

Potential Analgetic Agents.

1-Acyl-4-aralkylhexahydro-1,4-diazepines

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Certain 8-propionyl-3,8-diazabicyclo[3.2.1]octanes have been shown to possess analgetic activity,² but analogous piperazines and 2,6-dialkylpiperazines lacking the endoethylenic bridge, showed either a loss or low order of activity.^{3,4} Based on these works and the known analgetic drug ethoheptazine (ethyl hexahydro-1-methyl-4-phenylazepine-4-carboxylate) the synthesis of the current series of hexahydro-1,4-diazepine (homopiperazine) derivatives was undertaken.

Experimental Section

The boiling points are uncorrected; melting points were taken on a Fisher-Johns melting apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer (KBr). All compounds were analyzed for C, H.

N-Benzylhexahydro-1,4-diazepine⁵ was obtained in 44% yield; bp 102-112° (1 mm); lit.⁶ bp 91-101° (0.2 mm); mp (-2HBr) 201-203°. *Anal.* (C₁₃H₁₈N₂·2HBr) H; C: calcd, 54.70; found, 54.16.

N-(2-Phenylethyl)hexahydro-1,4-diazepine.—This intermediate was prepared as above; yield 45%; bp 137-140° (1 mm); mp (-2HBr) 226-229°. *Anal.* (C₁₃H₂₀N₂·2HBr) C, H.

Acylation of *N*-Aralkylhexahydro-1,4-diazepine.—To 0.05 mole of the *N*-aralkylhexahydro-1,4-diazepine was slowly added 0.15 mole of the appropriate acid anhydride. The reaction mixture was chilled during the addition and then heated under reflux condenser and drying tube for 1 hr at 95-97°. The clear mixture which resulted was then treated with 0.25 mol of ice 20% NaOH to liberate the product. It was extracted into Et₂O, dried overnight (Na₂SO₄), and purified by distillation. The compounds were characterized as HBr salts (Table I).

Quaternization Products of *S*(-)-Nicotine. 2¹JAMES A. SCHAEFER AND CHARLES H. JARBOE²*Medicinal Chemistry Section, Department of Pharmacology,
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S(-)-Nicotine has had a preeminent role in the development of peripheral nervous system pharmacology and its mechanism of cholinergic action is still being clarified.³ Despite the substantial pharmacodynamic information on the compound very little is known of those structural features which make it a reasonably selective agonist for autonomic ganglia and the neuromuscular junction.⁴⁻⁹ We are concerned with those aspects of *S*(-)-nicotine biochemistry which deal with the selective introduction of permanent positive charges at N and N' by quaternization with various alkyl halides. By controlled quaternization it has been possible to vary the degree of hindrance at either or both N and N' so that steric and inductive effects in their reactions with ganglionic and myoneural junction receptor systems may be investigated.

Experimental Section

Microanalyses were performed by Midwest MicroLab Inc., Indianapolis, Ind. Where analyses are indicated only by elemental symbols, analytical results for those elements were within ±0.4% of theoretical values.

***N*-Alkyl-*S*(-)-nicotinium Iodides.**—To 3.2 g (0.02 mole) of redistilled *S*(-)-nicotine, 0.04 mole of the appropriate alkyl iodide was slowly added. Reactions were conducted for 72 hr at room temp. The crude product was washed free of unreacted material with two 25-ml fractions of Et₂O. Residual solvent was evaporated under vacuum at room temp. The crude product (5-g fractions) was chromatographed on 50 g of Woelm Activity Grade I neutral Al₂O₃. Possible products of reaction were

TABLE I
1-ACYL-4-ARALKYLHEXAHYDRO-1,4-DIAZEPINES

Compd	<i>x</i>	<i>y</i>	Bp, °C (mm)	yield	HBr salt mp, °C	Recrystn solvent	Formula	Ir amide absorbance (cm ⁻¹) ³
1	0	1	148-151 (2.0)	76	178-179	EtOH-Et ₂ O	C ₁₄ H ₂₀ N ₂ O·HBr	1630
2	1	1	156-160 (2.0)	73	175-176	EtOH-Et ₂ O	C ₁₅ H ₂₂ N ₂ O·HBr	1662
3	2	1	162-165 (0.5-1.0)	72	160-161	EtOH-Et ₂ O	C ₁₆ H ₂₄ N ₂ O·HBr	1659
4	0	2	155-159 (1.0)	71	172-173	<i>i</i> -PrOH-Et ₂ O	C ₁₃ H ₂₂ N ₂ O·HBr	1652
5	1	2	166-171 (1.5)	70	167-169	<i>i</i> -PrOH-Et ₂ O	C ₁₆ H ₂₄ N ₂ O·HBr	1666
6	2	2	176-180 (2.0)	78	146-147	<i>i</i> -PrOH-Et ₂ O	C ₁₇ H ₂₆ N ₂ O·HBr	1660

(1) Taken in part from the M.S. Thesis of B. W. Sutton, Rutgers University, The State University of New Jersey, New Brunswick, N. J., 1969.

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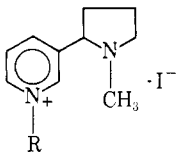
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N-alkyl-*S*(-)-nicotinium iodide, *N'*-alkyl-*S*(-)-nicotinium iodide, and *N,N'*-bisalkyl-*S*(-)-nicotinium diiodide which may be separated conveniently by chromatography. The compounds in Table I were eluted with 2% MeOH-C₆H₆. Identification was accomplished by uv spectroscopy in MeOH and acidified (6 *N* H₂SO₄) MeOH.

TABLE I
N-ALKYL-*S*(-)-NICOTINIUM IODIDES



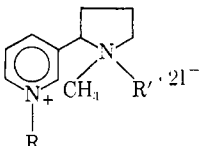
No.	R	Mp, °C ^a	Hygroscopic ^b	Yield, %	Empirical formula ^c
1	C ₂ H ₅	89-92	Yes	15	C ₁₂ H ₁₃ N ₂
2	<i>n</i> -C ₃ H ₇	82-85	Yes	60	C ₁₃ H ₂₁ N ₂
3	<i>i</i> -C ₃ H ₇	120-122	No	75	C ₁₃ H ₂₁ N ₂
4	<i>n</i> -C ₄ H ₉	78	Yes	70	C ₁₄ H ₂₃ N ₂
5	<i>i</i> -C ₄ H ₉	110	Yes	23	C ₁₄ H ₂₃ N ₂

^a Corrected. ^b Dried *in vacuo* over P₂O₅. ^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 Al₂O₃. The compounds in Table II were eluted with 5-10% MeOH-C₆H₆.

TABLE II
N,N'-BISALKYL-*S*(-)-NICOTINIUM DIIODIDES



No.	R	R'	Mp, °C ^a	Hygroscopic ^b	Yield, %	Empirical formula ^c
6	C ₂ H ₅	C ₂ H ₅	230-233	No	60	C ₁₄ H ₂₄ I ₂ N ₂
7	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	220-222	No	40	C ₁₆ H ₂₈ I ₂ N ₂
8	<i>n</i> -C ₃ H ₇	CH ₃	176-178	No	95	C ₁₄ H ₂₄ I ₂ N ₂
9	<i>n</i> -C ₃ H ₇	C ₂ H ₅	206-209	No	90	C ₁₅ H ₂₆ I ₂ N ₂
10	<i>i</i> -C ₃ H ₇	CH ₃	235-238	No	93	C ₁₄ H ₂₄ I ₂ N ₂
11	<i>i</i> -C ₃ H ₇	C ₂ H ₅	236-239	No	95	C ₁₅ H ₂₆ I ₂ N ₂
12	<i>n</i> -C ₄ H ₉	CH ₃	176-178	No	85	C ₁₆ H ₂₈ I ₂ N ₂
13	C ₂ H ₅	CH ₂ C ₆ H ₅	205-208	Yes	60	C ₁₉ H ₂₆ I ₂ N ₂
14	<i>n</i> -C ₁₄ H ₂₉	CH ₃	196-198	Yes	95	C ₂₃ H ₄₆ I ₂ N ₂

^a Corrected. ^b Dried *in vacuo* over P₂O₅. ^c See footnote c, Table I.

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Preparation of α-Methylhistamine from L-Histidine

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α-Methylhistamine has been shown to possess weak histamine-like agonist activity² 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 before³ 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 method⁴ 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-Et₂O). *Anal.* (C₈H₁₃Br₂N₃) 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 Br₂ 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 Et₂O 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 anhydrous dipicrate derivative (0.39 g), mp 182-183° (H₂O) (lit.³, dipicrate monohydrate, 202-204°). *Anal.* (C₁₀H₁₇N₃O₁₄) 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 H₂O which precluded any easy separation of the amine base for formation of hydrohalide salts.

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