Nicotine Chemistry. The Addition of Alkyl Radicals to (S),(-)-Nicotine: Synthesis of Optically Active 6-Alkynicocines

Jeffrey L. Seeman, Leigh E. Clawson, Henry V. Secor
Philip Morris U.S.A. Research Center, P.O. Box 26583, Richmond, Virginia 23261, U.S.A.

Radical alkylation of (S)-nicotine (1) with alkanolic acids (6) in the presence of ammonium peroxysulfate and silver nitrate to give optically active 6-alkynicocines 4 is described.

The preparation of nicotine analogues is a topic of continuing interest. While we and others have had success in preparing a wide range of racemic nicotinoids, the preparation of their optically active enantiomers has lagged behind. We were particularly interested in preparing a series of optically active 6-alkynicocines, since 6-methylnicotine (4a) has been found to be more active than nicotine (1) in a variety of pharmacological tests, in contrast to 2-methylnicotine (2) and 4-methylnicotine (3). We now report the homolytic alkylation of nicotine (1) which yields a series of 6-alkynicocines 4 having high optical activity.

The radical methylation of nicotine (1) leading to a mixture of 6- and 4-methylnicocines (~4:1) has been reported in 1978. We were interested in this report for two reasons: first, because it was suspected that the resultant methylnicocines would have high optical purity; and second, 2-methylnicotine (2) was not reported as a product, contrary to what would be expected.

Scheme A

We have now reinvestigated this reaction using the microorganism Pseudomonas putida to aid in the purification of closely related alkynicocines formed. Contrary to the literature report, we were able to isolate 2-, 4- and 6-methylnicocines (2, 3 and 4a) as well as small quantities of 4,6-dimethylnicotine (5). The optical rotations of these compounds (Table 1) indicate specific rotations equal to, or in some cases, significantly greater than that for optically pure nicotine (x100° = -171°). Unfortunately, we have been unsuccessful to date in applying various techniques, e.g., use of enantiometric 1H-N.M.R. shift reagents, to quantify optical purity for 6-methylnicotine (or the other alkynicocines reported below). Nonetheless, because of the method of synthesis and of the large values for these specific rotations, we tentatively conclude that the compounds are optically pure. It is worth noting that no racemization was observed in the recovered nicotine, nor in those recovered optically active products which we resubjected to these methylation conditions.

Table 1. Radical Methylation of (S)-Nicotine (1) according to Scheme A

<table>
<thead>
<tr>
<th>Product No.</th>
<th>Yield (%)</th>
<th>[x]100° (CH2Cl2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8</td>
<td>-216° (0.18600)</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>-194° (0.1375)</td>
</tr>
<tr>
<td>4a</td>
<td>32</td>
<td>-172° (0.2345)</td>
</tr>
<tr>
<td>5</td>
<td>&lt;5</td>
<td>-174° (0.0195)</td>
</tr>
</tbody>
</table>

- Ratio of t-buty1 hydroperoxide: nicotine = 6:1. Minor products (< 3%) other than those listed were not identified.
- Nicotine (1) was recovered in 34% yield; [x]100° = -174° (0.2125, CH2Cl2).
- Yield obtained by preparative G.L.C. analysis.
- At 22°C in chloroform; partial racemization has occurred according to Ref. 11, in the alternative preparation.
- At 23°C in chloroform; partial racemization has occurred according to Ref. 11, in the alternative preparation.

In order to prepare homologues of 6-methylnicotine (4a), we were attracted by the work of Minisci and co-workers, who have extensively studied the addition of alkyl and other radicals to heteroaromatic systems, e.g., pyridine, usually mediated via the strong oxidant, peroxydisulfate ion. We had some concern regarding the facility of the Minisci alkylation procedure with nicotine, in that most of the successful radical alkylations reported involved heterocycles suitably activated with strongly electron-withdrawing groups, e.g., cyano.

However, when nicotine (1) was reacted with a variety of alkanolic acids 6, ammonium peroxydisulfate, and silver nitrate under the conditions of Minisci alkylation procedure, we could isolate 6-alkynicocines (4) as major products (Table 2). These radical reactions were performed under a variety of experimental conditions, in an attempt to ascertain the optimum procedures. What we consider to be

Scheme B

In some cases, small amounts of 2- and 4-alkynicocinoids and over-alkylation products (e.g., 2,6- and 4,6-dialkynicocinoids) were obtained as well. Since we were particularly in-
Table 2. 6-Alkynicinotes 4b–g prepared\textsuperscript{a,b} according to Scheme B

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield\textsuperscript{c} [%]</th>
<th>[x]\textsubscript{D}\textsuperscript{a} (CH\textsubscript{3}Cl)\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4b</td>
<td>28</td>
<td>(-160°) (c. 0.2665)</td>
</tr>
<tr>
<td>4c\textsuperscript{d}</td>
<td>35</td>
<td>(-150°) (c. 1.5)</td>
</tr>
<tr>
<td>4d</td>
<td>41</td>
<td>(-149°) (c. 0.229)</td>
</tr>
<tr>
<td>4e</td>
<td>13</td>
<td>(-165°) (c. 0.446)</td>
</tr>
<tr>
<td>4f</td>
<td>13</td>
<td>(-163°) (c. 0.401)</td>
</tr>
<tr>
<td>4g</td>
<td>42</td>
<td>(-146°) (c. 0.0716)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} For 6-methylnicotine (4a), see Table 1.

\textsuperscript{b} All the products except 4e are characterized by their 1H- and 13C-N.M.R. spectral data, which are identical with those obtained from the analogous, racemic 6-alkynicotinates prepared by us previously\textsuperscript{11–13,20}.

\textsuperscript{c} [\textit{H}]-N.M.R. (CDCl\textsubscript{3}/TMS): \(\delta = 0.22–1.09\) (m, 5H); 1.12–2.12 (m, 6H); 2.18 (s, 3H); 2.22–3.40 (m, 5H); 7.09 (d, 1H, J = 8 Hz); 7.63 (dd, 1J, J = 8.2 Hz); 8.45 ppm (d, 1J, J = 2 Hz).

\textsuperscript{d} Analysed as the di-palmitate.

\textsuperscript{e} C\textsubscript{23}H\textsubscript{29}N\textsubscript{2}O\textsubscript{4.5} calc. C 45.32 H 3.96 N 16.91

\textsuperscript{f} Found 44.92 3.94 17.01

\textsuperscript{g} m.p. of dipalmitate 157–159° C.


**Synthesis**

Intersted in obtaining the 6-alkyl product\textsuperscript{19}, our efforts were directed primarily at maximizing the production of these materials and at isolating them in high purity. In some cases we did examine the product mixture in detail. For example, reaction of (S)-nicotine (1) with propanoic acid (6b) led to the isolation and identification of three monoethylnicotinoids, namely 2-, 4-, and 6-ethynicotin, and two diethylnicotinoids, namely 2,4- and 4,6-diethynicotin (Table 3). The major product, the desired 6-ethynicotine (4b) was formed in \(\sim 39\%\) yield and in a separate experiment was isolated by preparative chromatography in \(28\%\) yield. In the product mixture, recovered nicotine was the second largest component (\(37\%)\) yield) and the four other constituents were formed in much lower proportions. Table 3 also indicates that the recovered nicotine was optically pure \(\{[\text{x}]\text{D}^{10} = -171°\}\) and that the rotations of the ethylated nicotine derivatives ranged from \([\text{x}]\text{D}^{10} = -160°\) to \(-211°\). In the n-propylation of nicotine with butanoic acid (6c) (Table 2), 2-n-propynicotin, 2,6-di-n-propynicotin, and 4,6-di-n-propynicotin were isolated and identified by H-N.M.R. whereby the pyridine ring resonances were particularly informative.

In summary, the procedures described herein allow the simple, one step preparation of a variety of 6-alkynicotinoids 4a–g having what we believe to be very high enantiomeric excess.

1\textsuperscript{H}- and 13C-N.M.R. spectra were obtained on a Bruker WP-80 and on a Varian XL-300 spectrometer operated in the F.T. mode. Mass spectra were obtained on a Finnigan 3300 GC/MS/DS-6000. High performance liquid chromatography (H.P.L.C.) in the normal phase was performed on a Waters isocratic system using a Whatman Partisil\textsuperscript{®} M9 10/50 column with hexane/acetone/triethylamine (90:10:1.5) or with 2,2,4-trimethylpentane/acetone/triethylamine (80:20:1) and refractive index detection. Reverse phase H.P.L.C. was performed on the same system using Waters Radial-PAK\textsuperscript{®} C\textsubscript{18} column with acetonitrile: 2\% aqueous phosphoric acid/triethylamine (pH 7.5) (40:50) and UV detection at 254 nm. Optical rotations were determined on a Perkin-Elmer Model 241 MC polarimeter at 20 °C. The optical rotations of three samples of authentic (S)-(–)-nicotine at two different concentrations each were determined in order to show that within these operating concentration limits, we can expect the rotations of nicotine to be essentially concentration independent. The percent composition of products was determined on either a Varian 1400 or a Varian 4600 gas chromatograph modified for capillary columns. The separations were accomplished with either a 60-m SP-1000 capillary column (0.25 mm ID) or a 30-m SE-54 capillary column (0.25 mm ID). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

**Radical Methylation of (S)-Nicotine (1): Isolation of 2-, 4-, and 6-Methylnicotinotes (2, 3, and 4a):**

A stirred solution of oxygen-free water (870 ml) containing nicotine (1.1456 g, 0.09 mol), sulfuric acid (87 ml, 1.64 mol) and iron(II) sulfate heptahydrate (150 g, 0.54 mol) is treated with 2-buty1 hydroperoxide (48.5 g, 0.54 mol) over a 30 min period. Stirring is continued for 3 h after which additional ferrous sulfate heptahydrate (150 g, 0.54 mol) is added followed by 2-buty1 hydroperoxide (48.5 g, 0.54 mol) over a 30 min period. After stirring for an additional 30 min, the solution is cooled, and basified with 50% potassium hydroxide solution (excess). The mixture is filtered with difficulty through celite and the filter cake washed with chloroform (200 ml). The aqueous phase is extracted with chloroform (2 x 300 ml), the chloroform extracts are combined and concentrated. The resulting oily residue is taken up in ether (500 ml) and extracted with 20% acetic acid (3 x 10 ml). The combined acetic acid extracts are washed with ether (30 ml), basified with 50% potassium hydroxide solution (15 ml) and extracted with ether (3 x 40 ml). The ether extract is concentrated to give a brown oil which is distilled from bulb to bulb to give 9.14 g of a light-yellow colored oil; b. p. 85°C/0.025 mm. A portion (5.78 g) of the reaction mixture is incubated in 5.78 l of the culture medium containing *Pseudomonas putida*\textsuperscript{19} at 30°C in a water bath shaker for 20 h. Reverse phase H.P.L.C. is used to monitor the disappearance of (S)-nicotine (1) from the microbial fermentation. This allowed determination of the optimum time for fermentation to eliminate (S)-nicotine (1) without metabolizing the methylnicotinotes. A nicotine-free mixture of methylation products resulted which is more amenable to preparative scale chromatography. The aqueous medium is filtered, acidified with excess 6 normal hydrochloric acid and concentrated on a rotary evaporator. The residue is diluted with water (50 ml), filtered, basified with 50% potassium hydroxide solution (20 ml) and thoroughly extracted with ether (3 x 200 ml). The ether solution is dried with sodium sulfate, concentrated and distilled from bulb to bulb to give 3.3 g of a colorless oil. A 500 mg sample of this material is dissolved in a solvent mixture of petroleum ether, acetone, and triethylamine (80:20:3.3 ml) and chromatographed on a Harrison Chromatotron\textsuperscript{®} utilizing a 4 mm silica gel plate and the same solvent mixture as eluent. A second Chromatotron\textsuperscript{®} is utilized with the eluate from the first passing directly to the second Chromatotron\textsuperscript{®} in series for additional separation. The appropriate fractions which are assayed by capillary G.L.C. are combined, concentrated and distilled from bulb to bulb to give 170 mg of pure (S)-6-methylnicotine (4a) as a colorless oil; yield: 170 mg (32%)

**Ethylation of Nicotine (1): Typical Procedure:**

In general, from the alkylation of nicotine (1), only the major product, the 6-alkylated product is isolated (Table 2). However, in the typical case reported below, all the products have been isolated and identified (Table 3).

A solution of (S)-nicotine (1; 5.0 g, 31 mmol) in 10% aqueous sulfuric acid (40 ml, 72.6 mmol) containing silver nitrate (1.1 g, 6.5 mmol) is stirred and heated under a nitrogen atmosphere at 70°C. Propanoic acid (6b; 4.83 g, 64 mmol) and a solution of ammonium peroxysulfate (14.21 g, 62 mmol) in water (30 ml) are added over a period of 10 min simultaneously from two separate addition flasks. The mixture is then stirred and heated at 70°C for 1 h, cooled to room temperature, basified with cold ammonium hydroxide (65 ml), thoroughly extracted with chloroform (3 x 100 ml), the chloroform extracts concentrated and the residue is distilled from bulb to bulb (oven temp. 115°C/0.01 mm) to give 4.16 g of a light yellow oil. Product analysis (Table 3) is carried out by gas chromatography using a DB wax column (J&W Scientific), 30 m x 0.25 mm, 0.5 mm film thickness, isothermally at 150°C with a split injection. Product purification is carried out using a 750 mg
Table 3. Products Obtained from the Ethylation of (S)-Nicotine (I)  

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Yield&lt;br&gt;[%]</th>
<th>G.L.C. retention time [min]&lt;br&gt;a</th>
<th>Elution order&lt;sup&gt;b&lt;/sup&gt; from Chromatotron&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Molecular Formula&lt;sup&gt;d&lt;/sup&gt; or Lit. data</th>
<th>[α]&lt;sup&gt;b&lt;/sup&gt; (CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;)&lt;br&gt;δ&lt;sup&gt;b&lt;/sup&gt; ppm&lt;sup&gt;e&lt;/sup&gt;</th>
<th>1H-N.M.R. (CDCl&lt;sub&gt;3&lt;/sub&gt;/TMS)&lt;br&gt;δ&lt;sup&gt;b&lt;/sup&gt; ppm&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Ethylnicotine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6</td>
<td>6.39</td>
<td>2</td>
<td>C&lt;sub&gt;8&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt; (190.3)</td>
<td>−211°&lt;sup&gt;’&lt;/sup&gt; (c, 0.2065)</td>
<td>1.28 (s, 3H, J = 7.5 Hz); 2.18 (s, 3H); 1.4-2.9 (m, 5H); 2.86 (q, 2H, J = 7.5 Hz); 3.2-3.38 (m, 2H); 7.18 (dd, 1H, J = 8.0, 4.7 Hz); 7.87 (dd, 1H, J = 8.0, 1.8 Hz); 8.41 (dd, 1H, J = 4.7, 1.8 Hz)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4-Ethylnicotine</td>
<td>9</td>
<td>11.69</td>
<td>6</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt; (190.3)</td>
<td>−196°&lt;sup&gt;’&lt;/sup&gt; (c, 0.0675)</td>
<td>1.22 (t, 3H, J = 7.6 Hz); 2.18 (s, 3H); 1.65-2.33 (m, 5H); 2.69 (q, 2H, J = 7.6 Hz); 3.32-3.37 (m, 2H); 7.05 (d, 1H, J = 5.1 Hz); 8.37 (d, 1H, J = 5.1 Hz); 8.71 (s, 1H) See Ref. 13</td>
</tr>
<tr>
<td>6-Ethynicotine&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39</td>
<td>7.74</td>
<td>3</td>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt; (218.3)</td>
<td>−160°&lt;sup&gt;’&lt;/sup&gt; (c, 0.2665)</td>
<td>1.25 (t, 3H, J = 2.4 Hz); 1.29 (t, 3H, J = 2.4 Hz); 1.45-2.33 (m, 5H); 2.17 (s, 3H); 2.79 (q, 2H, 2.4 Hz); 2.83 (q, 2H, 2.4 Hz); 3.26-3.31 (m, 2H); 7.01 (d, 1H, J = 8.1 Hz); 7.76 (d, 1H, J = 8.1 Hz)</td>
</tr>
<tr>
<td>2,4-Diethylnicotine</td>
<td>5</td>
<td>6.77</td>
<td>1</td>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt; (218.3)</td>
<td>−178°&lt;sup&gt;’&lt;/sup&gt; (c, 0.1625)</td>
<td>1.22 (t, 3H, J = 7.5 Hz); 1.30 (t, 3H, J = 7.5 Hz); 2.18 (s, 3H); 1.7-2.3 (m, 5H); 2.66 (q, 2H, J = 7.5 Hz); 2.79 (q, 2H, J = 7.5 Hz); 3.20-3.40 (m, 2H); 6.92 (s, 1H); 8.59 (s, 1H)</td>
</tr>
<tr>
<td>4,6-Diethylnicotine</td>
<td>4</td>
<td>13.14</td>
<td>5</td>
<td>C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt; (218.3)</td>
<td>−168°&lt;sup&gt;’&lt;/sup&gt; (c, 0.1055)</td>
<td>1.22 (t, 3H, J = 7.5 Hz); 1.30 (t, 3H, J = 7.5 Hz); 2.18 (s, 3H); 1.7-2.3 (m, 5H); 2.66 (q, 2H, J = 7.5 Hz); 2.79 (q, 2H, J = 7.5 Hz); 3.20-3.40 (m, 2H); 6.92 (s, 1H); 8.59 (s, 1H)</td>
</tr>
</tbody>
</table>

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1. For a recent review of nicotine chemistry, see: Seeman, J. I. Heterocycles 1984, 22, 165.
12. We have previously reported the reaction of nicotine with various alkylthiol reagents yielded thiolethyl derivatives with only small enantiomeric excesses. See: Ref. 11-13.
17. For the successful determination of enantiomeric excesses of nicotine and 2-methyl nicotine using optically active 1H-N.M.R. shift reagents, see: Reference 1.

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a Nicotine (I) was recovered in 57% yield; [α]<sup>b</sup> = −171° (c 1.317, CH<sub>2</sub>Cl<sub>2</sub>).
b Yield obtained by G.L.C. analysis of distilled, total reaction mixture.
c See experimental section for details. Nicotine eluted fourth from the Chromatotron<sup>c</sup>.
d Retention time for nicotine (I) = 6.033 min.
e Satisfactory microanalyses obtained: C ± 0.14, H ± 0.11, N ± 0.10.
f Identical 1H-N.M.R. spectrum as reported was obtained.
g Analysed as the dipicrate derivative; m.p. 174-176° C. C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>14</sub> C 46.16 H 4.17 N 16.56 (648.5) 45.99 4.21 16.24
h The 1H-N.M.R. spectrum of this material is identical with that obtained from the authentic racemate prepared by treatment of (R,S)-2-methyl nicotine<sup>10</sup> with phennylthioformic acid followed by reaction with iodomethane.

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sample dissolved in a solvent mixture of hexane, acetone and triethylamine (80:20:3.5 ml) which is chromatographed on a Chromatotron<sup>c</sup> utilizing a 4 mm silica gel plate and the same solvent mixture as eluent. The fractions collected are assayed by capillary G.L.C., concentrated, distilled from bulb to bulb and the pure components are isolated by preparative G.L.C. (Table 3). The spectroscopic properties of the major product, 6-ethynicotine (4b) are identical to those of its partially racemized analogue reported previously<sup>13</sup>. We thank Mr. R. L. Bassfield, Mr. C. R. Howe, Dr. J. B. Wooster, and Dr. D. Ingham for their technical contributions, and Mrs. Anne Donathan for preparing the manuscript for publication. We also thank Dr. R. McCuen for his assistance with the Pseudomonas putida experiments.