CONVENIENT SYNTHESES OF N-CD_3 LABELLED NICOTINE AND NICOTINE ANALOGUES

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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_3I 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

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0362-4803/79/0316-0387$01.00
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Received April 26, 1978
Revised July 31, 1978

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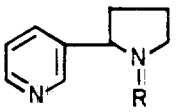
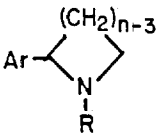




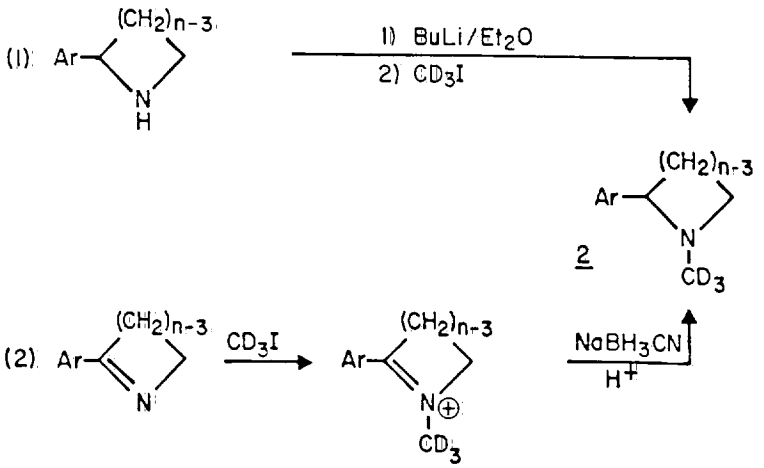
1, R=CH_3 2, R=CD_3

3, R=CD_3 5, R=H

4, R=H

has also been prepared by treatment of 4 with $^{14}CH_3I$, though in only 23% radiochemical yield (5). Methyl-^{11}C-nicotine has been prepared from nornicotine and $^{11}CH_2O$ (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* deuteroiodomethylation 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

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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 alkylation 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 nornicotine (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).

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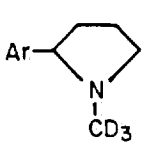
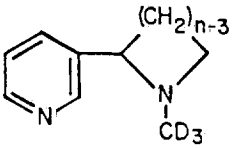
Table 1. Summary of Deuteromethylation Preparations





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 unlabelled 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.

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Alkylation of 2-(4-methylphenyl)-1-pyrroline (15) with CD_3I 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

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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_3I. 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_2SO_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_3I. 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),

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

1-Methyl-2-(4-methylphenyl)pyrrolidine-1-d_3 (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 maintain 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).

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8. The N-unsubstituted pyrrolidines (5) and the corresponding 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.

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14. Recently, Nguyen reported (4f) an alternntive 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.

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