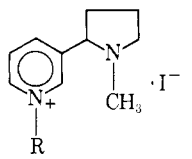
N-alkyl-*S*-(−)-nicotinium iodide, *N'*-alkyl-*S*-(−)-nicotinium iodide, and *N,N'*-bisalkyl-*S*-(−)-nicotinium diiodide which may be separated conveniently by chromatography. The compounds in Table I were eluted with 2% MeOH–C_6H_6. Identification was accomplished by uv spectroscopy in MeOH and acidified (6 *N* H_2SO_4) MeOH.

Table I
N-Alkyl-*S*-(−)-nicotinium Iodides



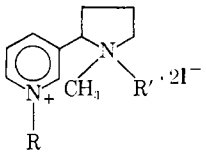
No.	R	Mp, °C[a]	Hygroscopic[b]	Yield, %	Empirical formula[c]
1	C_2H_5	89–92	Yes	15	$C_{12}H_{19}IN_2$
2	*n*-C_3H_7	82–85	Yes	60	$C_{13}H_{21}IN_2$
3	*i*-C_3H_7	120–122	No	75	$C_{13}H_{21}IN_2$
4	*n*-C_4H_9	78	Yes	70	$C_{14}H_{23}IN_2$
5	*i*-C_4H_9	110	Yes	23	$C_{14}H_{23}IN_2$

[a] Corrected. [b] Dried *in vacuo* over P_2O_5. [c] 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 mμ in acid solution. The analogous N-quaternized 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_2O_3. The compounds in Table II were eluted with 5–10% MeOH–C_6H_6.

Table II
N,N'-Bisalkyl-*S*-(−)-nicotinium Diiodides



No.	R	R'	Mp, °C[a]	Hygroscopic[b]	Yield, %	Empirical formula[c]
6	C_2H_5	C_2H_5	230–233	No	60	$C_{14}H_{24}I_2N_2$
7	*n*-C_3H_7	*n*-C_3H_7	220–222	No	40	$C_{16}H_{28}I_2N_2$
8	*n*-C_3H_7	CH_3	176–178	No	95	$C_{14}H_{24}I_2N_2$
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_4H_9	CH_3	176–178	No	85	$C_{15}H_{26}I_2N_2$
13	C_2H_5	$CH_2C_6H_5$	205–208	Yes	60	$C_{19}H_{26}I_2N_2$
14	*n*-$C_{14}H_{29}$	CH_3	196–198	Yes	95	$C_{25}H_{46}I_2N_2$

[a] Corrected. [b] Dried *in vacuo* over P_2O_5. [c] See footnote *c*, Table I.

Acknowledgments.—This research and the related pharmacology has been generously supported by the American Medical Association Education and Research Foundation, Committee for Research on Tobacco and Health and the A. H. Robins Company, Richmond, Virginia. The authors express sincere gratitude for their assistance.

Preparation of α-Methylhistamine from L-Histidine

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Received March 31, 1970

α-Methylhistamine has been shown to possess weak histamine-like agonist activity[2] 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[3] 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[4] 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_2O). *Anal.* ($C_6H_{13}Br_2N_3$) C, H.

An experiment using a fresh solution of HBr in AcOH (straw-colored) afforded only unchanged L-histidinol and it is therefore possible that traces of free Br_2 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_2O 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_2O) (lit.[3], dipicrate monohydrate, 202–204°). *Anal.* ($C_{18}H_{17}N_9O_{14}$) C, H, N.

Hydrogenolysis of α-bromomethylhistamine to α-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_2O which precluded any easy separation of the amine base for formation of hydrohalide salts.

Acknowledgment.—The authors thank the Medical Research Council of Canada for financial support.

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