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NICOTINE CHEMISTRY

THE ADDITION OF ORGANOLITHIUM REAGENTS TO (−)-NICOTINE

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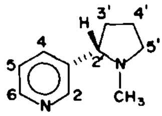
Abstract– Organolithium reagents (RLi; where R = ethyl, isopropyl, cyclopropyl, n-butyl, sec-butyl, t-butyl, vinyl) have been found to add *regiospecifically* to (−)-nicotine to provide a series of 6-substituted nicotinoids of low optical activity. The data presented for the organolithium additions coupled with an analysis of the addition of t-BuLi to (−)-nicotine and [2′-^{2}H]nicotine have provided strong evidence for a novel racemization process caused by pyrrolidine ring-opening and reclosure involving nicotine's N′—C′$_2$ bond.

Requisite to an understanding of the pharmacology of (−)-nicotine (**1**)[1] is the synthesis of nicotine analogues[2–4] for the development of structure–activity relationships. Nicotinoids substituted with a methyl group in the pyridine ring are among the best known examples.[4–6] 6-Methylnicotine (**2**) exhibits activity on a par with nicotine, whereas the 2-Me and 4-Me isomers are nearly inactive.[5,7] Due to the high activity of **2**, we were interested in the preparation of additional 6-substituted analogues.



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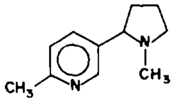

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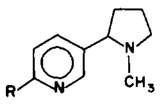


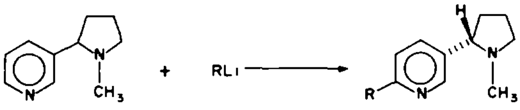
3

We now report (a) the regiospecific formation of partially racemized 6-alkylnicotinoids from the reaction of optically pure nicotine with seven alkyllithium reagents; (b) experimental results and a proposed mechanism involving reversible pyrrolidine ring cleavage–recyclization which accounts for the loss of optical purity; and (c) the observation of two novel reaction pathways in the reaction of nicotine and t-BuLi which involve pyrrolidine ring scission.

RESULTS AND DISCUSSION

In previous work, we and others have observed the simultaneous formation of 2-, 4- and 6-methylnicotines by the addition of methyllithium to (−)-nicotine (Eq. 1).[4,5a,6] Abramovitch[8] obtained 2-phenylnicotine and 6-phenylnicotine in a ratio of 1 : 1 from the reaction of phenyllithium and nicotine. Utilizing phenyllithium and n-butyllithium, Haglid[5b] reported the preparation of 6-phenylnicotine and 6-n-butylnicotine; however, these compounds were only briefly mentioned and neither experimental details nor characterization results were provided (e.g. no indication as to the degree of regioselectivity was reported).

In contrast with the nicotine–methyllithium and nicotine–phenyllithium reactions, we have now found that more highly substituted alkyllithium reagents add regiospecifically to nicotine.[3] For ethyllithium, isopropyllithium, cyclopropyllithium, n-BuLi, sec-BuLi, t-BuLi and vinyllithium, the 6-alkylnicotinoid **3** is formed to the exclusion of both the 2- and 4-adducts. As shown in Table 1, most experiments were performed in ether–tetramethylethylenediamine (3 : 1) at −70° with a small excess of reagent.



1

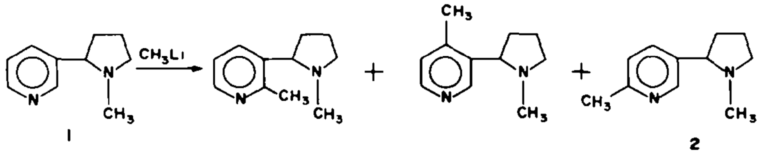
3a – 3g; 4

3a, R = Me
3b, R = Et
3c, R = i-Pr
3d, R = c-Pr
3e, R = n-Bu
3f, R = s-Bu
3g, R = vinyl
4, R = t-Bu

(2)

When (−)-nicotine was treated with t-BuLi in THF under a variety of conditions (Table 2), two novel pyrrolidine ring-cleaved products, **5** and **6**, were isolated in addition to the normal product, 6-t-butylnicotine (**4**) (Eq. 3).

The identification of **3b**–**3g** and **4** was based on ^{1}H-NMR spectroscopic data, mass spectral analysis and elemental analysis (Experimental). With regard to the spectroscopic studies, comparisons were made with the spectra of nicotine[2,9,10] and 6-methylnicotine, the latter compound having been prepared previously by us[2b,2c,4] and by others[5,6] via different routes.



1

2

(1)

Table 1. 6-Alkylnicotine (3) from (−)-nicotine (1) and RLi (1.3 equiv) in ether–TMEDA (3 : 1) at −70°

Alkyllithium	% yield of 6-alkylnicotine*	$[\alpha]_D^{20}$ of 6-alkylnicotine (3)	$[\alpha]_D^{20}$ of recovered nicotine†
Methyllithium‡	26	−2.8°	−166°
Ethyllithium	30	−16°	−169°
Isopropyllithium	43	−17.5°	§
Cyclopropyllithium‖	17	−38°	§
n-Butyllithium	43	−12°	−170°
sec-Butyllithium	28	−29.5°	−132°
t-Butyllithium¶	33	−20°	−43°
Vinyllithium	6**	−58°	−150°

* Based on purification and GC analysis.

† The $[\alpha]_D^{20}$ for optically pure (*S*)-(−)-nicotine is −169.8 ± 2.3° (CH_2Cl_2) (see reference 4b).

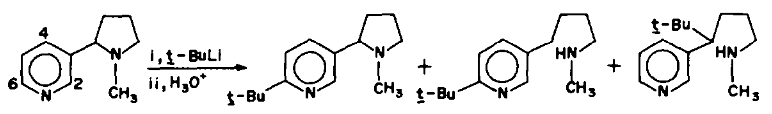
‡ Reference 4.

§ Not observed.

‖ Prepared from cyclopropyl bromide and lithium in ether.

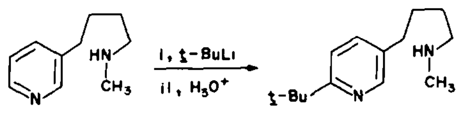
¶ Only minor amount of aberrant product observed under these reaction conditions.

** Also obtained 6-ethylnicotine (2%), presumably from isomerization of the intermediate 6-vinyl dihydropyridine intermediate.



1 4 5 6 (3)

The ^{1}H-NMR spectrum of **5** [Fig. 1(b)] is consistent with a 2,5-disubstituted pyridine, but the resonances at *ca* 3 ppm which are indicative of the 2′ and 5′β protons of a nicotinoid are not present. The mass spectrum and elemental analysis of **5** were indicative of a dihydro-**4**. As the chemical shift of the t-Bu protons were indicative of its being substituted on the pyridine ring, our tentative assignment of its structure as **5** was supported by the very marked similarity that its spectra had to those of dihydrometanicotine **7**.[11,12] The structure of **5** was further confirmed by an independent synthesis from the reaction of **7** with t-BuLi (Eq. 4).



7 5 (4)

Isomeric with **5**, **6** was shown by analysis of its ^{1}H-NMR spectrum [Fig. 1(c)] to lack a pyrrolidine ring, to have a t-Bu group attached to a non-aromatic carbon, and to be a 3-mono-substituted pyridine derivative. Given these considerations, the most likely addition-cleavage location of the pyrrolidine ring is the N′—$C_{2'}$ bonds leading to **6**. The chemical shifts of the acyclic portion of **6** likewise shows the expected positions for this substitution pattern.

Conformation of this assignment was made by mass spectral analysis. The base peak in the spectrum of **6** (Scheme 1) is due to cleavage α to the aliphatic C—N bond, leading to a $[CH_3NHCH_2]^+$ (*m/z* 44) fragment. The other significant peaks are at *m/z* 134, 120 and 106. Exact mass measurements show that all three ions incorporate one N atom. Information about the precursors for these ions reveal that *m/z* 164 → *m/z* 106, *m/z* 176 → *m/z* 120, and *m/z* 149 → *m/z* 134 are the most likely direct pathways for formation.

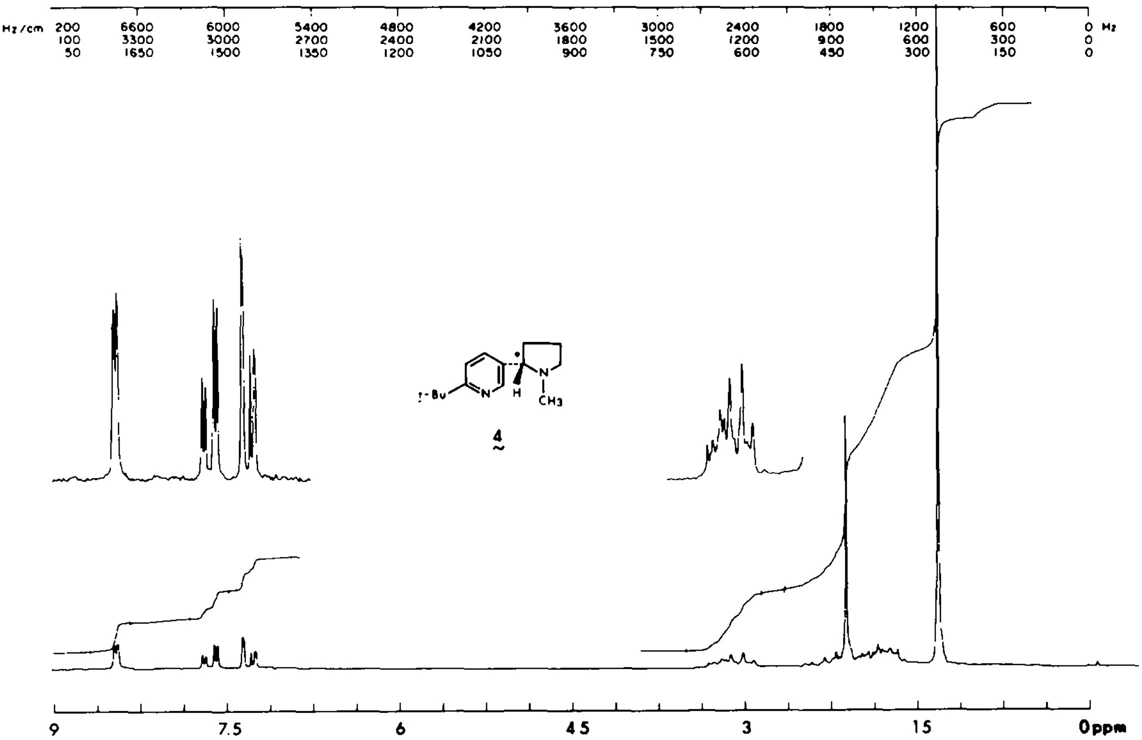
Table 2. Product mixtures from nicotine + t-BuLi in THF

Reaction conditions*	Deoxygenation	Product distribution (%) 1	4	5	6	Yield (%)†
0°/N_2	No	12	23	9	56	83
0°/N_2	No	16	41	43	< 1	23
0°/N_2	No	12	42	18	28	37
0°/N_2	No	17	28	4	51	39
0°/Ar	Yes‡	22	46	25	7	40
0°/Ar	Yes‡	21	48	27	4	40
−70°/N_2	No	25	62	13	< 1	50

* Temperature/atmosphere over reaction mixture. THF was distilled from $LiAlH_4$ prior to use; t-BuLi was obtained from Alfa Chemicals and used as received.

† Distilled yield except for 83% yield which is crude.

‡ Performed by bubbling argon through all solvents and reagents prior to reaction.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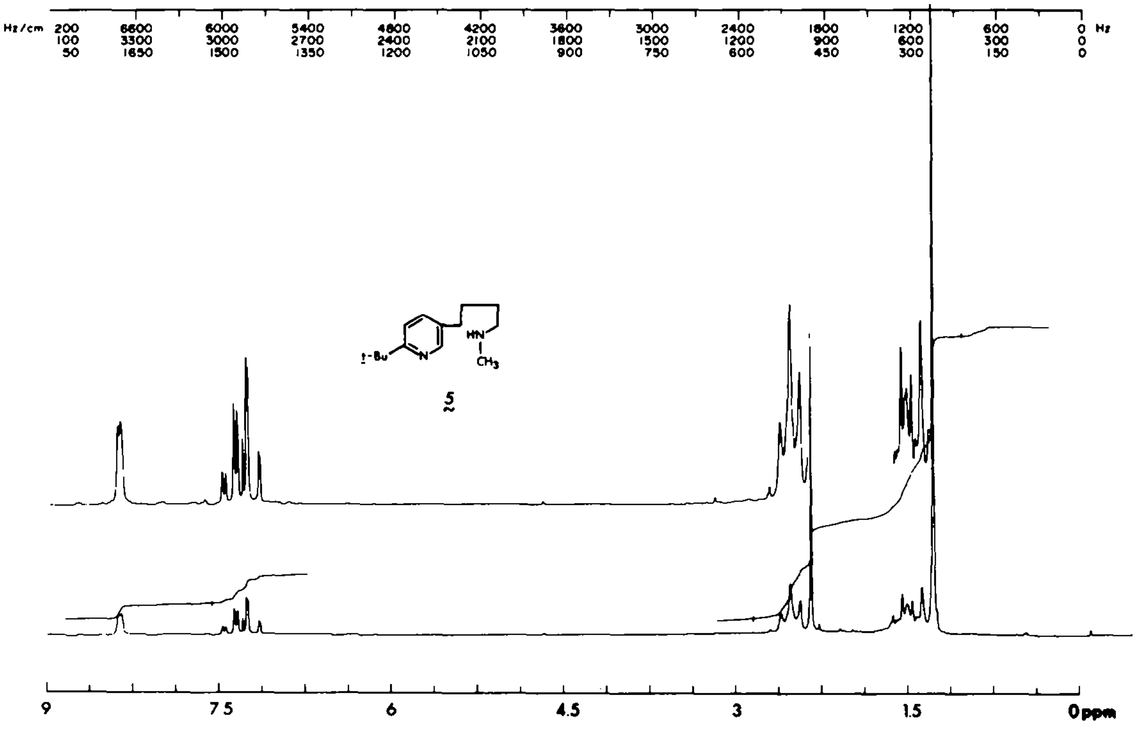
6600 3300 1650
6000 3000 1500
5400 2700 1350
4800 2400 1200
4200 2100 1050
3600 1800 900
3000 1500 750
2400 1200 600
1800 900 450
1200 600 300
600 300 150
0 0 0 Hz
t-Bu
N
H
CH3
4
9
7.5
6
4.5
3
1.5
0ppm

Fig. 1(a).


Hz/cm 200 100 50
6600 3300 1650
6000 3000 1500
5400 2700 1350
4800 2400 1200
4200 2100 1050
3600 1800 900
3000 1500 750
2400 1200 600
1800 900 450
1200 600 300
600 300 150
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CH3
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Fig. 1(b).

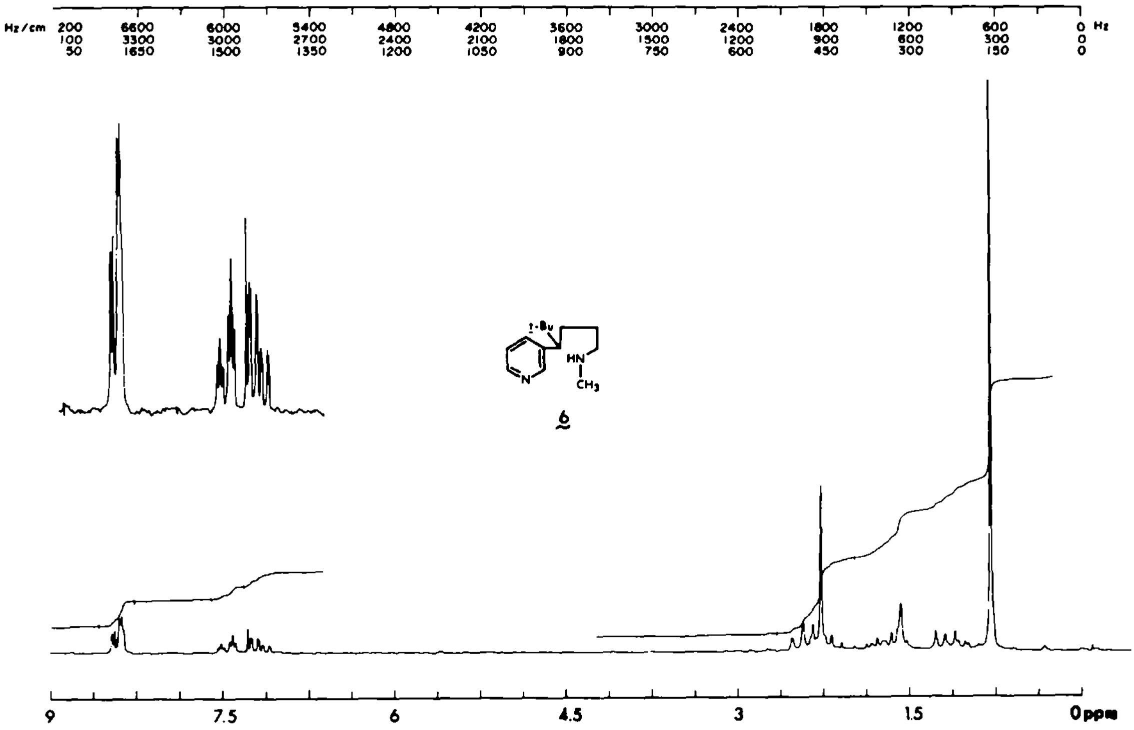


Fig. 1(c).

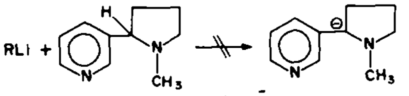
Scheme 1 shows that hydrogen rearrangement to the pyridyl ring from either the t-butyl or N-methyl butyl group will yield ions of *m/z* 164 or 149 respectively. Loss of C_3H_8N from *m/z* 164 produces the ion at *m/z* 106, while methyl loss from *m/z* 149 forms the *m/z* 134 ion. The formation of the *m/z* 120 ion can be rationalized first by new bond formation to yield a bicyclic intermediate (*m/z* 176) followed by loss of isobutene, as illustrated in Scheme 2.

The t-butylation reaction was unique in three ways: (a) it led to two unprecedented reaction products, **5** and **6**; (b) of all the alkylation reactions, only the t-butylation resulted in any product in significant yield (> 5%) other than the 6-alkylnicotinoid **3**; and (c) as indicated in Table 2, the product mixture was strongly dependent on reaction conditions. In particular, the product distribution and percentage yield were non-reproducible when we did not rigorously exclude oxygen from the reaction mixture. These observations suggest the possibility of electron transfer in the t-butylation reaction in addition to a two-electron, nucleophilic addition process. We will discuss these points subsequently.

Aberrant products such as **5** or **6** were not observed for the other organolithium reactions listed in Table 1, with the possible exception of the vinyllithium addition which afforded in low (< 3%) yield a compound tentatively assigned (by EIMS) as 6-vinyldihydrometanicotine. All product mixtures were analyzed by capillary GC-EIMS, using the significantly different mass spectral fragmentation patterns of **4**–**6** as a guide for structural assignment of minor (< 3% yield) reaction components. The addition of isopropyllithium to nicotine was also performed at 0° in THF, comparable to the t-BuLi runs which led to sizeable quantities of **5** and **6**. No pyrrolidine ring-opened product was observed. Further attempts to prepare opened derivatives with the other organolithium reagents were not pursued.

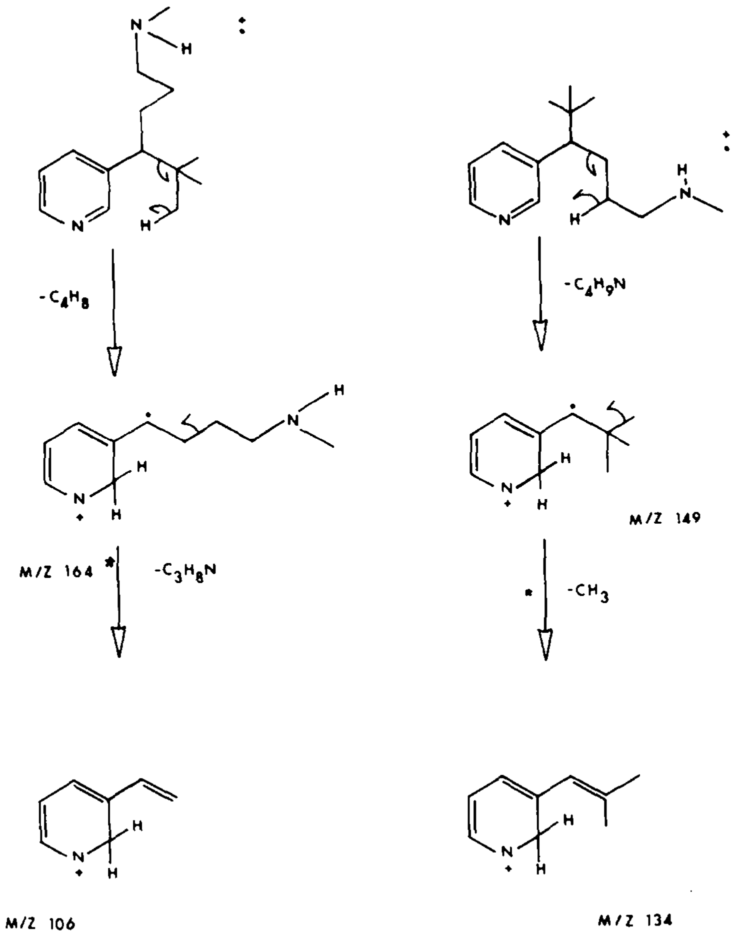
Racemization studies

In order to gain an understanding as to the mode of partial racemization[13] for the alkyllithium reactions, we determined the optical rotation of the recovered nicotine from several of the runs (Table 1). It is important to note that in every case except the t-BuLi entry, the recovered nicotine is either unracemized or racemized to a minor extent (12–22%). In contrast, the 6-alkylnicotinoids **3** are formed with a sizeable degree of racemization in each instance. The data again speak against a "classical" deprotonation–racemization of (–)-nicotine[14] prior to organolithium addition (Eq. 5), and by inference, against deprotonation–racemization of optically pure 6-alkylnicotinoid.

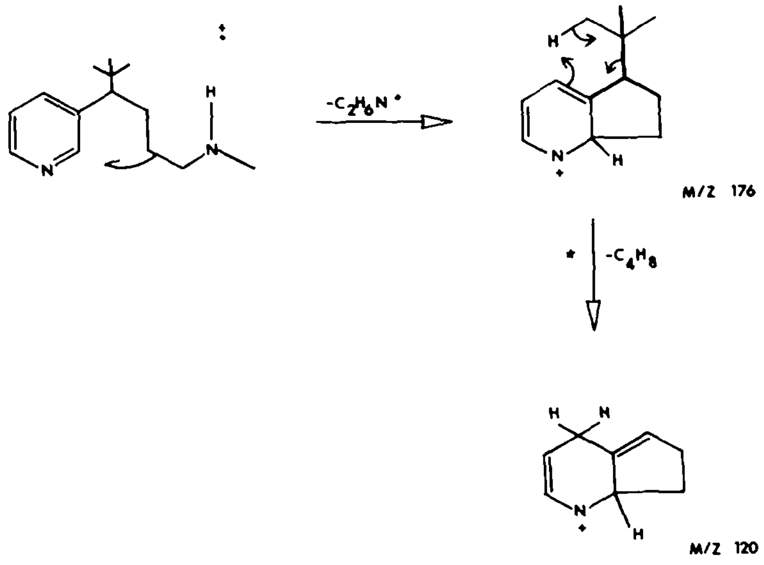


(5)

Confirmation that the 2′-substituted proton in nicotine was *not* lost to any significant degree by a racemization process of deprotonation–reprotonation was obtained by examining the fate of the deuterium atom in the t-butylation of (±)-nicotine-2′-d_1(**9**)[15] under reaction conditions known to produce partial racemization of both 6-t-butylnicotine and (–)-nicotine. Recovered **9** and 6-t-butylnicotine-2′-d_1 (**10**) were analyzed by mass spectrometry for deuterium incorporation at $C_{2'}$.[16] As shown in Table 3, the high deuterium incorporation in **9** and **10** confirms that the major (and nearly exclusive) racemization process that occurs in the addition of t-BuLi to **1** does *not* involve deprotonation at $C_{2'}$ (Eq. 5).



Scheme 1.



Scheme 2.

Table 3. Racemization analysis of product mixtures from the independent reactions of (*S*)-(−)-nicotine (**1**) with t-BuLi and (*R*, *S*)-nicotine-2′-d_1 (**9**) with t-BuLi

Experimental conditions*	% e.e. of recovered **1**†‡	% e.e. of **4**†§	D incorporation in recovered **9**	% D incorporation in **10**
THF, 0°, Ar‖	71	4.1	> 95	> 95
THF, 0°, Ar‖	69	4.8	—	—
THF, −70°, N_2	25	21	> 95	> 95

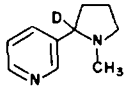
* Utilized 1.2 equiv. of t-BuLi for all experiments.

† All rotations performed with GC purified nicotinoids in CH_2Cl_2.

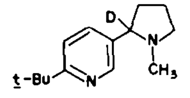
‡ Optically pure (*S*)-(−)-nicotine has $[\alpha]_D^{20}$ −169.8 ± 2.3° (CH_2Cl_2) (ref. 4b).

§ The maximum rotation observed for **4** by an alternate procedure is $[\alpha]_D^{25}$ −146° (CH_2Cl_2). From reference 13b.

‖ Deoxygenation performed prior to reaction.

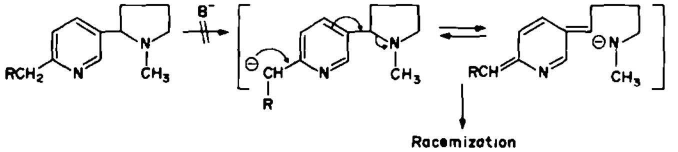


9



10

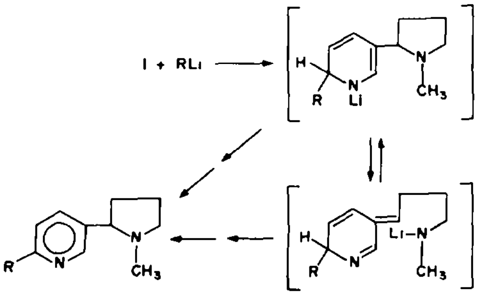
We have previously observed that 6-methylnicotine is optically stable toward both methyllithium and lithium diisopropylamide (Eq. 6).[4b] We have obtained additional evidence against the operation of an Eq. 6 process for these more highly substituted alkyllithium reagents and 6-alkylnicotinoids by reacting optically active 6-ethylnicotine (**3b**) with one equivalent of isopropyllithium; the recovered, unreacted **3b** had specific rotation identical to that of the starting material.[17] We conclude that these 6-alkylnicotinoids **3** do *not* racemize by initial deprotonation of a $C_{6\alpha}$—$H_{6\alpha}$ proton.



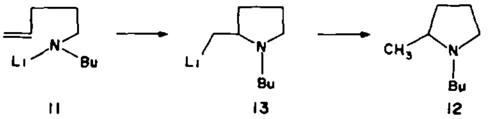
(6)

We propose the mechanism shown in Scheme 3. The key feature of this mechanism is the reversible cleavage of the pyrrolidine ring at the chiral center. The formation of **5** and **6** provides additional support for this hypothesis.

Some published observations support the N'—$C_{2'}$ ring scission–ring closure reactions illustrated in Scheme 3. Firstly, regarding ring scission, the addition of alkyl- and aryllithium reagents to pyridines is well known to form lithiated dihydropyridines which have excess electron density at C_5 and which can form C_5—E bonds with a variety of E^+ electrophiles.[18] Extension of this concept to cleavage of the N'—$C_{2'}$ bond as in Scheme 3 is therefore quite reasonable. Secondly, with regard to ring closure, Newcomb and Burchill[19] have recently reported that lithium N-butyl-4-pentenylamide (**11**) cyclizes to the pyrrolidine **12** via **13** (Eq. 7).



Scheme 3.



(7)

A more complex mechanism must be advanced to account for the product distribution, oxygen sensitivity, and loss of optical purity of recovered (−)-nicotine in the t-butylations. The formation of ring-cleaved intermediates having radical or radical anion character may best explain the results.[20] Metal salts of dihydropyridines have previously been postulated[5a] as intermediates in the reaction of nicotine with methyllithium and are known intermediates in a number of reactions of other organolithium reagents with pyridine.[21,22] A [1,5]-alkyl migration from a dihydropyridine may lead to **6** while dealkylative oxidation and loss of a t-butyl group could lead back to nicotine or even to **6**.[21] As noted above (Table 2), the yields of **1**, **4**, **5** and **6** were found to vary considerably when the reaction was performed without rigorous exclusion of oxygen. As a result, competitive routes involving both anionic, radical anion and radical intermediates may be involved.[19,20,23] The role of oxygen in product composition favors the involvement of intermediates formed *via* electron transfer.[19,20,23]

We cannot estimate the relative importance of electron transfer–radical anion processes *vs.* direct two electron 1,2-nucleophilic additions. Newcome and Hager recently showed that lithium diisopropylamide is an efficient one-electron donor to pyridine and an electron transfer process is the key step in the pyridine dimerization reaction.[24] Still and Mitra[25]showed that methyllithium was more likely to add in a 1,2-sense to enones *via* a direct nucleophilic addition because methyl anion is *more* stable than the methyl radical; however, they observed that t-BuLi added *via* a 1,4-electron transfer process since the t-Bu radical is much more stable than the t-Bu anion.[25] This evidence suggests that there may well be a change-over in mechanism as a function of the alkyllithium reagent used and that the aberrant products observed in the t-butylations are due to differences in alkyl radical/anion stabilities and reactivities.

EXPERIMENTAL

M.ps and b.ps are uncorrected. The ^{1}H-NMR spectra were determined on a Bruker WP-80 spectrometer. Low-resolution mass spectra were obtained on a Finnigan MAT 3300 mass spectrometer. Precise mass measurements were obtained on a Varian MAT 112S mass spectrometer. Optical rotations were obtained with a Perkin–Elmer 241 MC polarimeter at 20°. Microanalyses were performed by Gailbreath Laboratories, Inc., Knoxville, Tennessee. All organolithium reagents are commercially available except cyclopropyllithium which was prepared from cyclopropylbromide and lithium in ether.

General procedure for the addition of organolithium reagents to nicotine (Table 1). To a soln of 2.0 g (12.3 mmol) of (−)-nicotine dissolved in 30 ml ether/10 ml TMEDA and maintained under N_2 at − 70° was added the organolithium reagent over 10 min. The yellow or orange soln was stirred at − 70° for 1 hr and room temp overnight (minimum of 16 hr). The mixture was quenched with 20 ml of water, followed by the addition of 10 ml of 10% NaOH aq. The mixture was extracted with ether, and the combined ethereal layers dried with $MgSO_4$ and evaporated. Bulb-to-bulb distillation of the crude product provided the product contaminated with nicotine starting material. The 6-substituted nicotinoid and the nicotine were efficiently separated by the use of the Harrison Chromatotron® [4 mm-thick Silica Gel PF rotor; with either $CHCl_3$—EtOH—NH_4OH (92.5 : 7 : 0.5) or petroleum ether–acetone–triethylamine (80 : 20 : 8) as eluents]. The separated product and starting material were often bulb-to-bulb distilled under high vacuum.

GC/MS/DS studies. Reaction products were separated and identified using a computerized GC/MS system. Mixture separation was achieved using a Bendix 2200 gas chromatograph containing a 6′ × 1/8″ OD stainless steel column packed with 1% SE-30 on 100/120 mesh Gas Chrom Q. The column temperature was programmed in order to achieve chromatographic resolution. Helium was used as the carrier gas. The effluent passed into a Finnigan MAT 3300 mass spectrometer *via* a single stage, glass jet, molecular separator. The 70 eV EI spectra were obtained every three seconds. The control, storage, and manipulation of mass spectral data were achieved using a Finnigan MAT 6300 data system.

Exact mass measurements and metastable data were obtained using a Finnigan MAT 112S reversed geometry, double focusing mass spectrometer. Exact mass measurements were made at a resolving power of 7500 and used perfluorokerosene to generate the reference peaks. Metastable data were recorded in two linked-scan modes, B^2/E (parents from a designated daughter ion) and B/E (daughters from a designated parent ion).

(−)-6-*Ethylnicotine* (**3b**) was obtained in 30% yield following bulb-to-bulb distillation [oven temp 60–70° (0.1 torr)]; dipicrate, m.p. 168–170°; $[\alpha]_D^{20}$ − 16° (*c* 1.869, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 8.48 (d, J = 2 Hz, 2), 7.66 (dd, J = 8, 2 Hz, 1), 7.18 (d, J = 8 Hz, 1), 3.0–3.5 (m, 2), 2.83 (q, J = 7.5 Hz, 2), 1.5–2.5 (m, 5), 2.18 (s, 3), 1.31 (t, J = 7.5 Hz, 3); EI mass spectrum, *m/z* 190 (M^+). (Found: C, 44.55; H, 3.81; N, 17.21. Calc for $C_{24}H_{24}N_8O_{14}$ (dipicrate): C, 44.44; H, 3.70; N, 17.28%.)

(−)-6-*Isopropylnicotine* (**3c**) was obtained in 43% yield following bulb-to-bulb distillation [oven temp 70–75° (0.15 torr)]; dipicrate m.p. 183–186°; $[\alpha]_D^{20}$ − 17.5° (*c* 2.515, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 8.48 (d, J = 2 Hz, 1), 7.68 (dd, J = 8, 2 Hz, 1), 7.18 (d, J = 8 Hz, 1), 2.75–3.38 (m, 3), 1.5–2.5 (m, 5), 2.18 (s, 3), 1.3 (d, J = 7 Hz, 6); EI mass spectrum, *m/z* 204 (M^+). (Found: C, 45.44; H, 4.10; N, 16.74. Calc for $C_{25}H_{26}N_8O_{14}$ (dipicrate): C, 45.32; H, 3.93; N, 16.92%.)

(−)-6-*Cyclopropylnicotine* (**3d**) was obtained in 17% yield following bulb-to-bulb distillation [oven temp 65–75° (0.1 torr)]; dipicrate m.p. 143–147°; $[\alpha]_D^{20}$ − 38° (*c* 1.086, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 8.38 (d, J = 2 Hz, 1), 7.6 (dd, J = 8, 2 Hz, 1), 7.1 (d, J = 8 Hz, 1), 2.88–3.73 (m, 3), 1.38–2.63 (m, 4), 2.15 (s, 3), 0.98 [d (br), J = 8 Hz, 4]; EI mass spectrum, *m/z* 202 (M^+). (Found: C, 45.21; H, 3.74; N, 16.68. Calc for $C_{25}H_{24}N_8O_{14}$ (dipicrate): C, 45.45; H, 3.64; N, 16.97%.)

(−)-6-*n-Butylnicotine* (**3e**) was obtained in 43% yield following bulb-to-bulb distillation [oven temp 70–80° (0.1 torr)]; dipicrate m.p. 163–166°; $[\alpha]_D^{20}$ − 12° (*c* 1.676, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 8.35 (d, J = 2 Hz, 1), 7.55 (dd, J = 8, 2 Hz, 1), 7.05 (d, J = 8 Hz, 1), 2.58–3.33 (m, 4), 1.1–2.43 (m, 9), 2.11 (s, 3), 0.9 [t(br), J = 6 Hz, 3]; EI mass spectrum, *m/z* 218 (M^+). (Found: C, 45.98; H, 4.19; N, 16.40. Calc for $C_{26}H_{28}N_8O_{14}$ (dipicrate): C, 46.16; H, 4.17; N, 16.56%.)

(−)-6-*sec-Butylnicotine* (**3f**) was obtained in 28% yield following bulb-to-bulb distillation [oven temp 95–110° (0.35 torr)]; dipicrate m.p. 158–164°; $[\alpha]_D^{20}$ − 29.5° (*c* 2.258, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 8.35 (d, J = 2 Hz, 1), 7.56 (dd, J = 8, 2 Hz, 1), 7.03 (d, J = 8 Hz, 1), 2.5–3.45 (m, 3), 1.38–2.38 (m, 5), 2.15 (s, 3), 0.58–1.25 (m, 8); EI mass spectrum, *m/z* 218 (M^+). (Found: C, 45.91; H, 4.18; N, 16.58. Calc for $C_{26}H_{28}N_8O_{14}$ (dipicrate): C, 46.16; H, 4.17; N, 16.56%.)

(−)-6-*t-Butylnicotine* (**4**) was obtained in 33% yield following bulb-to-bulb distillation [oven temp 80–95° (0.1 torr)]; $[\alpha]_D^{20}$ − 20° (*c* 0.22, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 8.41 (d, J = 2 Hz, 1), 7.6 (dd, J = 8, 2 Hz, 1), 7.26 (d, J = 8 Hz, 1), 2.86–3.34 (m, 2), 1.56–2.46 (m, 5), 2.09 (s, 3), 1.29 (s, 9); EI mass spectrum, *m/z*: 218 (M^+), 10%; 217, 11%; 189, 13%; 133, 22%; 85, 11%; 84, 100%; 83, 18%; 42, 24%; 41, 11%. (Found: C, 76.89; H, 10.14; N, 12.95. Calc for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83%.)

(−)-6-*Vinylnicotine* (**3g**) was obtained in 6% yield following bulb-to-bulb distillation [oven temp 90–105° (0.4 torr)]; $[\alpha]_D^{20}$ − 58° (*c* 0.203 CH_2Cl_2); EI mass spectrum, *m/z* 188 (M^+).

General procedure for the addition of t-butyllithium to nicotine to provide compounds **5** *and* **6** (Table 2). To a soln of 1.0 g (6.17 mmol) of (−)-nicotine in 15 ml of THF under N_2 or Ar at 0° was added 5.3 ml (7.4 mmol) of 1.4 M t-BuLi in pentane gradually over 5 min. The soln was stirred at 0° for 30 min and room temp for 2 hr, and then quenched with 15 ml of 10% HCl aq. The mixture was washed with 15 ml of ether, followed by basification of the aqueous layer. The aqueous layer was extracted with ether (3 × 15 ml), and the combined ethereal layer was dried ($MgSO_4$) and evaporated to an oil. The crude product mixtures obtained in this fashion, consisting of **1**, **4**, **5** and **6**, were analyzed by GC-EI mass spectrometry and purified by preparative GC.

N-*Methyl-4-(2-t-butyl-5-pyridyl)butylamine* (**5**). ^{1}H-NMR ($CDCl_3$): δ 8.45 (d, J = 2 Hz, 1), 7.49 (dd, J = 8, 2 Hz, 1), 7.28 (d with fine coupling, J = 8 Hz, 1), 2.6 (m, 4), 2.44 (s, 3), 1.3–1.75 (m, 4), 1.35 (s, br, NH, 1), 1.28 (s, 9); Precise mass determined for M^+: Calc for $C_{14}H_{24}N_2$: 220.19395. Found: 220.1909; EI mass spectrum, *m/z*: 220 (M^+), 1%; 163, 7%; 149, 31%; 134, 10%; 133, 7%; 57, 7%; 44, 100%; 43, 11%.

N-*Methyl-5,5-dimethyl-4-(3-pyridyl)hexylamine* (**6**). ^{1}H-NMR ($CDCl_3$): δ 8.4 (m, 2), 7.44 (dt, J = 8, 2 Hz, 1), 7.15 (dd with fine coupling, J = 8, 4 Hz, 1), 2.13–2.53 (m, 3), 2.25 (s, 3), 1.5–1.88 (m, 2), 1.55 (s, br), NH, 1), 0.95–1.28 (m, 2), 0.78 (s, 9); $[\alpha]_D^{20}$ 0° (*c* 0.150, CH_2Cl_2). Precise mass determined for M^+: Calc for $C_{14}H_{24}N_2$: 220.19395. Found: 220.1935; EI mass spectrum, *m/z*: 220 (M^+), 2%; 176, 6%; 164, 1%; 163, 11%; 149, 7%; 134, 38%; 131, 10%; 120, 40%; 118, 10%; 106, 36%; 93, 19%; 57, 21%; 44, 100%; 41, 19%.

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[16] The fragmentation pathways determined for nicotine by Djerassi were utilized to assist in the quantification of the mass spectral data; see ref. 9.

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