SITE-SELECTIVE EFFECT OF N-OXIDE FUNCTION TO METHYL GROUPS ON SIX-MEMBERED N-HETEROAROMATICS

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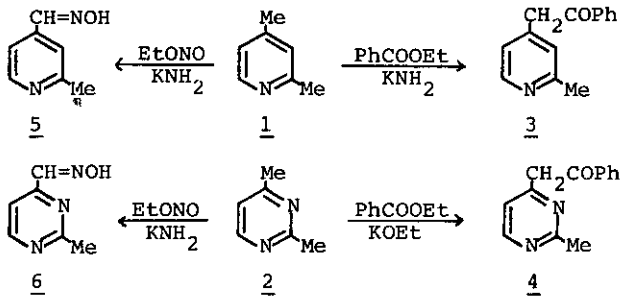
Abstract— Reaction of 2,4-dimethylpyridine 1-oxide with ethyl benzoate under basic conditions afforded 4-methyl-2-phenacylpyridine 1-oxide, while the same reaction of 2,4-dimethylpyridine itself is known to afford 2-methyl-4-phenacylpyridine. Concerning the above contrast, the effect of N-oxide function to the relative reactivity of the 2- and 4-methyl group was investigated on pyridine, quinoline, pyrimidine, and quinazoline homologues. The higher reactivity of α-methyl groups was concluded to be general in the N-oxides of these N-heteroaromatics.

Previously, we reported that in many 2,4-dimethyl homologues of six-membered N-heteroaromatics such as pyridine, quinoline, pyrimidine, and quinazoline, the reactivity of the 4-methyl group under basic conditions is generally higher than that of the 2-methyl group. For example, 2,4-dimethylpyridine (1) and 2,4-dimethylpyrimidine (2) reacted with ethyl benzoate under strongly basic conditions



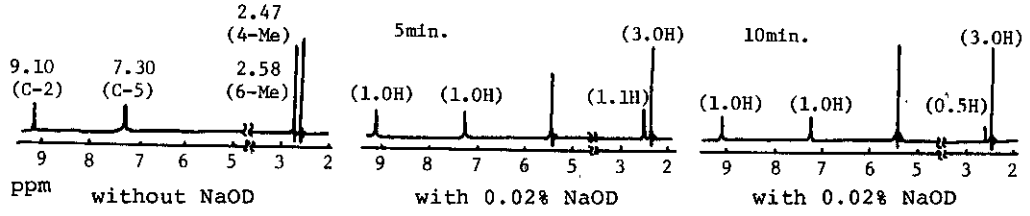
to give 2-methyl-4-phenacylpyridine (3) and 2-methyl-4-phenacylpyrimidine (4), respectively.[1] The same starting materials (1,2) were also transformed exclusively into the corresponding 4-aldoximes (5,6) by the action of ethyl nitrite with potassium amide in liquid ammonia.[2]

The above results on synthetic chemistry coincided with those of the deuterium-hydrogen exchange reaction of these dimethyl derivatives observed on the time-dependent deformation of their pmr spectra in basic medium. These experimental results can be reasonably interpreted in terms of the molecular orbital calculation on the stabilization energies due to the charge transfer interaction between N-heteroaromatics and the anion formed in the deprotonation step of the reaction.[3]

These findings stimulated us to investigate the behavior of various methyl-heteroaromatics more extensively. In the present communication, we describe the reversion of reactivity between the 2-methyl and 4-methyl groups caused by the introduction of an N-oxide function into parent compounds.

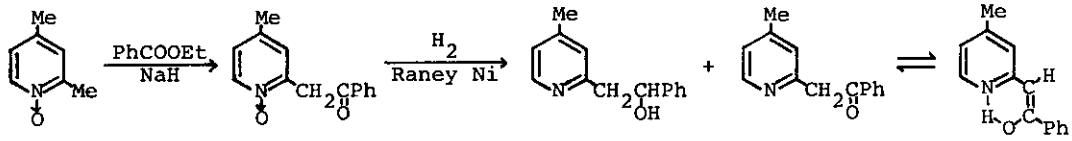
Thus, the time-dependent deformation of pmr spectra of 2,4-dimethylpyridine 1-oxide (7), 2,4,6-trimethylpyridine 1-oxide (8), and 2,4-dimethylquinoline 1-oxide (9) was investigated by the procedure as reported previously,[2] and disappearance of the signals due to the 2-methyl groups was unexpectedly observed, before decrease of the areal intensity of the 4-methyl signals. In the case of 4,6-dimethylpyrimidine 1-oxide (10), the signal due to a remote methyl group from the N-oxide group was intact while the areal intensity of another methyl signal is remarkably diminished (Fig. 1).

Fig. 1 Time-Dependent Deformation of the PMR Spectra of 10 at 20° in CD_3OD-D_2O-C_5D_5N with NaOD



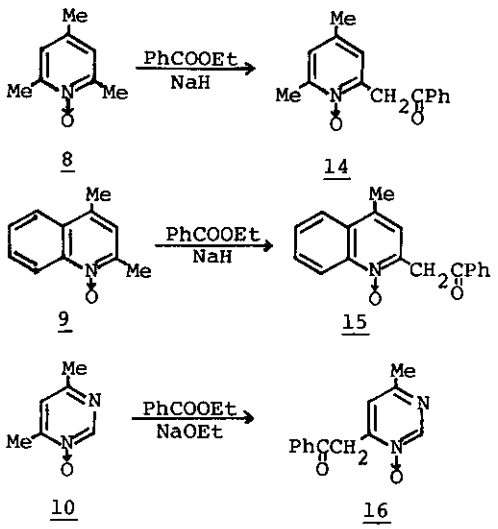
In order to confirm the above observation by chemical reaction, 7 was allowed to react with ethyl benzoate in warm tetrahydrofuran in the presence of sodium hydride, and a benzoylmethylpyridine derivative, $C_{14}H_{13}NO_2$, mp 149-150°, was obtained as a sole product in 47 % yield. The structure of the product was proved to be 4-methyl-2-phenacylpyridine 1-oxide (11) as follows. The pmr spectrum of this compound shows singlet signal due to methylene protons of a phenacyl group and

methyl protons of a pyridine nucleus at 4.51 and 2.31 ppm, respectively. When the spectrum was taken in the presence of tris(heptafluorobutanoylpivaloylmethanato)-europium, $Eu(fod)_3$, the signal of the methylene protons largely shifted and that of the methyl protons did not.[4] This observation suggests that the phenacyl group is attached to the α-position of the N-oxide group. The catalytic reduction of 11 over Raney nickel afforded 2-(2-hydroxyphenethyl)-4-methylpyridine (12), mp 93-94°, in 52 % yield, together with a small amount (5 %) of 2-phenacyl-4-methylpyridine (13), mp 59-60.5°. The latter compound (13) was unidentical with an authentic 3. Furthermore, the pmr spectrum of 13 suggested that the compound was a 1:1 mixture of a keto (13) and enol form (13') showing signals at 4.45 (1H, s, $-CH_2-$), 5,90 (0.5H, s, -CH=C<), and 15.3-15.8 ppm (0.5H, broad, >C=COH) together with signals due to a methyl group (2.30 ppm, 3H, s) and a phenyl and pyridine ring protons (6.6-8.5 ppm, 8H, m). The presence of the above tautomerism is one of the good evidence for structure 13, because such keto-enol tautomerism is frequently observed on α-acylmethyl-N-heteroaromatics.



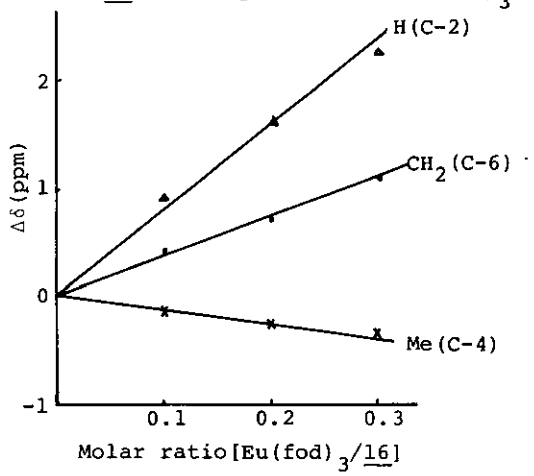
7 11 12 13 13'

Similarly, 8, 9, and 10 were treated with ethyl benzoate under similar conditions, and 4,6-dimethyl-2-phenacylpyridine 1-oxide (14), mp 131-133°(53 %), 4-methyl-2-phenacylquinoline 1-oxide (15), mp 198-200°(68 %), and 4-methyl-6-phenacylpyrimidine 1-oxide (16), mp 133-134°(22 %), were obtained as sole products, respectively.



8 14 9 15 10 16

Fig. 2 Induced Signal Shifts of PMR spectra of 16 in the presence of $Eu(fod)_3$

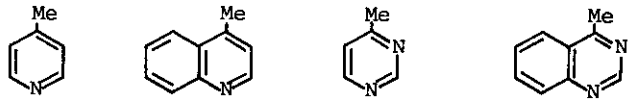


The structures of these products are supported by investigating the signal shift in their pmr spectra induced by the addition of $Eu(fod)_3$. In all the cases, the large signal shift appeared at the methylene group of the side chain. The magnitude of the signal shift observed on 16 was represented in Fig. 2 as a typical example.

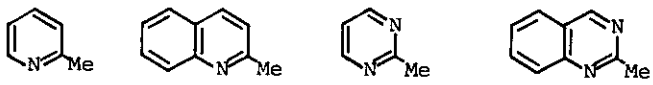
The above-mentioned results clearly demonstrated that the introduction of an N-oxide function into six-membered N-heteroaromatics activated the neighboring methyl group more than the romote one. In connection with these results, the approximate rate constants of hydrogen-deuterium exchange reaction on various monomethyl derivatives were estimated by measuring the time-dependent decrease of the areal intensity of the pmr signals due to the testing methyl groups in D_2O-CD_3OD solution under an appropriate concentration of NaOD. Relative rate constants converted from the observed value are listed in the following Table, where the value of 2-methylpyridine is fixed to be 1.0, as standard. The rate of 2-methylquinazoline 1-oxide is not given, because this compound has not yet been synthesized.

In conclusion, it is noteworthy that the values in the Table suggest the activation effect of an N-oxide function to methyl groups to be rather concentrated at its α-position.

Table Relative Rate Constants of Hydrogen-Deuterium Exchange Reaction of Methylheteroaromatics



N-oxide	6×10^4	8×10^5	2×10^8 (1-oxide) 3×10^8 (3-oxide)	1×10^9 (1-oxide) 4×10^9 (3-oxide)
tert. base	8×10^1	3×10^3	2×10^6	1×10^8



N-oxide	1×10^5	1×10^7	3×10^7	9×10^7 (3-oxide)
tert. base	1.0	1×10^3	2×10^4	7×10^5

REFERENCES

1. H. Yamanaka, H. Abe, and T. Sakamoto, Chem. Pharm. Bull., 1977, 25, 3334.
2. H. Yamanaka, H. Abe, T. Sakamoto, H. Hiranuma, and A. Kamata, Chem. Pharm. Bull., 1977, 25, 1821.
3. Y. Goto, T. Niiya, H. Yamanaka, T. Sakamoto, T. Kubota, K. Ezumi, and R. Shimada, Chem. Pharm. Bull., 1980, 28, 1117.
4. T. Sakamoto, S. Niitsuma, M. Mizugaki, and H. Yamanaka, Chem. Pharm. Bull., 1979, 27, 2653.

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