

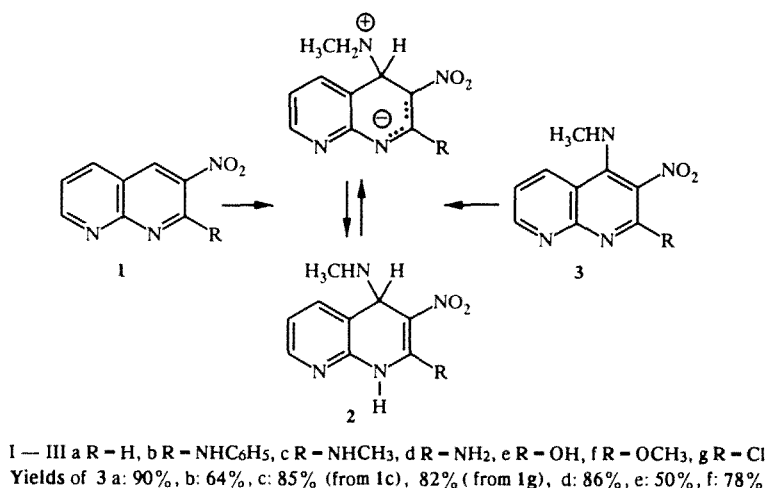
LETTERS TO THE EDITOR

METHYLAMINO-DEHYDROGENATION OF 3-NITRO-1,8-NAPHTHYRIDINES*

Marian Wozniak, Piotr Suryio, and Henk van der Plas

Use of liquid ammonia/potassium permanganate has been found a very useful reagent for the amino-dehydrogenation in highly electron-deficient heteroaromatics [1]. This methodology has successfully provided access to the preparation of aminoheterocycles, which otherwise could not be obtained or only in small yields. Our ongoing interest in the amino-dehydrogenation reactions of naphthyridines [2] induced us to investigate whether this methodology could also be applied for introducing methylamino groups in 3-nitro-1,8-naphthyridines, using liquid methylamino (-7°C) /potassium permanganate as reagent. In this communication we will report that this reagent is indeed very effective to introduce selectively on position C-4 in 3-nitro-1,8-naphthyridines (**1a**) and several of its derivatives (**1b-g**) a methylamino group, yielding the 4-methylamino-3-nitro-1,8-naphthyridines (**3a-f**) in reasonable-to-good yields (see scheme).

Scheme



In the case of the 2-chloro compound (**1g**) in addition to methylamino-dehydrogenation, methylamino-dechlorination took place, yielding 2,4-dimethylamino-3-nitro-1,8-naphthyridine (**3c**).

It seems reasonable to suggest that the actual species being oxidized is the intermediary Meisenheimer adduct **2**, i.e., 4-(methylanionium)-3-nitro-1,8-naphthyridine (or its 1,4-dihydroadduct). Evidence for the presence of intermediate **2** was provided by ^1H NMR spectroscopy. When the position of the proton signals of **1a**, dissolved in a solution of liquid methylamine at (-12°C), were compared with those of **1a**, present in a solution of DMSO, it was found that all signals attributed to the ring protons were found to be upfield shifted. Particularly, H-4 shows a considerable upfield shift of 4.10 ppm. This can be considered as good evidence for the formation of the 4-methylamino intermediate **2a**, formation of which causes rehybridization of C-4 from sp^2 to sp^3 . Literature data concerning amide or ammonia addition complexes to heterocycles support the magnitude

*This paper is dedicated to the 60th anniversary of Prof. É. Lukevits.

of this upfield shift [3]. This selective and exclusive formation of the C-4 adduct is not unprecedented. It has already been observed in the amino-dehydrogenation of these compounds.

In order to understand the selectivity in this methylamino-dehydrogenation reaction, we calculated the interaction energy ΔE between the frontal molecular orbitals of the HOMO of the methylamine and the LUMO and LUMO+1 orbitals of 3-nitro-1,8-naphthyridine. Using the simplified second-order perturbation equation [4], it was found that C-4 has the highest ΔE value of all the carbon positions in the naphthyridine ring. The conclusion seems justified that the addition is orbital controlled.

The details of the experiments and calculations will be published in a forthcoming paper.

REFERENCES

1. O. N. Chupakhin, V. N. Charushin, and H. C. van der Plas, *Nucleophilic Aromatic Substitution of Hydrogen*, Academic Press, San Diego, California (1994).
2. M. Wozniak, H. C. van der Plas, and B. van Veldhuizen, *Heterocyclic Chem.*, **20**, 9 (1983).
3. H. C. Van der Plas, M. Wozniak, and H. J. W. van der Haak, *Adv. Heterocyclic Chem.*, **33**, 95 (1983).
4. J. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, Chichester, Sussex, England (1976).