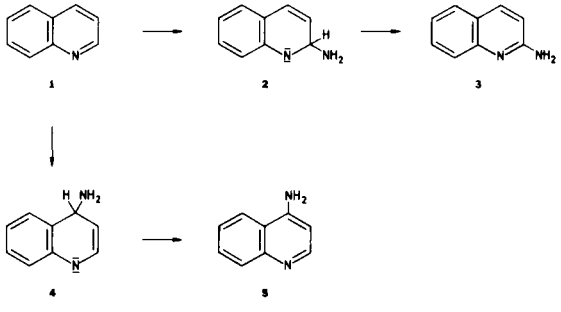
Recent reports have described the low temperature amination of 1,5-, 1,6-, 1,7-, 1,8-, 2,6- and 2,7-naphthyridine using potassium amide/liquid ammonia/potassium permanganate [2]. The amination procedure is very simple and efficient and usually lead to introduction of the amino group into a position, adjacent to the ring nitrogen. 3-Nitro-1,X-naphthyridine (X = 5,6,8) were found to undergo amination into the corresponding 4-amino-3-nitronaphthyridines with a less reactive reagent, *i.e.* liquid ammonia/potassium permanganate [3-5]. Due to the presence of the nitro group the 3-nitro-1,5(6,8)-naphthyridines have an enhanced electron-deficiency, allowing the use of a weaker nucleophile.

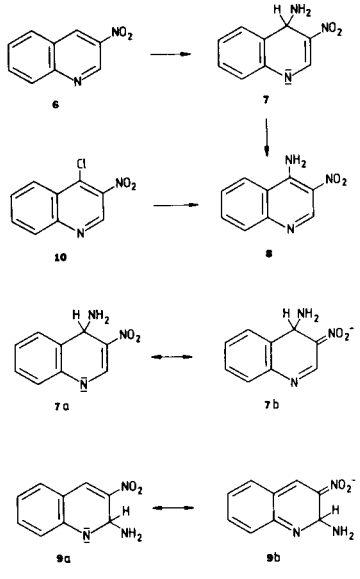
The ^{1}H-nmr studies on σ-adduct formation between quinoline (**1**) and potassium amide in liquid ammonia at -45° have shown [6] that C-4 as well as C-2 are attacked, leading to a mixture of the covalent σ-adducts 2-amino- (**2**) and 4-amino-1,4-dihydroquinolinides (**4**) in the ratio about 75/25. On warming above -45° the C-2 adduct **2** is converted into the more stable C-4 adduct **4**. The conversion of **2** into **4** is irreversible, indicating that the addition at C-2 is a kinetically controlled reaction and that the C-4 adduct is thermodynamically the most stable one. The preferred addition at C-2 is supported by theoretical calculations [7].

The above mentioned results induced us to study the possibility of using potassium amide/liquid ammonia/potassium permanganate at different temperatures to aminate quinoline. On dissolving **1** in potassium amide/liquid ammonia at -65° and adding potassium permanganate to the solution, in 50-55% yield 2-aminoquinoline (**3**) can be isolated. No indication for the presence of the isomeric 4-aminoquinoline (**5**) is found. When **1** is allowed to react with potassium amide/liquid ammonia at about +15° in a sealed tube, and potassium permanganate was added (after cooling of the solution to -40°) in 60-65% yield **5** is formed. By gas chromatographic analysis of the crude reaction mixture the presence of 6-7% of **3** can be detected. By extending this study towards the amination of 3-nitroquinoline (**6**) we found that with liquid ammonia/potassium permanganate at -33° 4-amino-3-nitroquinoline (**8**) is yielded (65%). The ^{1}H nmr-spectrum of a solution of **6** in liquid ammonia at -45° displays a low field singlet at δ 8.38 and a high field singlet at δ 5.05, indicating the presence of a σ-adduct. Compared to the ^{1}H-nmr spectrum of **6** in deuteriochloroform (H-2 at δ 9.63 and H-4 at δ 9.01) the upfield shift Δδ for C-4 is 3.96, a value which is in agree-

Scheme 1



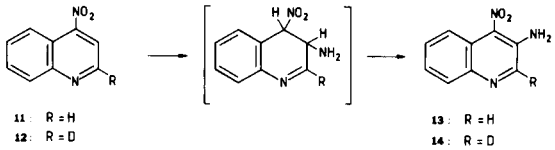
Scheme 2



ment with those generally found in σ-adduct formation [2]. Increase of the temperature from -45° to +20° did not change the ^{1}H-nmr spectrum. These results indicate that the addition of ammonia has taken place at C-4 and not at C-2 (see Table 1); the C-4 adduct **7** is apparently thermodynamically the most stable one.

That at +20° the addition at C-4 is preferred to addition at C-2 is probably due to the fact, that the thermodynamic stability of the C-4 adduct **7** is higher than that of the C-2 adduct **9**; the resonance contribution **7b** to the stability of **7** is of more importance than the contribution of **9b** to the stability of **9**, as the carbocyclic ring in **9b** has lost its 6π aromatic character. Attempts were made to introduce the amino group at C-2 by reacting at low temperature a C-4 substituted quinoline with liquid ammonia/potassium permanganate. We found that under such conditions 4-chloro-3-nitroquinoline (**10**) does not give a trace of 2-amino-4-chloro-3-nitroquinoline, but exclusively **8** (73%). Apparently the nucleophilic displacement of the highly labile chloro atom at C-4 takes place more easily than the oxidative amination at C-2. A further extension of this study concerned the amination of 4-nitroquinoline (**11**). Treatment of **11** with liquid ammonia/potassium permanganate at -40° gave in good yield a product which ir spectrum showed all characteristics of an amino and nitro group. Based on the ^{1}H-nmr spectrum, which features, besides the phenyl multiplet, a singlet at δ 8.38, the compound was assigned to be 3-amino-4-nitroquinoline (**13**). A rather unusual and interesting result since it is the first observation of the addition of liquid ammonia meta to the ring nitrogen. Apparently due to the activating effect of the nitro group at C-4, addition at C-3 is possible. In order to confirm the structure of **13**, we prepared 2-deuterio-4-nitroquinoline (**12**) and established that in the 2-deuterio-aminonitroquinoline obtained, *i.e.* **14** all deuterium is still present. By ^{1}H-nmr spectroscopy adduct formation could be observed, however due to the complexity of the spectrum, the site of addition of the amino group could not be determined. 3-Amino-4-nitroquinoline has been suggested to be formed by nitration of 3-acetylaminoquinoline and subsequent hydrolysis of the nitration product obtained [8]. Later work [9] has shown however that in fact in the nitration reaction a mixture of 3-acetylamino-5-nitro and 3-acetylamino-8-nitroquinoline is formed. Attempts to aminate 4-nitroquinoline *N*-oxide by liquid ammonia/potassium permanganate failed. After the reaction only starting material could be isolated; no σ-adducts, formed from the N-oxide and liquid ammonia could be detected.

Scheme 3



11: R = H
12: R = D

13: R = H
14: R = D

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler plate. The ^{1}H-nmr spectra were recorded on a Varian EM-390 spectrometer equipped with a Varian EM-3940 variable-temperature controller or on a Varian XL-100-15 spectrometer. TMS was used as internal standard (δ 0). In liquid ammonia, the solvent peak was used as the standard. The spectra were converted to the TMS scale by addition at 0.95 ppm. The ir spectra (potassium bromide) were measured using a Hitachi EPI-G3 apparatus. Starting materials, 3-nitro- and 4-nitroquinoline and 4-chloro-3-nitroquinoline were obtained according to the literature [10, 11, 14].

Preparation of 2-Deuterio-4-nitroquinoline (**12**).

As starting material we used 2-deuterioquinoline, being obtained according to the procedure given in the literature [6], however using somewhat milder conditions (220°, 30 hours). For the introduction of the nitro group at position 4 we used the prescriptions [11] given for the undeuterated compound. The ^{1}H-nmr analysis of 2-deuterio-4-nitroquinoline obtained showed that the deuterium content at position 2 was about 85%.

Amination of Quinoline (**1**) at -65°.

Compound **1** (0.260 g, 2 mmoles) was added to a solution of liquid ammonia (20 ml) containing an excess of potassium amide (2.5 eq) at -65°. After 10 minutes potassium permanganate (3.5 eq) was added in small portions under stirring. After additional reaction time of 15 minutes, the reaction mixture was quenched with ammonium sulphate, the ammonia was evaporated off and the residue was extracted with benzene. 0.152 g (52%) of light-yellow crystals of 2-aminoquinoline (**3**) could be isolated, mp 132° (lit [12] 129-130°). The ir spectrum is fully identical with that of a reference compound [12].

Amination of Quinoline (**1**) at Room Temperature.

Compound **1** (0.260 g, 2 mmoles) was added to the solution of liquid ammonia (20 ml) containing potassium amide (2,5 eq) at -45° and this mixture was sealed in a glass tube. After keeping this mixture for about one hour at room temperature, the tube was cooled to about -45°, then opened and potassium permanganate (3.5 eq) was added in small portions under stirring. After 15 minutes the reaction mixture was quenched with ammonium sulphate. The ammonia was evaporated and the whole mixture was extracted with ether. Gaschromatography of the ethereal solution showed two peaks in the ratio 1.4:20, which on comparison with refence compounds indicated the ratio of 2-aminoquinoline and 4-aminoquinoline, formed in the reaction. The residue, obtained after evaporating off the ether solvent, was recrystallized from benzene, yielding 0.185 g (64%) of 4-aminoquinoline (**5**), mp 149-150° (lit 156-157° [12], 151-152° [13]) ir- and nmr- spectrum are identical with those of a reference compound [12].

Amination of 3-Nitroquinoline (**6**).

3-Nitroquinoline (0.261 g, 1.5 mmoles) was dissolved in liquid ammonia (20 ml) and an excess of potassium permanganate (2-3 eq) was added in small portions under stirring. After additional stirring for two hours at -33° the ammonia was evaporated off, to the remaining residue 20 ml of water was added, and the mixture was continuously extracted with ether. The crude residue left after evaporation of the ether was crystallized from ethanol, yielding 0.18 g (65%) of yellow crystals of 4-amino-3-nitroquinoline (**8**), mp 274-275° (lit [14] 261-262°); ^{1}H-nmr (in DMSO): δ 9.19 (s, H-2), 9.00 (br s, NH_2); 8.59 (m, H-8) and 8.00-7.45 (m, H-5, H-6, H-7); ir: 3375, 3275 (NH_2 stretching).

Anal. Cacld. for $C_9H_7N_3O_2$: C, 57.13; H, 3.73. Found: C, 57.39; H, 3.98.

Amination of 4-Chloro-3-aminoquinoline (**10**).

Compound **10** (0.2 g, 1 mmole) was dissolved in 20 ml of liquid ammonia and this solution was treated with potassium permanganate as described for **6**. The product obtained was crystallized from methanol, yielding 0.138 g (73%) of **8**.

Amination of 4-Nitroquinoline (**11**) and 2-Deuterio-4-nitroquinoline (**12**).

The amination of **11** (0.35 g, 2 mmole) and isolation of the product was carried out similarly as described for **6**. Crystallization from methanol gave 3-amino-4-nitroquinoline (0.33 g, 86%), orange needles, mp 172-174°; ^{1}H-nmr (DMSO): δ 8.83 (s, H-2), 8.50 (m, H-8), 8.00-7.37 (m, H-5, H-6, H-7) and 8.10 (br s, NH_2); ir: 3390, 3250 (NH stretching).

Anal. Cacld. for $C_9H_7N_3O_2$: C, 57.13; H, 3.73. Found: C, 56.94; H, 3.60.

The amination of **12** into **14** was performed identical to that of given for the undeuterated compound **11**.

REFERENCES AND NOTES

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