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Organometallic Methylation of Nicotine and Nicotine *N*-Oxide. Reaction Pathways and Racemization Mechanisms[1]

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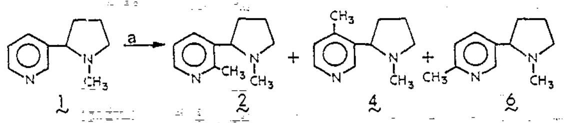
The reaction of nicotine with methyllithium leads to 2-methylnicotine as a major product in addition to the previously reported 4- and 6-methylnicotines. The reaction of nicotine *N*-oxide with methylmagnesium bromide furnishes both 2- and 6-methylnicotine. The product composition of these reactions is strongly dependent on the experimental conditions; the effects of solvent, temperature, and relative reagent concentration are presented. The methyllithium reactions lead to partially racemized methylnicotines, and the recovered nicotine is often nearly optically pure. Independently, (*S*)-(−)-6-methylnicotine was treated with methyllithium and was recovered with complete retention of optical activity. These results suggest that the loss of optical purity in the formation of methylnicotines in these methyllithium reactions occurs during the reaction itself and is not due either to racemization of the starting material or to subsequent racemization of the initially formed product.

Introduction

Investigations in the field of nicotine structure–activity remain a topic of considerable interest.[2] While almost all preparations of nicotine analogues involve lengthy synthesis from acyclic precursors,[3] some of these nicotinoids have been derived directly from nicotine itself.[4,5] This latter approach has appeal because optically pure (*S*)-nicotine is readily available as a starting material, and because this strategy can directly result in optically active analogues.

Some years ago, it was reported that reaction of nicotine (1) with methyllithium in a variety of solvents led to the isolation of 6-methylnicotine (6) with minor amounts of 4-methylnicotine (4) (eq 1).[6] In 1978, other workers reported repeating the original literature procedure and "obtaining essentially the same results" with the exception that the isolated 4 had a higher optical activity.[7,8]



(1)

(a) CH_3Li/toluene heat

Based on the well-documented propensity of alkyllithium reagents to attack in a regioselective manner at the 2-position of a 3-substituted pyridine in preference to the 6-position,[9] we were somewhat skeptical of the literature reports[6,7] which did not demonstrate the formation of 2-methylnicotine (2) as a reaction product. We were thus prompted to reexamine these methylations to confirm

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[1] For the previous paper in this series, see: Kao, J.; Seeman, J. I. *J. Comput. Chem.*, in press.

[2] For leading references, see: (a) Aceto, M. D.; Martin, B. R. *Med. Res. Rev.* 1982, *2*, 43–62. (b) Abood, L. G.; Reynolds, D. T.; Booth, H.; Bidlack, J. M. *Neurosci. Biobehav. Rev.* 1981, *5*, 479–487. (c) Romano, C.; Goldstein, A. *Science* 1980, *210*, 647–650. (d) Rondahl, L. *Acta Pharm. Suec.* 1980, *17*, 347–351. (e) Sanders, E. B.; Secor, H. V.; Seeman, J. I. U.S. Patent 4 155 909, 1979; U.S. Patent 4 220 781, 1980.

[3] (a) Hu, M. W.; Bondinell, W. E.; Hoffmann, D. *J. Labelled Compds.* 1974, *10*, 79–88. (b) Catka, T. E.; Leete, E. *J. Org. Chem.* 1978, *43*, 2125–2127. (c) Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. *Ibid.* 1981, *46*, 3040–3048. (d) Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L. *Ibid.* 1982, *47*, 1069–1073. (e) Cushman, M.; Castagnoli, N., Jr. *Ibid.* 1972, *37*, 1268–1271. (f) Hutchinson, C. R.; Nakane, M. *Ibid.* 1978, *43*, 3922–3931. (g) Castonguay, A.; Van Vunakis, H. *Ibid.* 1979, *44*, 4332–4337. (h) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *Ibid.* 1978, *43*, 324–330; 1976, *41*, 2658–2659. (i) Seeman, J. I. *Synthesis* 1977, 498–499.

[4] (a) For a preliminary communication of some of these results, see: Secor, H. V.; Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* 1981, *22*, 3151–3154. (b) Seeman, J. I.; Howe, C. R., unpublished results.

[5] Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* 1982, *23*, 2519–2522.

[6] (a) Haglid, F. *Acta Chem. Scand.* 1967, *21*, 329–334. (b) Haglid, F. *Acta Pharm. Suec.* 1967, *4*, 117–138. (c) Haglid indicates that a "third possible product",[6a] 2-methylnicotine, was present in "trace"[6d] quantities as judged by "the presence of trace amounts of 2-methylnicotinic acid methyl ester and quinolinic acid dimethyl ester"[6a] by packed column GC analysis of the permanganate oxidation mixture of the total methylation reaction product. (d) Haglid, F.; Norén, J. O. *Acta Chem. Scand.* 1967, *21*, 335–340.

[7] Leete, E.; Leete, S. A. S. *J. Org. Chem.* 1978, *43*, 2122–2125.

[8] The methylation of nicotine under homolytic radical conditions (t-$BuOOH/FeSO_4 \cdot 7H_2O/H_2SO_4$) leads to 2-, 4-, and 6-methylnicotines of higher optical purity than obtained in the methyllithium alkylations. See: ref 4 and Itokawa, H.; Inaba, T.; Haruta, R.; Kameyama, S. *Chem. Pharm. Bull.* 1978, *26*, 1295–1297.

[9] (a) Yale, H. L. in "Pyridine and Its Derivatives"; Abramovitch, R. A., Ed.; Wiley: New York, 1974; Vol. 14, Supplement, Part Two, Chapter VII. (b) Abramovitch, R. A.; Poulton, G. A. *J. Chem. Soc. B* 1969, 901–903. (c) Hauck, A. E.; Giam, C.-S. *J. Chem. Soc., Perkin Trans. 1* 1980, 2070–2076 and references cited in these papers.

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