*N*-alkyl-*S*-(-)-nicotinium iodide, *N*'-alkyl-*S*-(-)-nicotinium iodide, and *N*,*N*'-bisalkyl-*S*-(-)-nicotinium diiodide which may be separated conveniently by chromatography. The compounds in Table I were eluted with 2% MeOH–C<sub>6</sub>H<sub>6</sub>. Identification was accomplished by uv spectroscopy in MeOH and acidified (6 *N* H<sub>2</sub>SO<sub>4</sub>) MeOH.



<sup>*a*</sup> Corrected. <sup>*b*</sup> Dried in vacuo over  $P_2O_5$ . <sup>*c*</sup> All compounds were analyzed for C, H.

Derivatives of  $S_{-}(-)$ -nicotine which are N' quaternized show great enhancement of the maximum occurring at around 260 m $\mu$ in acid solution. The analogous N-quarternized isomers show neither enhancement or shift of the maximum when studied under the same conditions. The same situation obtains with N,N'-bis-quaternized  $S_{-}(-)$ -nicotinium salts.

N,N'-**Bisalkyl-**S-(-)-**nicotinium Diiodides.**—An excess of the appropriate alkyl halide was added to 3.2 g (0.02 mole) of *N*-alkyl-S-(-)-nicotinium bromide or iodide. Reaction was continued for 72 hr at room temp. Excess alkyl halide was evapd under vacuum at room temp. In instances when alkyl bromides were used in quaternization the reported diiodide products were obtained by halogen exchange with KI. The crude product (5 g) was chromatographed on 50 g of Woelm Activity Grade I neutral Al<sub>2</sub>O<sub>3</sub>. The compounds in Table II were eluted with 5–10% MeOH-C<sub>6</sub>H<sub>6</sub>.



| No.                     | R                               | R'  | Mp, °C <sup>a</sup> | Hygro-<br>scopic <sup>b</sup>     | Yield,<br>% | Empirical<br>formula <sup>c</sup>                            |
|-------------------------|---------------------------------|---|---------------------|-----------------------------------|-------------|--|
| 6                       | $C_2H_5$                        | $C_2H_5$                                      | 230-233             | No                                | 60          | $C_{14}H_{24}I_2N_2$   |
| 7                       | n-C <sub>3</sub> H <sub>7</sub> | $n-C_{3}H_{7}$                                | 220-222             | No                                | 40          | $C_{16}H_{28}I_2N_2$   |
| 8                       | n-C <sub>3</sub> H <sub>7</sub> | CH₃   | 176 - 178           | No                                | 95          | $\mathrm{C}_{14}\mathrm{H}_{24}\mathrm{I}_{2}\mathrm{N}_{2}$ |
| 9                       | $n-C_3H_7$                      | $C_2H_5$                                      | 206 - 209           | No                                | 90          | $C_{15}H_{26}I_2N_2$   |
| 10                      | $i-C_3H_7$                      | $CH_3$  | 235 - 238           | No                                | 93          | $C_{14}H_{24}I_2N_2$   |
| 11                      | $i-C_3H_7$                      | $C_2H_5$                                      | 236 - 239           | No                                | 95          | $C_{15}H_{26}I_2N_2$   |
| 12                      | n-C <sub>4</sub> H <sub>9</sub> | $CH_3$  | 176 - 178           | No                                | 85          | $\mathrm{C}_{15}H_{26}I_2N_2$                                |
| 13                      | $C_2H_3$                        | $\mathrm{CH}_{2}\mathrm{C}_{6}\mathrm{H}_{5}$ | 205 - 208           | Yes                               | 60          | $C_{19}H_{26}I_2N_2$   |
| 14                      | $n-C_{14}H_{29}$                | CHa   | 196 - 198           | Yes                               | 95          | $\mathrm{C}_{25}H_{46}l_2N_2$                                |
| <sup>a</sup> Corrected. |                                 | <sup>b</sup> Dried in                         | vacuo ove           | r P <sub>2</sub> O <sub>5</sub> . | See         | footnote c,  |
| Table I.                |                                 |   |                     |                                   |             |  |

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## Preparation of α-Methylhistamine from L-Histidine

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 $\alpha$ -Methylhistamine has been shown to possess weak histamine-like agonist activity<sup>2</sup> by its pharmacological effects on the blood pressure and gastric secretion of various test animals and by its stimulation of the contraction of isolated guinea pig ileum. The synthesis of this compound by a sequence of steps has been described only once before<sup>3</sup> and we now report a new and convenient route to the compound using L-histidine as the precursor.

## **Experimental Section**

Melting points were determined on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are uncorrected. The ir and pmr spectra were all as expected. During the reaction sequence for the preparation of L-histidinol from L-histidine, the literature method<sup>4</sup> was modified during the stage involving reduction of N-benzoylhistidine methyl ester to N-benzoylhistidinol; thus, a stirred suspension (rather than a solution) of LAH (12 g) was used to reduce 0.1 mole of the ester and the Al gel formed during the normal reaction work-up was thoroughly extracted with hot MeOH to obtain significant yields (ca. 75%) of the product.

α-Bromomethylhistamine.—L-Histidinol·2HBr (mp 185-186°) (1.80 g) was dissolved in an aged red-brown solution of 32% HBr in AcOH (40 ml) (Eastman Organics) contained in a 200-ml pressure bottle (Fisher Scientific Co.). The sealed vessel was heated at 110-120° (oil bath) with internal magnetic stirring for 19 hr, the solution cooled and the solvent removed *in vacuo*. The semisolid residue was triturated with EtOH to yield a buff **dihydrobromide** product, (1.86 g), mp 214-215° (EtOH-Et<sub>2</sub>O). Anal. (C<sub>8</sub>H<sub>12</sub>Br<sub>2</sub>N<sub>3</sub>) C, H.

An experiment using a fresh solution of HBr in AcOH (strawcolored) afforded only unchanged L-histidinol and it is therefore possible that traces of free Br<sub>2</sub> catalyze the reaction.

α-Methylhistamine.--α-Bromomethylhistamine 2HBr (0.40 g) was dissolved in a solution of NaOAc (0.5 g) in 10% aq AcOH (25 ml) containing 10% Pd-C (0.5 g), and the mixture hydrogenated at room temperature and pressure until gas absorption ceased (18 hr). The suspension was filtered via kieselguhr, the solvent removed *in vacuo* and the residual solid extracted with portions of hot EtOH. The organic solution was evaporated to dryness and the pink oily residue treated with anhyd Et<sub>2</sub>O to yield the crude **dihydrobromide** product (mp 110-115°) contaminated with NaOAc (pmr evidence). An ammoniacal solution of the product was treated with an excess of aq picric acid to afford the **andhydrous dipicrate** derivative (0.39 g), mp 182-183° (H<sub>2</sub>O) (lit.<sup>3</sup>, dipicrate monohydrate, 202-204°). Anal. (C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>14</sub>) C, H, N.

Hydrogenolysis of  $\alpha$ -bromomethylhistamine to  $\alpha$ -methylhistamine would not proceed when either EtOH or MeOH were used as the solvent. The product was isolated and characterized as the dipicrate derivative after noting the infinite solubility of the free base in H<sub>2</sub>O which precluded any easy separation of the amine base for formation of hydrohalide salts.

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