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AMINATION OF 4-NITROQUINOLINE WITH LIQUID METHYLAMINE/POTASSIUM PERMANGANATE

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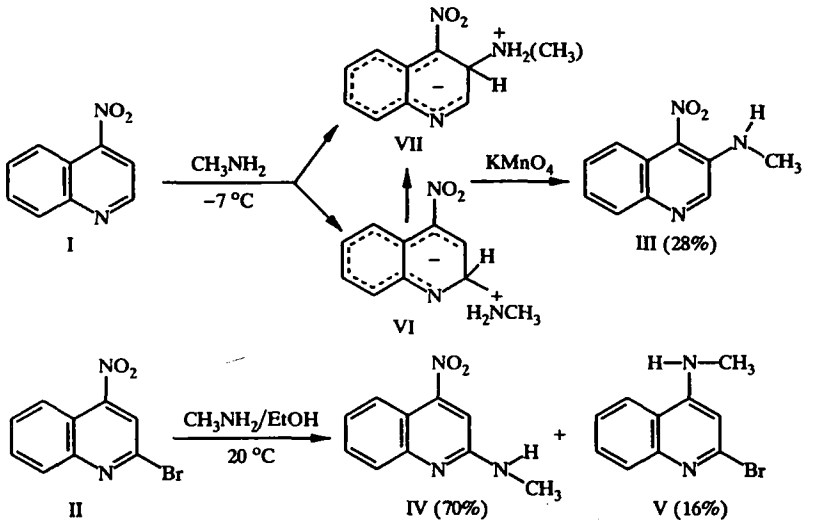
In a previous paper [1] we have described the results of the amination of all isomeric mononitroquinolines, except for 4-nitroquinoline, with liquid methylamine/potassium permanganate (LMA/PP). The mentioned amination proceeds via the intermediate methylamino σ-adducts which are subsequently oxidized to the amino products. 4-Nitroquinoline (I) is difficultly accessible, and our attempts to prepare it according to the literature data [2-5] either failed or the yield of I, after troublesome isolation, was very poor. Therefore the amination of compound I with LMA/PP was not studied exactly as before. Looking for a convenient preparation method of I we have found that deoxygenation of 4-nitroquinoline N-oxide by phosphorus tribromide in chloroform solution [3, 4] gives fair results if the reaction products are separated by column chromatography. This isolation method is easy, fully reproducible, and makes it possible to obtain compound I and the second product, 2-bromo-4-nitroquinoline (II), in 23-25% yields and in amounts of 2-2.5 g (see Experimental).

Treatment of 4-nitroquinoline (I) with LMA/PP at −7°C affords 3-(methylamino)-4-nitroquinoline (III) in 28% yield (Scheme).



Substantial tar formation and very small amounts of unidentifiable products were observed as well. To establish the exact position of methylamino group (3 or 2) in compound III, the second possible isomeric product, i.e., 2-(methylamino)-4-nitroquinoline (IV), was synthesized. The synthesis involves the reaction of bromide II with an ethanolic solution of methylamine at ~20°C and affords, besides IV, some amounts of 2-bromo-4-methylaminoquinoline (V) as well (Scheme). The properties (^{1}H NMR, IR, mp) of IV were different from those of compound III. It is noteworthy that the formation of 3-(methylamino)-4-nitroquinoline (III) from I and LMA/PP is a rather rare example [6] of a Chichibabin amination in *meta*-position to the ring nitrogen.

In order to detect the intermediate methylamino s-adduct of I in the reaction with LMA/PP, the ^{1}H NMR spectrum of 4-nitroquinoline in liquid methylamine was measured at −12°C. The spectrum is quite different from that of I in $CDCl_3$.

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TABLE 1. ^1H NMR Spectrum Data of 4-Nitroquinoline and Its Methylamino σ-Adduct

Compound	Solvent	Chemical shifts (δ values)						
		2-H	3-H	5-H	6-H		7-H	8-H
4-Nitroquinoline (I)	$CDCl_3$	9,22	8,03	8,37	8,00	—	7,88[b]	8,53
2-Methylamino σ-adduct VI	CH_3NH_2[a]	4,05	7,64		7,30	—	6,45[b]	
	Δδ	5,17	0,39	—	—		—	—
3-Methylamino σ-adduct VII	CH_3NH_2[a]	9.03	4,61		7,30	—	6,45[b]	
	Δδ	0,19	3,42	—	—		—	—

[a] The spectra were measured in liquid CH_3NH_2 at −12°C.

[b] The signals of these protons form a complex multiplet and cannot be exactly assigned.

It exhibits, besides the signals in the aromatic region, two high field doublets, one at δ 4.61 and one at δ 4.03. These data (cf. reviews [7, 8]) indicate the presence of two methylamino σ-adducts VI and VII formed by the addition of methylamine to $C_{(2)}$ and $C_{(3)}$ in I (Scheme). From the integrated area of the two adduct peaks the ratio of VI:VII was found to be ca. 1:1.

To assign unequivocally the ^1H NMR spectrum signals to each of these two methylamino σ-adducts we have synthesized 2-deuterio-4-nitroquinoline and have found that this compound when dissolved in liquid methylamine shows in its spectrum the signal at δ 4.61 as a singlet and no signal at δ 4.05. The results confirm the structure of the intermediate methylamino σ-adducts as VI and VII; their ^1H NMR spectrum data are given in Table 1.

The formation of 3-(methylamino)-4-nitroquinoline (III) is in agreement with the intermediate 3-methylamino σ-adduct VII. On the other hand, we do not observe detectable amounts of the oxidation product of 2-methylamino σ-adduct VI, i.e., 2-(methylamino)-4-nitroquinoline (IV). It is possible that the kinetically controlled σ-adduct VI is either decomposed or converted during oxidation to the thermodynamically most stable σ-adduct VII.

For the interpretation of the amination regioselectivity of 4-nitroquinoline with LMA/PP we applied the theory of perturbation of molecular orbitals to this reaction. The calculations of the π-electron energy (ΔE) for all positions in 4-nitroquinoline, ΔE = 0.033 ($N_{(1)}$), 0.051 ($C_{(2)}$), 0.064 ($C_{(3)}$), 0.059 ($C_{(4)}$), 0.023 (C_5), 0.038 ($C_{(6)}$), 0.035 ($C_{(7)}$), and 0.024 ($C_{(8)}$), were carried out according to an extremely simplified second-order perturbation equation [9].

$$\Delta E \approx 2 \left[\frac{C^2_S\,(\mathrm{LUMO})}{|E^N_{\mathrm{HOMO}} - E^A_{\mathrm{LUMO}}|} + \frac{C^2_S\,(\mathrm{LUMO}+1)}{|E^N_{\mathrm{HOMO}} - E^A_{\mathrm{LUMO}+1}|} \right]$$

The values of the LUMO and LUMO + 1 energy levels (E^A) and the respective coefficients C_s for 4-nitroquinoline were calculated by the MNDO method. They are available on request. For the molecule of methylamine the value E^N HOMO = −10.57 eV was found. The methylamination and formation of methylamino σ-adducts of 4-nitroquinoline occurs in these positions ($C_{(3)}$ and $C_{(2)}$), for which the highest calculated values of ΔE have been found. Therefore it is reasonable to suppose that methylamination of 4-nitroquinoline is controlled, similarly as in other isomeric mononitroquinolines [1], by interaction of frontier molecular orbitals (FMO) of the reagents.

EXPERIMENTAL

Melting points (uncorrected) were obtained using a Kofler plate. IR spectra (KBr pellets) were registered with an UR-20 spectrometer, ^1H NMR spectra with a Tesla BS-587A (80 MHz) instrument, TMS as internal standard, and mass spectra with an LKB GC/MS 9000 (EJ, 70 eV) apparatus. Silica gel (Merck, 230-400 mesh) was used for column chromatography. Quantum-chemical calculations were by the MNDO method using the MOPAC program (version 6.00) available from Research Laboratory, U.S. Air Force Academy, Colorado Springs, U.S.A.

4-Nitroquinoline (I) and 2-Bromo-4-nitroquinoline (II). To a solution of 9.5 g (50 mmol) of 4-nitroquinoline N-oxide [10] a solution of 25 g (92 mmol) of PBr_3 was introduced dropwise at 8-13°C with stirring, under ice cooling. Then the reaction mixture was stirred at room temperature for a further 0.5 h, poured onto ca. 200 g of crushed ice, made alkaline with sodium carbonate, and extracted with chloroform (4 × 50 ml). The chloroform solution was washed with a 10% water solution of sodium hydrosulfite, dried over a mixture of anhydrous magnesium sulfate and sodium carbonate, and the chloroform was evaporated. The residue was separated by column chromatography (4 × 75 cm) using dichloromethane as the eluent. The first fraction (500 ml) gave, after crystallization from hexane, 2.9 g (23%) of 2-bromo-4-nitroquinoline (II) as light-yellow needles with mp 96-97°C ([3], 99-100°C). Mass spectrum, *m/z*, %: 254(22), 252(22) [M^+], 208(33), 206(33), [$M^+ - NO_2$], 127(100). ^1H NMR spectrum ($CDCl_3$): 8.1 (d.d, 8H), 8.22 (d.d, 5H), 8.01 (s, 3H), 8.02-7.73 (m, 6H, 7H), $J_{56} = J_{78} = 7.5$ Hz, $J_{57} = J_{68} = 2.0$ Hz. The second fraction (3.51) was crystallized from hexane to afford 2.2 g (25%) of 4-nitroquinoline (I) as light-yellow needles with mp 91-92°C ([4], 87-89°C; [2], 89°C); for ^1H NMR spectrum data see Table 1.

2-Deuterio-4-nitroquinoline. The compound was prepared according to the above procedure starting from 2-deuterio-4-nitroquinoline N-oxide, which was obtained from 2-deuterioquinoline [6, 11] according to the procedure given for the undeuterated compound [10]. The ^1H NMR spectrum of 2-deuterio-4-nitroquinoline obtained showed that the deuterium content at position 2 was >95%.

Amination of 4-Nitroquinoline (I) with LMA/PP. To 30 ml of liquid methylamine 0.5 g (2.9 mmol) of 4-nitroquinoline and 1.0 g of potassium permanganate were added and the resulting mixture was stirred at −7°C for 10 min. After evaporation of methylamine the residue was extracted with boiling chloroform (4 × 30 ml). The chloroform was evaporated and the dark residue was separated by column chromatography (2.5 × 70 cm). The first fraction (800 ml of chloroform) gave 0.13 g (26%) of unreacted substrate. The second fraction (1.6 liters of chloroform) was crystallized from octane to yield 0.16 g (28%) of 3-(methylamino)-4-nitroquinoline (III). Red needles which above 180°C are transformed into cubes with mp 214-215°C. Mass spectrum, *m/z*, %: 203(100) [M^+]. ^1H NMR spectrum ($CDCl_3$): 8.95 (s, 2H), 8.75 (d.d, 8H), 8.33 (br.s, NH), 8.09 (d.d, 5H), 7.84-7.50 (m, 6H, 7H), 3.37 (d, CH_3), $J_{56} = J_{78} = 7.5$ Hz, $J_{57} = J_{68} = 1.3$ Hz, $J_{CH3,NH} = 5.0$ Hz. IR spectrum: 3315 (NH), 1505 (NO_2, as), 1345 (NO_2, s). Found, %: C 58.97; H 4.16; N 20.64. $C_{10}H_9N_3O_2$ (M 203.2). Calculated, %: C 59.11; H 4.46; N 20.68. The third fraction eluted with a 1:4 mixture of methanol−chloroform (300 ml) gave very small amounts of a few unidentifiable products.

Amination of 2-Bromo-4-nitroquinoline (II) with Methylamine/Ethanol. 2-Bromo-4-nitroquinoline (0.1 g, 0.4 mmol) was dissolved in 7 ml of a 33% solution of methylamine in ethanol and stirred at room temp. for 2 h. The solvent was removed on a water bath and to the residue water (20 ml) was added. The mixture obtained was extracted with chloroform (4 × 25 ml), the chloroform solution was dried with anhydrous magnesium sulfate and, after evaporation of the chloroform, the residue was separated by column chromatography (2.5 × 40 cm). The first fraction was eluted with 1.2 liters of dichloromethane, additionally purified by column chromatography (2.5 × 30 cm) using ethyl ether−hexane, 1:1 (300 ml) as the eluent and crystallized from hexane to afford 56 mg (70%) of 2-(methylamino)-4-nitroquinoline (IV) as red needles with mp 129.5-130.5°C. Mass spectrum, *m/z*, %: 203(100) [M^+]. ^1H NMR spectrum ($CDCl_3$): 8.1 (d.d, 5H or 8H), 7.87-7.56 (m, 6H, 7H), 7.42 (d.d, 8H or 5H), 7.22 (s, 3H), 5.16 (br.s, NH), 3.17 (d, CH_3), $J_{56} = J_{78} = 7.5$ Hz, $J_{57} = J_{68} = 1.5$ Hz, $J_{CH3,NH} = 5.0$ Hz. IR spectrum: 3285 (NH), 1525 (NO_2, as), 1350 (NO_2, s). Found, %: C 59.08; H 4.50; N 20.44. $C_{10}H_9N_3O_2$ (M 203.2). Calculated, %: C 59.11; H 4.46; N 20.68. The second fraction was eluted with dichloromethane−methanol, 5:0.2 (250 ml) and crystallized from hexane to give 15 mg (16%) of 2-bromo-4-(methylamino)quinoline (V) as light-yellow needles with mp 219-221°C. Mass spectrum, *m/z* , %: 238(100), 236(100) [M^+], 157(64) [$M^+ - Br$]. ^1H NMR spectrum ($CDCl_3$): 7.93 (d.d, 5H or 8H), 7.78-7.33 (m, 6H, 7H, 8H or 5H), 6.55 (s, 3H), 5.48 (br.s, NH), 3.06 (d, CH_3), J_{56} or $J_{78} = 8.0$ Hz, J_{57} or $J_{68} = 1.5$ Hz, $J_{CH3,NH} = 5.0$ Hz. IR spectrum: 3300 (NH). Found, %: C 51.03; H 3.80; N 11.70. $C_{10}H_9BrN_2$ (M 237.1). Calculated, %: C 50.65; H 3.82; N 11.81.

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