CONVENIENT SYNTHESES OF N-CD$_3$ LABELLED NICOTINE

AND NICOTINE ANALOGUES

Jeffrey I. Seeman,* Henry V. Secor, and Gary Forrest
Philip Morris Research Center, Richmond, Virginia 23261

SUMMARY

Two procedures for the preparation of N-CD$_3$ labelled

nicotine and nicotine analogues are reported. These

include: (a) the deuteroiodomethylation of the

lithium amide of the corresponding secondary amine;

and (b) the alkylation of the corresponding cyclic

imine followed by sodium cyanoborohydride reduction

of the resulting alkyl iminium salt. Products having

both high chemical and isotopic purity are formed.

Key Words: Nicotine-N'-d$_3$, Methyl Anabasine-N'-d$_3$, Alkaloids

INTRODUCTION

As part of our study of the structure (1,2) and

chemical reactivity (3) of nicotine (1) and related compounds,

we required moderate quantities of a number of N-CD$_3$

labelled nicotine analogues (4) (*e.g.*, 2). Nicotine-N'-d$_3$

(3) has been prepared previously by the treatment of

nornicotine (4) with CD$_3$I with (4b) and without (4d) added

base; in both of these reports, preparative glc was

required for the isolation of pure 3. Methyl-^{14}C-nicotine

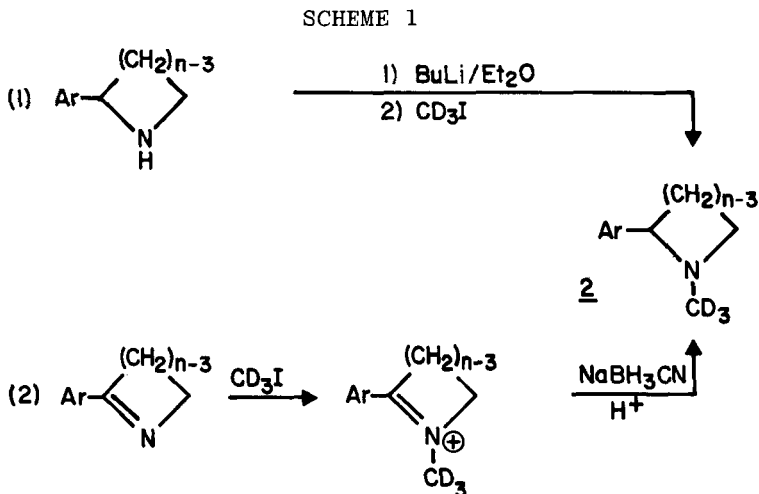1, R=CH$_3$ 2, R=CD$_3$
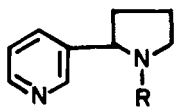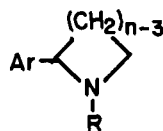
3, R=CD$_3$ 5, R=H

4, R=H

has also been prepared by treatment of 4 with ^{14}CH$_3$I, though in only 23% radiochemical yield (5). Methyl-^{11}C-nicotine has been prepared from nornicotine and ^{11}CH$_2$O (4g). We now report two routes to (2) (n=5, 6, and 7) as shown in Scheme 1.

SCHEME 1

RESULTS AND DISCUSSION

The most evident route to (2) is *via* deuteroiodomethyla-tion of the corresponding secondary amine (5). One problem with such a route is the formation of HI in the reaction, leading in part to protonation of the pyrrolidine nitrogen

of either unreacted nornicotine or the initial product, nicotine.
Pyridine alkylation of either of these compounds could then
result. A second difficulty involves the competitive alkyla-
tion of the pyrrolidine nitrogen of nornicotine with the
pyrrolidine nitrogen of nicotine. A third possibility is
competitive nitrogen alkylation for nornicotine. A literature
precident for the last suggestion is available. We have shown
(3,6) that treatment of nicotine with less than one equivalent
of iodomethane leads to both N'-methylnicotinium iodide and N-
methylnicotinium iodide in a ratio of 2.2:1 even though nicotine's
pyrrolidine nitrogen is considerably more basic than its
pyridine nitrogen (pK_{a_1} 7.8, pK_{a_2} 3.04). In addition, we
observed that iodomethylation of nicotine with one equivalent
of iodomethane results in dialkylation products and unreacted
starting material (3,6). These three suggestions may explain
reports of low nicotine yields on iodomethylation of nornic-
otine (4b, 4d, 4e, 5).

To circumvent these problems, nornicotine was treated
with a slight excess of n-BuLi in ether at low temperature and
the resulting anion in turn treated with a slight excess of
CD_3I (7). Nicotine-N'-d_3 was obtained in 92% distilled yield
in high isotopic purity (see Table 1) following the usual
isolation procedures. This route (eq. 1) was applied to a
number of other nornicotine analogues yielding the corresponding
1-deuteromethyl-2-arylazacycloalkanes as shown in Table 1.

The starting material in the above procedure is the
secondary amine obtained by reduction of the corresponding
imine (Scheme 1) (8). It was therefore of interest to examine
the possibility of a more direct conversion of the imine to the
desired N-CD_3 material (12).

Table 1. Summary of Deuteromethylation Preparations
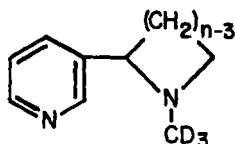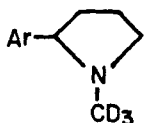
6, Ar = phenyl
7, Ar = 2-pyridyl
8, Ar = 2-fluorophenyl
9, Ar = 3-methylphenyl
12, Ar = 4-methylphenyl
13, Ar = 4-trifluoromethylphenyl
14, Ar = 4-fluorophenyl

3, n = 5

10, n = 6

11, n = 7

Compound[a,b]	Mode of Preparation	Distilled Yield (%)	Isotopic Purity[c]			
			d_3	d_2	d_1	d_0
3	eq. 1	92	94.4	2.1	1.9	1.5
6	eq. 1	35	95.6	3.2	0.9	0.3
7	eq. 1	67	91.7	3.8	2.9	1.6
8	eq. 1	74	93.9	3.7	1.8	0.6
9	eq. 1	84	93.5	4.5	1.5	0.6
10	eq. 1	83	96.8	2.1	0.9	0.2
11	eq. 1	84	93.5	2.7	3.2	0.1
12	eq. 2	78	92.4	4.6	2.9	0.2
13	eq. 2	26	92.8	4.9	2.1	0.2
14	eq. 1	46	92.6	4.0	2.0	1.4

[a] The spectroscopic properties of the compounds prepared compared excellently with those of the respective un-labelled materials with due consideration of isotope incorporated.

[b] Greater than 95% chemically pure by glc and tlc analysis.

[c] Determined using a CEC/duPont 21-104 mass spectrometer at low ionizing voltage.

Alkylation of 2-(4-methylphenyl)-1-pyrroline (15) with CD$_3$I in acetonitrile was followed by tlc and a spot of low R$_f$ grew in importance concurrent with a decrease in intensity of the spot corresponding to the starting imine. After thirteen days, the precipitated iminium salt was reduced with sodium cyanoborohydride. 1-Methyl-2-(4-methylphenyl)-pyrrolidine-1-d$_3$ (12) was isolated by distillation in 78% yield (see Table 1). In a similar fashion, 2-(4-trifluoromethylphenyl)-1-pyrroline was treated with iodomethane-d$_3$ with alkylation appearing to proceed more slowly than for (15) as judged by tlc. The product, 1-methyl-2-(4-trifluoromethylphenyl)-pyrrolidine-1-d$_3$ (13), was obtained in a 26% yield. This low yield may be ascribed to a significant rate deceleration in the alkylation step due to the trifluoromethyl group (σ+ 0.612) destabilization of the developing positive charge in the pyrroline ring.

Treatment of the readily available myosmine (9-11) with iodomethane in acetonitrile led exclusively *via* pyridine alkylation to 1-methyl-3-(3,4-dihydro-2H-5-pyrrolyl)pyridinium iodide (13). Thus, the lower reactivity of imine nitrogen of myosmine compared to its pyridyl nitrogen renders the sequence shown by eq. 2 unfeasible in this case.

In conclusion, two straightforward, generally high yield procedures for the preparation of N'-deuteromethyl nicotinoids of high chemical and isotopic purity are now available. In contrast to some of the literature methods (4b, 4d, 5) for the preparation of (2), neither of the procedures used herein (cf. Scheme 1) requires chromatographic techniques for product purification. While we have not used either of these procedures

for the preparation of carbon labelled (^{13}C or ^{14}C) materials,
no difficulty would be anticipated in applying these techniques
(14). Typical procedures are given below.

EXPERIMENTAL SECTION

Nicotine-N'-d$_3$ (3)--To a solution of 4.0 g (24.7 mmol) of
nornicotine (4) (9, 11) in 100 ml of anhydrous ether at
-65° was added *via* syringe 11.8 ml (27.1 mmol) of a 2.3 M n-
BuLi solution. After 15 minutes, the yellow heterogeneous
mixture was treated dropwise with an ether solution containing
4.00 g (27.6 mmol) of CD$_3$I. The resulting mixture was allowed
to warm to room temperature and stirred for an additional 1.5
hr, acidified with 6N HCl and allowed to stand overnight. The
separated aqueous phase was washed with ether, basified (KOH)
and extracted with ether. The combined organic extracts were
dried (Na$_2$SO$_4$), rotary evaporated, and distilled yielding 3.75
g (92%) of (3) as a colorless oil: b.p. 50-51° (0.02 mm).

1-Methyl-2-phenylpyrrolidine-1-d$_3$ (6)--A solution of 1.0
g (6.8 mmol) of 2-phenylpyrrolidine in 40 ml of anhydrous
ether was cooled to -55° and treated dropwise with 3.4 ml (7.5
mmol) of a 2.2 M n-butyllithium/hexane solution. The resulting
mixture after stirring under nitrogen at -50° for 35 min was
treated at -50° with an ether solution (*ca.* 5.5 ml) of 1.1 g
(7.6 mmol) of CD$_3$I. The reaction was allowed to warm to room
temperature and stirred for an additional two hours. A solution
of 0.5 ml of glacial acetic acid in 3 ml of water was added to
the mixture and an emulsion resulted. Dilute hydrochloric
acid was added and the resultant mixture rotary evaporated to
give an aqueous mixture which was filtered. The resulting
clear solution, after washing with ether, was basified (KOH),

extracted with ether, dried (Na_2SO_4), filtered, rotary evap-
orated, and distilled giving 430 mg (35%) of (6) as a color-
less oil: b.p. 35-37° (0.02 mm).

1-Methyl-2-(4-methylphenyl)pyrrolidine-1-d₃ (12)--A
solution of 1.0 g (6.25 mmol) of 2-(4-methylphenyl)-1-pyrroline
(15) in 25 ml of acetonitrile was treated with 4.9 ml of an
ethereal solution containing 970 mg (6.68 mmol) of CD_3I at
room temperature. After standing for 13 days, the resulting
mixture was rotary evaporated to give a tan oil which was
washed with ether to remove any ether solubles including
starting material. The tan semisolid residue (1.86 g) was
dissolved in *ca.* 50 ml of methanol and 380 mg (6.1 mmol) of
sodium cyanoborohydride was added. A blue color resulted
following the addition of a trace amount of bromcresol green.
A 2 N HCl/ methanol solution (15) was added dropwise to main-
tain the solution in the yellow-green pH range (~pH 5) (15).
After completion of the reaction as evidenced by the persistence
of the yellow color for two hours, the reaction was quenched
with dilute HCl to destroy any remaining sodium cyanoborohydride
and rotary evaporated to remove the methanol. The residual
material was partitioned between water and methylene chloride
(16). The combined methylene chloride extracts were rotary
evaporated and the residual oil basified with aqueous KOH and
extracted with ether. The combined organic phases were dried
(Na_2SO_4), rotary evaporated, and distilled yielding 870 mg
(78%) of (12) as a colorless oil: b.p. 54-55° (0.025 mm).

REFERENCES

1. Whidby, J. F. and Seeman, J. I. -J. Org. Chem. <u>41</u>: 1585
    (1976).

2. Seeman, J. I. and Bassfield, R. L. -J. Org. Chem. <u>42</u>:
    2337 (1976)

3. Seeman, J. I. and Whidby, J. F. -J. Org. Chem. <u>41</u>: 3824
    (1976)

4. For recent syntheses of isotopically labelled nicotine
    and related compounds, see: (a) Munson, J. W. and
    Hodgkins, T. G. -J. Labelled Compounds and Radiopharmaceu-
    ticals <u>13</u>: 461 (1977)
    (b) Glenn, D. F. and Edwards, W. B., III -J. Org. Chem.
    <u>43</u>: 2860 (1978).
    (c) Cymerman Craig, J. and Lee, S. -Y. C. -J. Org. Chem.
    <u>40</u>: 663 (1975)
    (d) Duffield, A. M., Budzikiewicz, H., and Djerassi,
    C. -J. Am. Chem. Soc. 87: 2926 (1965)
    (e) Pitner, T. P., Edwards, W. B., III, Bassfield, R. L.
    and Whidby, J. F. -J. Am. Chem. Soc. <u>100</u>: 246 (1977)
    (f) Nguyen, T. -L., Ph.D. Thesis, Univ. of California,
    San Francisco, CA., 1977; Chem. Abstr. -87: 113275h. We
    thank Dr. Neal Castagnoli for making this thesis available
    to us.
    (g) Maziere, M., Comar, D., Marazano, C., and Berger, G.
    Eur. J. Nucl. Med. <u>1</u>: 255 (1976)

5. Leete, E. and Bell, V. M. -J. Am. Chem. Soc. <u>81</u>: 4538
    (1959)

6. Seeman, J. I., Secor, H. V., Whidby, J. F., and Bassfield,
    R. L. -Tetrahedron Lett., 1901 (1978). See also American

Chemical Society Centennial Meeting, Abstract Nos. ORGN-224 (September 3, 1976).

7. For the use of this technique in the preparation of un-labelled sparteine analogues, see Smissman, E. E. and Ruenxitz, P. C. -J. Org. Chem. 41: 1593 (1976)

8. The N-unsubstituted pyrrolidines (5) and the correspond-ing pyrrolines used as starting materials in this work were prepared following literature procedures (6,9-11). See also Seeman, J. I., Sanders, E. B., Secor, H. V., Atkins, G. L., Quagliato, D., and Armstrong, D., in preparation.

9. Hu, M. W., Bondinell, W. E., and Hoffman, D. -J. Label. Compounds 10: 79 (1974)

10. Spitzner, D. -Synthesis: 242 (1977)

11. Seeman, J. I. -Synthesis: 498 (1977)

12. Although the alkylation of imines is well-known, the resulting alkyl iminium salts have generally not been isolated or reduced but immediately hydrolyzed. See, for example, Abdel-Monem, M. M. -J. Med. Chem. 18: 427 (1975).

13. Seeman, J. I., unpublished result.

14. Recently, Nguyen reported (4f) an alterntive procedure for the preparation of (3) involving the lithium aluminum deuteride reduction of N'-ethoxycarbonylnornicotine. Unfortunately, an excess (10-20%) deuterium incorporation resulted, presumably (4f) from partial reduction-oxidation of the pyridine ring.

15. Prepared from con. HCl and anhydrous methanol. See Borch, R. F., Bernstein, M. D., and Durst, H. D. -J. Am. Chem. Soc. 93: 2897 (1971).

16. The pyrrolidinium salt in some cases will be found in the aqueous phase.