Potential Analgetic Agents. 1-Acyl-4-aralkylhexahydro-1,4-diazepines

Bruce W. Sutton[1] and John H. Shinkai

College of Pharmacy, Rutgers University, Newark, New Jersey 07104

Received March 3, 1970

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 etoheptazine (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. Ir spectra were determined on a Perkin-Elmer Model 21 spectrophotometer (KBr). All compounds were analyzed for C, H.

N-Benzylhexahydro-1,4-diazepine[5] was obtained in 44% yield: bp 102–112° (1 mm); lit.[6] bp 91–101° (0.2 mm); mp (·2HBr) 201–203°. *Anal.* ($C_{12}H_{18}N_2$·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.* ($C_{13}H_{20}N_2$·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 iced 20% NaOH to liberate the product. It was extracted into Et_2O, dried overnight (Na_2SO_4), and purified by distillation. The compounds were characterized as HBr salts (Table I).

Quaternization Products of S-(−)-Nicotine, 2[1]

James A. Schaefer and Charles H. Jarboe[2]

Medicinal Chemistry Section, Department of Pharmacology, School of Medicine, University of Louisville, Louisville, Kentucky 40202

Received January 5, 1970

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 biochemorphology 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.

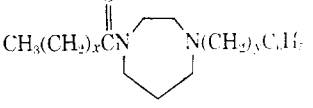
Experimental Section

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 Et_2O. Residual solvent was evapd under vacuum at room temp. The crude product (5-g fractions) was chromatographed on 50 g of Woelm Activity Grade I neutral Al_2O_3. Possible products of reaction were

Table I

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



Compd	x	y	Bp, °C (mm)	% yield	HBr salt mp, °C	Recrystn solvent	Formula	Ir amide absorbance (cm^{-1})
1	0	1	148–151 (2.0)	76	178–179	EtOH–Et_2O	$C_{14}H_{20}N_2O$·HBr	1630
2	1	1	156–160 (2.0)	73	175–176	EtOH–Et_2O	$C_{15}H_{22}N_2O$·HBr	1662
3	2	1	162–165 (0.5–1.0)	72	160–161	EtOH–Et_2O	$C_{16}H_{24}N_2O$·HBr	1659
4	0	2	155–159 (1.0)	71	172–173	*i*-PrOH–Et_2O	$C_{15}H_{22}N_2O$·HBr	1652
5	1	2	166–171 (1.5)	70	167–169	*i*-PrOH–Et_2O	$C_{16}H_{24}N_2O$·HBr	1666
6	2	2	176–180 (2.0)	78	146–147	*i*-PrOH–Et_2O	$C_{17}H_{26}N_2O$·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.

(2) (a) G. Cignarella, E. Occelli, G. Maffii, and E. Testa, *J. Med. Chem.*, **6**, 385 (1963); (b) G. Cignarella, E. Occelli, G. Cristiani, L. Paduano, and E. Testa, *ibid.*, **6**, 764 (1963).

(3) G. Cignarella, G. Maffii, and E. Testa, *Gazz. Chim. Ital.*, **93**, 226 (1963).

(4) G. Cignarella and E. Testa, *J. Med. Chem.*, **11**, 592 (1968).

(5) R. Baltzly, J. S. Buck, E. Lorz, and W. Schön, *J. Amer. Chem. Soc.*, **66**, 263 (1944).

(6) R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *J. Med. Chem.*, **5**, 944 (1962).

(1) Paper I: C. H. Jarboe and C. M. Schmidt, *J. Med. Chem.*, **13**, 333 (1970).

(2) To whom inquiries should be directed.

(3) P. Th. Henderson, E. J. Ariens, and A. M. Simonis, *Eur. J. Pharmacol.*, **4**, 62 (1968).

(4) R. B. Barlow and J. T. Hamilton, *Brit. J. Pharmacol.*, **18**, 510 (1962).

(5) R. B. Barlow and J. T. Hamilton, *ibid.*, **18**, 543 (1962).

(6) M. Mattila and A. Vartianian, *Ann. Med. Exp. Biol. Fenn.*, **42**, 27 (1964).

(7) R. B. Barlow and J. T. Hamilton, *Brit. J. Pharmacol.*, **25**, 206 (1965).

(8) K. S. Kim, J. F. Borzelleca, E. R. Bowman, and H. McKennis, Jr., *J. Pharmacol. Exp. Ther.*, **161**, 59 (1968).

(9) R. B. Barlow and N. A. Dobson, *J. Pharm. Pharmacol.*, **7**, 27 (1955).