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THE RADICAL AND ORGANOMETALLIC METHYLATION OF NICOTINE AND NICOTINE N-OXIDE[1]

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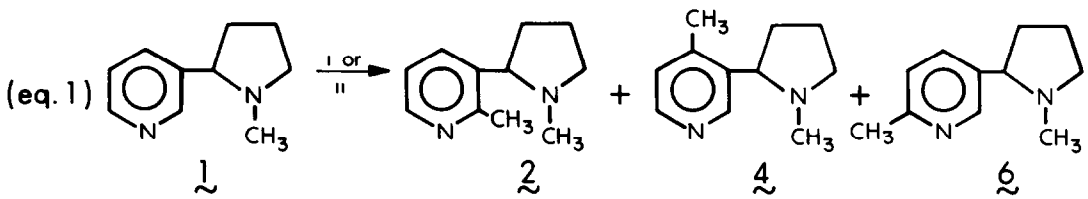
SUMMARY. 2-Methylnicotine is a major product in the reaction of nicotine with methyllithium and methyl radical, in addition to the previously reported 4- and 6-methylnicotines. The reaction of nicotine N-oxide with methylmagnesium bromide furnishes both 2- and 6-methylnicotine.

2-Methylnicotine (2), 4-methylnicotine (4) and 6-methylnicotine (6) have proven to be important compounds in the development of structure-activity relationships in nicotine (1) pharmacology.[2-4] These methylnicotinoids have been prepared: (a) by lengthy procedures from alkylnicotinic acid esters[3,5]; (b) by Sommelet-Hauser rearrangement of monosubstituted pyridines[6]; and (c) by radical[7] and methyllithium[2,3] methylation of nicotine itself. As the reaction of methyllithium and methyl radical with optically pure (-)-nicotine seemed to be the most direct route to optically active nicotine analogues, we were particularly interested in studying procedures which would, in one step, furnish these compounds. We describe herein the results of our investigation of the latter two literature procedures[2,3,7] (items c above), and report the observation, in all cases, of an additional major product not previously observed.

Some time ago, Haglid reported that nicotine reacts with methyllithium to form mostly 6 and minor quantities of 4 (eq. 1i).[2] Leete and Leete recently attested[3] to Haglid's results[2] without citing the presence of 2.[5b] The possible lack of formation of 2 is interesting in that methyllithium has generally been observed to react regioselectively with 3-substituted pyridines at the 2-position.[8]



In our hands, the total distilled mixture from the reaction of 1 with two equiv of methyllithium in refluxing toluene showed only three peaks (corresponding to 4, 6, and 1) by packed column gas chromatography (5% SE-30, 5' x 1/4", 150°C/10°C/min), consistent with the literature reports [2,3] However, capillary gas chromatographic analysis (4% FFAP, 100 m, 150°C) led to the observation of four peaks, the additional major product shown to be 2 by comparison with an authentic sample.[5b,6] ^{13}C-nmr analysis of the reaction mixture confirmed the formation of both

2 and 6 in nearly equal amounts. The yields obtained were 2:4:6:1 = 17%:<1%.19%:32%.

In an effort to convert more 1 to product, the molar ratio of methyllithium to nicotine was increased to four. While the recovered yield of nicotine dropped significantly, the yields of products (2:4:6:1 = 19%:0.8%·21%:15%) were essentially unchanged. This indicates that product decomposition is competitive with product formation under these conditions.

Table I shows the ^{13}C chemical shifts of the pure methylnicotines obtained from independent synthetic routes.[9] Figure 1 displays the ^{13}C-nmr spectrum of the total distilled reaction product mixture of 1 with four equiv of methyllithium. The observation of fifteen pyridine resonances in Figure 1 was an early indication to us that 2 was present in significant quantities in reaction 11. Based on the chemical shift information, identification of both 2-methylnicotine and 6-methylnicotine as major products is evident.

Recently, Itokawa and co-workers reported[7] that radical methylation of nicotine (see eq. 111) led to a mixture of 4 and 6 in a ratio of 1:4.3. They suggested that steric hindrance at nicotine's C-2 and C-4 position by its N-methylpyrrolidinyl group was responsible for the lack of formation of 2. In our hands, the reaction of a six-fold excess of t-butylhydroperoxide/

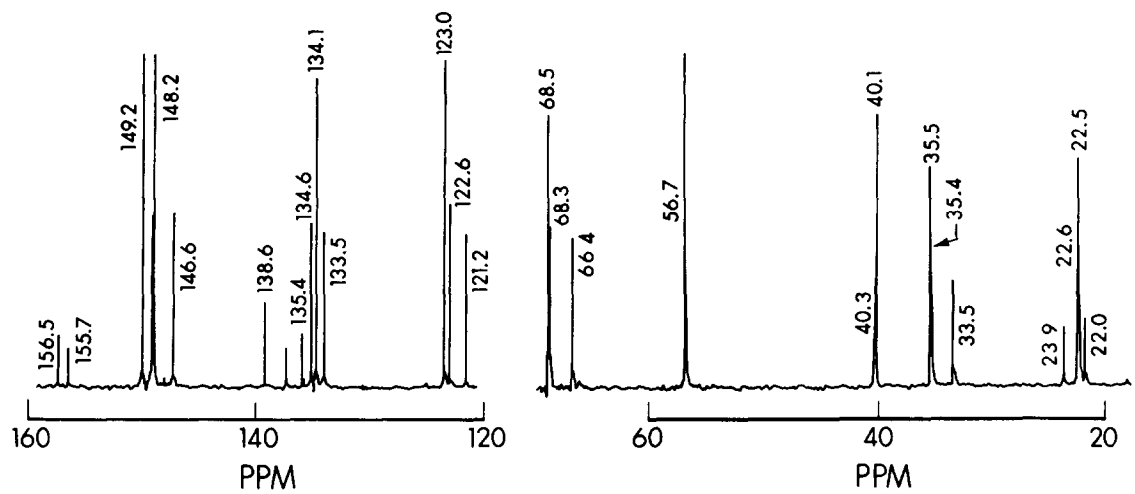


Figure 1. ^{13}C-nmr spectrum of the total reaction mixture of nicotine and 4 equiv of CH_3Li.

TABLE I. ^{13}C-NMR RESONANCES (ppm)[a]

	C(2)	C(3)	C(4)	C(5)	C(6)	C-CH_3	C(2')	C(3')	C(4')	C(5')	N-CH_3
Nicotine[b]	149.7	139.1	134.8	123.5	148.7	--	68.8	35.4	22.7	57.0	40.3
2-Methylnicotine	156 1	137.0	134.0	121.4	146.8	21.9	66.5	33.4	22.5	56 7	40.3
4-Methylnicotine	148.9	137.1	145.0	125.1	147.7	18.6	66.0	33.5	22.7	57.0	40.6
6-Methylnicotine	148.5	135.3	134.8	122.8	156.7	23.9	68.4	35.2	22.5	56.8	40.1

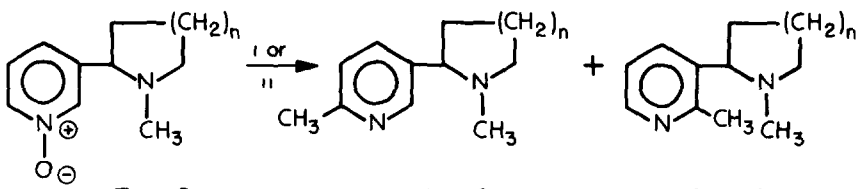
a Spectra were obtained in $CDCl_3$ or CD_2Cl_2 solution on either a Varian XL-100 NMR spectrometer equipped with a Digilab NMR-3 FT accessory or a Bruker WP-80 spectrometer.

b Pitner, T. P., Seeman, J. I ; Whidby, J. F. J. Heterocyc. Chem. 1978, 15, 585-587.

$FeSO_4 \cdot 7H_2O/H_2SO_4$ with nicotine led to a mixture of 2:4:6 = 8%:11%:32% with 34% recovered starting material as determined by capillary GC analysis.

Related to the above discussion is the report of Otroshchenko, et. al.,[10] that the reaction of methylmagnesium iodide with N'-methylanabasine N-oxide (7) in "heated" benzene results in the formation of a single product, 6,1'-dimethylanabasine (8) in 33% yield (eq. 21). As our current interest relates primarily to nicotine derivatives, we reacted nicotine N-oxide[11] (9) with methylmagnesium bromide in THF and obtained the following products and yields at the stated temperatures: at 50°C, (2:6:1 = 6%:9%:6%); at -70°C, (2:6:1 = 25%:26%:14%) (eq. 211). In both cases, nearly equal amounts of 2 and 6 were formed in the absence of 4. We suspect that careful examination of the N'-methylanabasine N-oxide reaction mixture[10] would reveal significant quantities of 2,1'-dimethylanabasine (10).

(eq. 2)



7, n=2; 9, n=1 — 6, n=1; 8, n=2 — 2, n=1; 10, n=2

i, CH_3MgBr/benzene, heat (ref. 10); ii, CH_3MgBr/THF.

In conclusion, the methyllithium and methyl radical reactions with nicotine and the methyl Grignard reaction with nicotine N-oxide all give 2 and 6 as major products. The only literature report that either methyllithium or methyl radical attacks regioselectively at C-6 of a 3-monosubstituted pyridine derivative involves 3-tert-butylpyridine.[8c] For example, a comparison of the methyllithium reaction with 3-isopropylpyridine (2,3-/2,5-isomer ratio = 2.2) and with 3-tert-butylpyridine (2,3-/2,5-isomer ratio = 0.04) indicates that a sufficiently bulky group at C-3 can direct attack away from C-2.[8c] We have previously obtained chemical evidence that the N-methylpyrrolidinyl moiety presents substantial steric hindrance at nicotine's C-2 position.[12] Nonetheless, the formation of both 2 and 6 in nearly equal amounts indicates that the N-methylpyrrolidinyl group influences the methyllithium and methyl radical reactions of a β-substituted pyridine more like an isopropyl than a tert-butyl substituent. The steric bulk of an N-methylpyrrolidinyl moiety is not sufficient to prevent C-2 attack, be it from methyllithium, methylmagnesium bromide, or methyl radical.

Since 6-methylnicotine has been found to be pharmacologically active while 2-methyl- and 4-methylnicotine are essentially inactive,[2-4] we have extended the scope of these reactions to obtain other 6-substituted nicotinoids regioselectively Preliminary results with ethyllithium, sec-butyllithium, vinyllithium, and cyclopropyllithium at -70° in ether/TMEDA have been encouraging, especially considering the lengthy procedures necessary to prepare these compounds by alternative methods. We have, to date, found the 6-alkylnicotinoid to be the major product in each reaction to the exclusion of the corresponding 2- and 4-alkylnicotine.[14,15]

REFERENCES AND NOTES

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(9) Prepared either by a [2,3]-sigmatropic rearrangement[6] or by the reaction of the lithium salt of N-trimethylsilylpyrrolidinone with the corresponding methyl nicotinic acid ester.[5a]

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(12) Information is now available[1,13] which indicates that the rate of alkylation of the pyrrolidine nitrogen of 2-methylnicotine is substantially less than that of nicotine. That aromatic methyl groups ortho to the N-methylpyrrolidinyl moiety cause steric hindrance at the pyrrolidine nitrogen indicates that the pyrrolidine N-methyl group likewise increases steric hindrance at the ortho carbons.

(13) Seeman, J I ; Secor, H. V.; Chavdarian, C. G., Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. J. Org. Chem. in press.

(14) We will report full details of the synthesis of additional alkylnicotinoids and their spectral and optical properties in a full paper.

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