Tetrahedron Letters, Vol.32, No.10, pp 1311-1314, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

6-NITRO-2,3-DIPIPERIDINOQUINOXALINE: ITS UNEXPECTED FORMATION FROM 2-CHLORO-7-NITROQUINOXALINE.

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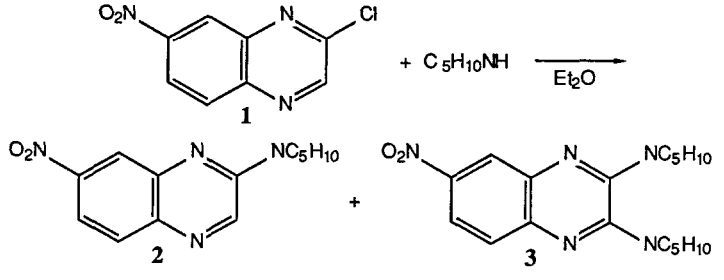
Summary. Excess piperidine and 2-chloro-7-nitroquinoxaline **1** in diethyl ether give large amounts of the unexpected disubstitution product 6-nitro-2,3-di-piperidinoquinoxaline **3**. The mechanism of this very unusual nucleophilic substitution of hydrogen is suggested to involve the oxidation of the dipiperidino-dihydroquinoxaline **10** by dissolved oxygen.

Chloro-nitroquinoxalines are π-deficient aza-aromatic systems having several electrophilic sites; their reactivity towards nucleophiles often raises the question of chemoselectivity since nucleophiles may replace the halogen atom or the nitro group. We previously examined the behaviour of 2-chloro-3-nitroquinoxaline towards several nucleophiles [1]; we now report on an unexpected result obtained with 2-chloro-7-nitroquinoxaline **1**.

When 2-chloro-7-nitroquinoxaline **1** and excess piperidine are kept in peroxide-free dry diethyl ether for a short time, the major compound isolated from the medium is not always the expected monosubstitution product 7-nitro-2-piperidinoquinoxaline **2** but often the disubstitution product 6-nitro-2,3-dipiperidinoquinoxaline **3**.

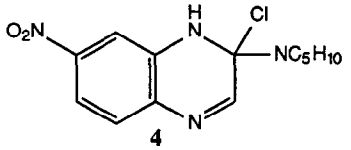


This unexpected result led us to systematically explore the requirements for this double substitution which combines the obvious replacement of a chlorine atom with that, less documented, of a hydrogen atom. The results of our experiments are collected in Table 1.

Two conclusions emerge from these results: a high disubstitution-to-monosubstitution ratio requires a high piperidine-to-quinoxaline ratio and the presence of dissolved oxygen. It was found furthermore that a reaction with a piperidine-to-chloronitroquinoxaline of 30, which showed a **3/2** ratio of 0.9 after half an hour under air, kept in these conditions for four additional days showed a complete transformation of **2** into **3**.

Discussion.

a) We shall assume that piperidine reversibly attacks 2-chloro-7-nitroquinoxaline **1** either at position 2 to give the intermediate dihydroquinoxaline **4** or at position 3 to give the isomeric dihydroquinoxaline **5**.



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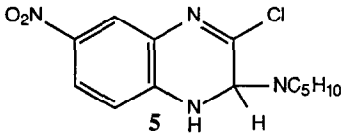

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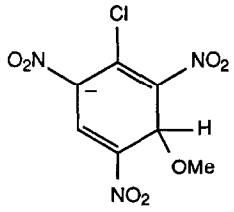
Crampton *et al.* [2] have shown that 2,4,6-trinitrochlorobenzene (picryl chloride) and methoxide ion initially give adduct **6**, with the methoxy group at the unsubstituted position; the preferred formation of this adduct, rather than **7**, is to be ascribed to steric hindrance by the chlorine atom.



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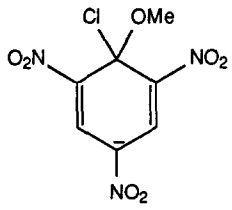

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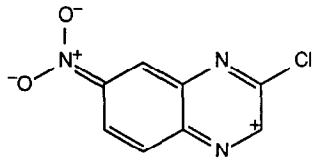

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When two carbon atoms experience the same activation by powerful electron-withdrawing substituents, the unsubstituted one is thus attacked faster by a nucleophile than the one carrying a chlorine atom. Atoms 2 and 3 of 2-chloro-7-nitroquinoxaline undergo identical activations by the ring nitrogen atoms, and a nucleophile shall thus add preferentially to carbon atom 3 of 2-chloroquinoxaline for the same reason. This preference is furthermore enhanced by the nitro group at position 7 which induces an additional activation of position 3 as suggested by resonance structure **8**.

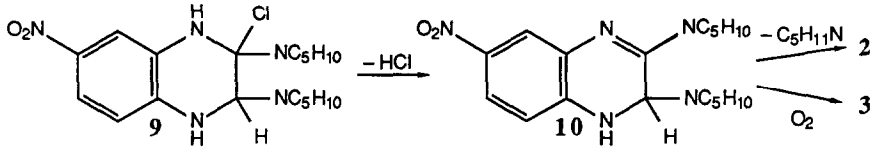
Van der Plas has shown that moderately activated π-deficient aza-aromatic compounds require sodium amide to form such σ-adduct, but that highly activated hetero-aromatic systems such as naphtyridines already add ammonia at -33 °C [3]. In our case, the 3 position of 2-chloro-7-nitroquinoxaline is activated by the ring N(2) atom and by the nitro group; moreover, our reactions are run at a higher temperature (about 20°C).

A preferential attack of piperidine at position 3 seems thus fully justified, and we shall now discuss the fate of **5** along the available reaction paths.

b) When the concentration of piperidine is low, and there is no oxidizing reagent present in the system, adduct **5** can only dissociate into its constituent reagents and thus equilibrate with adduct **4**; this then looses HCl, yielding the expected monosubstitution product **2**.In this connection, it should be noticed that Van der Plas [3] has found that intermediate adducts such as **5** can be rapidly oxidized by added permanganate, and that oxidative substitution of hydrogen can be faster than the classical nucleophilic substitution of halogen *via* adduct **4**.

For high concentrations of piperidine, **5** adds a second molecule of nucleophile to the remaining double bond, which is no more part of an aromatic ring; the bis-adduct, 2-chloro-1,2,3,4-tetrahydro-7-nitro-2,3-dipi-

peridino quinoxaline **9**, looses HCl yielding now dihydroquinoxaline **10** whose fate depends on the presence or absence of oxygen.



In an oxygen-free medium, **10** can only loose a molecule of piperidine, giving again the monosubstitution product **2**; when oxygen is present, the 1,2-dihydropyridine analog **10** can be oxidized to the disubstitution product **3**. The competition between the unimolecular decomposition of **10** to **2** and the bimolecular oxidation of **10** to **3** depends on the concentration of dissolved oxygen.

c) The nucleophilic substitution of hydrogen in the presence of an oxidizing reagent goes back to the historical work of Tchitchibabine on the amination of pyridine by sodium amide, and has been reviewed in 1976 [4]; a far-going application of this principle has been developed by Van der Plas [3] who used permanganate in liquid ammonia (LAP) to oxidize the intermediate σ-adduct to the corresponding amino-heterocycle with good to excellent yields. Air is obviously able to perform the same oxidation.

Table I. Influence of experimental parameters on the formation of 6-nitro-2,3-dipiperidinoquinoxaline **3** from 2-chloro-3-nitroquinoxaline in ether at room temperature.

Exp nr°	N	$[C_5H_{10}NH]/[1]$	atmosphere	time (hours)	3 / 2
1	6	3.3 ± 0.3	air	4.0	0.15 ± 0.10
2	3	51 ± 1	"	0.5	0.80 ± 0.20
3	3	130 ± 30	"	0.5	1.7 ± 0.5
4	3	3.4 ± 0.3	argon	2.0	0.02 ± 0.01
5	6	200 ± 70	"	2.0	0.11 ± 0.01
6	3	6.6 ± 0.3	oxygen	1.5	0.45 ± 0.10
7	2	113 ± 4	"	0.7	25 ± 9

N is the number of independent runs performed within the given range of piperidine-to-**1** ratio; the ± in the last column is the range of observed values and are not statistical deviations; "argon" means that the medium was degassed by three freeze-pump-thaw cycles; pure argon was then admitted at atmospheric pressure. A 25 ± 9 ratio of **3/2** means that the relative yield of **3** is 94 to 97 %.

Experimental part.

^{1}HNMR spectra were recorded in $CDCl_3$ on a Bruker VM250 spectrometer; chemical shifts are given in ppm downfield from internal TMS and J values are given in Hz. A Bruker IFS 25 spectrophotometer was used for the IR spectra. Mass spectra were obtained with a VG Micromass 70-70F instrument; peaks less than 10 % of the base peak are usually omitted. HPLC's were run on a Waters Associates apparatus fitted with a UV (254 nm) detector, on 25 cm long and 4.6 mm inner diameter columns packed with Rosil 5 μ; flow rate: 2 mL/min. Relative amounts of **2** and **3** were obtained by the ratio of peak areas and by the ratio of peak heights, after standardization with known mixtures. Melting points, recorded on a Reichert hot stage microscope, are uncorrected.

Piperidine and ether were purified according to Perrin *et al.*[5].

2-Chloro-7-nitroquinoxaline was synthesized according to Cheeseman [6] : nitration of 2-hydroxyquinoxaline gave 2-hydroxy-7-nitroquinoxaline which was recristallized from nitromethane instead of acetone; yield 62 % , litt [6] 45 %; MP 274-275° C, litt [6] 272-274° C. 2-Hydroxy-7-nitroquinoxaline (335 mg, 1.8 mmol) was refluxed for 4 h in 3 mL of freshly distilled phosphoryl chloride containing 600 mg phosphorus pentachloride. The product was isolated after thorough removal of excess $POCl_3$, recristallized from cyclohexane (instead of benzene) and sublimed under 1.3 Pa at 160° C. Yield 90 %, litt [6] 94 %; MP 187-188° C, litt [6] 185-186° C.

Reactions with piperidine. Piperidine and 2-chloro-7-nitroquinoxaline, in the concentrations stated, are stirred in 1.5 mL ether; the medium becomes yellow, and the reaction is monitored by TLC. After removal of the ether and extraction with water/chloroform, the organic layer is dried over $MgSO_4$, evaporated to dryness,and a CH_2Cl_2 solution of the residue is analyzed by HPLC. The collected product of several runs is flash-chromatographed [7] with dichloromethane/hexane 9:1. 7-Nitro-2-piperidinoquinoxaline was recristallized from nitromethane. MP 134-136° C; Rf (silicagel, CH_2Cl_2/ethyl acetate 9:1) = 0.26. ^1H NMR ($CDCl_3$): 8.67 (1 H, s, H_3); 8.49 (1 H, d, H_8); 8.75 (1 H, dd, H_6); 7.92 (1 H, d, H_5); $J_{5,6}$ = 8.96 Hz, $J_{6,8}$ = 2.48 Hz; 3.83 (4 H, m, piperidino α-CH_2); 1.70 (6H, m, piperidino β, γ CH_2).IR (KBr, cm^{-1}): 2940-2850 (ν_{CH}); 1554, 1340 (nitro); 850 (Ar–N). MS: m/z = 259 (27, M^+ + 1); 258 (100 %, M^+); 257 (18, M^+ - 1); 229 (42, M^+ - C_2H_5); 228 (8, M^+ - NO); 203 (21, 229 - 26); 175 (39); 129 (11, 175 - NO_2); 102 (10). Accurate mass: calculated for $C_{13}H_{14}N_4O_2$: 258.11167; found : 258.11195. 6-Nitro-2,3-dipiperidinoquinoxaline was recristallized from nitromethane. MP 147-148° C; Rf (silicagel, CH_2Cl_2/ethyl acetate 9:1) = 0.78. ^1H NMR ($CDCl_3$): 8.52 (1 H, d, H_8); 8.11 (1 H, dd, H_6);.7.63 (1 H, d, H_5); $J_{5,6}$ = 8.99 Hz, $J_{6,8}$ = 2.55 Hz; 3.5-3.6 (8 H, m, piperidino α-CH_2); 1.7 0 (12 H, m, piperidino β, γ CH_2). IR (KBr, cm^{-1}) 2940-2810 (ν_{CH}); 1610 (ν_{CC}); 1514, 1336 (nitro); 890 (Ar–N). MS: m/z = 342 (26 %, M^+ + 1); 341 (100 %, M^+); 340 (5, M^+ - 1); 298 (21, M^+ - C_3H_7); 284 (19, M^+ - C_4H_9); 272 (13, 298 - C_2H_2); 270 (18, 298 - C_2H_4); 258 (8, M^+ - C_5H_9N); 229 (10, 258 - C_2H_5 and 270 - C_3H_5). Analysis : calculated for $C_{18}H_{23}N_5O_2$ (FW : 341.49) : C 63.3, H 6.8, N 20.5; found : C 63.2, H 6.7, N 20.6.

Acknowledgements. C. R. thanks the IRSIA (Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture) for a doctoral fellowship. The HPLC analyses were performed by Mrs A. Remacle; the NMR spectra were recorded Dr R. Ottinger; we are grateful to Dr M. Kaisin for his invaluable help in the analysis of the mass spectra recorded by Mr C. Moulard; the elemental analysis was performed by Mr R. Van Nerum. This work was supported in part under contract n° 1.5.100.87F of the National Fund for Scientific Research.

References.

(1) Nasielski-Hinkens, R.; Kaisin, M.; Grandjean, D.; Loos M., and Nasielski, J.; Bull. Soc. Chim. Belg., **1988**, *97*, 919
(2) Crampton, M. R.; El Ghariani, M. A. and Khan, H. A., Chem. Comm., **1971**, 834
(3) Wozniak, M; van der Plas, H. C; Tomula, M; and van Veldhuizen, A., Recl. Trav. Chim. Pays-Bas, **1983**, *102*, 511-513, and references cited therein.
(4) Chupakhin O. N. and Postovskii I. Ya., Russ. Chem. Revs., **1976**, *45*, 454-468.
(5) Perrin, D. D.; Armarego, W. L. F.; and Perrin, D. R.; *Purification of Laboratory Chemicals*, 2d Edition, Pergamon Press, London, **1980**.
(6) Cheeseman, G. W. H.; J. Chem. Soc., **1961**, 1246.
(7) Still, W. C.; Kahn, M.; Mitra, A.; J. Org. Chem., **1978**, *43*, 2923.

(Received in France 17 December 1990)