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Conformationally Restricted Analogs of Histamine H_1 Receptor Antagonists: *trans*- and *cis*-1-Benzyl-3-dimethylamino-6-phenylpiperidine†

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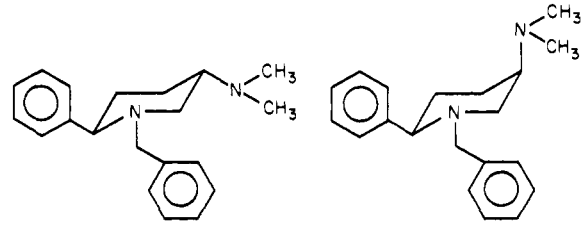
The syntheses of *trans*- and *cis*-1-benzyl-3-dimethylamino-6-phenylpiperidine (1 and 2) are described. Compounds 1 and 2 were found to be inhibitors of histamine, acetylcholine, and barium chloride induced contractions of the isolated guinea pig ileum. Compounds 1 and 2 do not exhibit appreciable stereoselectivity in their ability to inhibit smooth muscle contractions. The cis compound 2 is a more effective inhibitor of histamine *N*-methyltransferase than the trans isomer 1.

Recent reports from this laboratory have described the results of studies directed toward elucidating the stereochemical factors involved in the interaction of antagonists with histamine H_1 receptors.[1,2] Our approach has involved the use of conformationally restricted analogs of ethylenediamine histamine antagonists to ascertain the role of the conformation about the C–C bond of the dimethylaminoethyl group in determining antagonist activity. It was concluded from our earlier work that a fully extended trans N–C–C–N conformation is not necessary for H_1 receptor blockade by ethylenediamine antagonists and that the model proposed by Casy and Ison[3] represents a reasonable approximation of the molecular conformation of H_1 receptor-bound histamine antagonists.

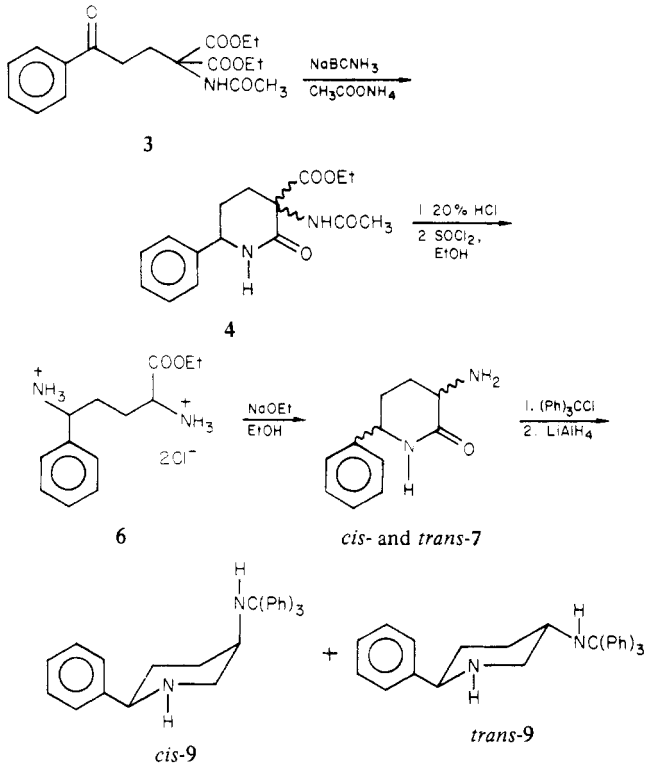
The purpose of the present report is to describe the synthesis and pharmacological evaluation of *trans*- and *cis*-1-benzyl-3-dimethylamino-6-phenylpiperidine (1 and 2). These compounds are cyclic analogs of the ethylenediamine histamine antagonists and they contain the essential structural features usually associated with antagonist activity.[4] Compounds 1 and 2 were selected for study in order to further assess the importance of conformational factors in determining the effectiveness of antagonist–receptor interaction. The trans compound 1 would be expected to exist almost exclusively in the conformation in which the 3-dimethylamino group and the 6-phenyl group are equatorial. In this conformation, the N–C–C–N dihedral angle is 180°. On the other hand, compound 2 would be expected to exist as an equilibrium mixture of the axial and equatorial 3-dimethylamino conformers with only the equatorial 3-dimethylamino, axial 6-phenyl conformer, or a boat conformation, exhibiting the 180° N–C–C–N arrangement. Therefore, if molecular



1 2

† This work is dedicated to the memory of Edward E. Smissman.

Scheme I



conformation plays a key role in the interaction of compounds 1 and 2 with H_1 receptors, significant differences in activity should be observed with the two compounds. Differences in the activity of the two diastereoisomers, interpreted within the framework of existing information on the interaction of conformationally restricted antagonists with H_1 receptors, should provide further insight into the conformational aspects of antagonist–receptor binding.

Synthesis. The departure point for the preparation of 1 and 2 was the reaction of β-chloropropiophenone with diethyl acetamidomalonate to produce 3 (Scheme I). The condensation product 3 was reductively aminated using the sodium cyanoborohydride method of Borch et al.[5] Upon reductive amination of the ketone carbonyl of 3, intramolecular cyclization occurred between the primary amino group and one of the carboethoxy groups to yield a diastereomeric mixture of δ-lactams 4. Treatment of the mixture of lactams 4 with 6 *N* HCl resulted in hydrolysis of the lactam, amide, and ester groups with decarboxylation to give a mixture of *erythro*- and *threo*-5-phenylornithine dihydrochloride (5) which was converted to the diastereomeric mixture of ethyl ester dihydrochlorides 6. The mixture 6 was cyclized to *cis*- and *trans*-3-amino-6-phenylpiperidin-2-one (7) upon treatment with 2 equiv of sodium ethoxide.

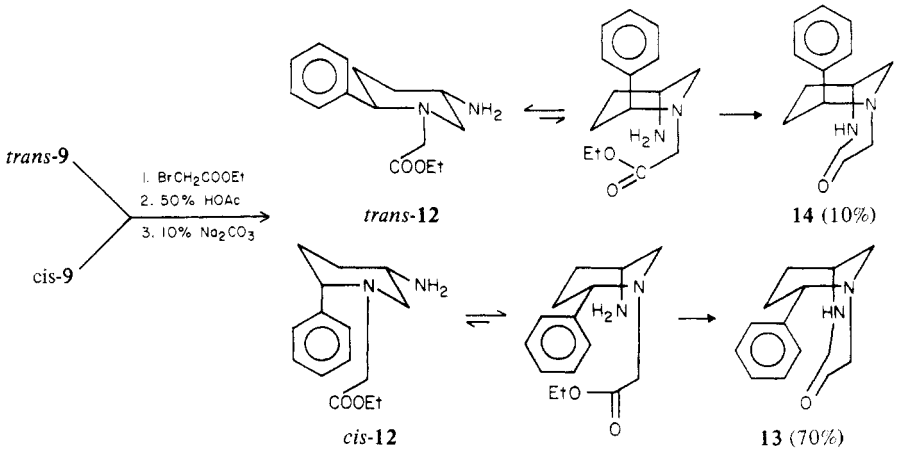
When the diastereoisomeric mixture of *cis*- and *trans*-7 was equilibrated by heating in the presence of sodium ethoxide, the product obtained consisted exclusively of a single isomer (TLC) which was assigned the trans configuration (vide infra).

Diborane reduction of the mixture of *cis*- and *trans*-7 yielded *cis*- and *trans*-3-amino-6-phenylpiperidine which was successfully, but very inefficiently, separated by preparative thin-layer chromatography on silica gel. Because of the difficulties encountered in separating substantial quantities of the compounds by this method, isomer separation was delayed until a later step.

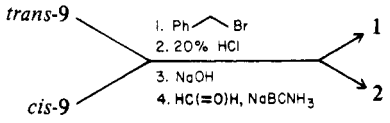
cis- and *trans*-7 were converted to their 3-triphenylmethyl derivatives 8 and this diastereomeric mixture was reduced with lithium aluminum hydride to *cis*- and *trans*-3-triphenylmethylamino-6-phenylpiperidine (9) which were readily separated by dry-column chromatography. When *trans*-7, which had been obtained by equilibration of *cis*- and *trans*-7 in the presence of sodium ethoxide, was converted to its 3-triphenylmethyl derivative and reduced with lithium aluminum hydride, the product was identical in all respects with the compound of lower R_f value obtained by dry-column chromatography of *cis*- and *trans*-9. Therefore, equilibration of 7 followed by tritylation and reduction provides a method for stereoselective synthesis of *trans*-9.

In order to confirm the relative stereochemistry of *cis*- and *trans*-9, the designation of which had been tentatively based on the results of the sodium ethoxide equilibration of *cis*- and *trans*-7 and the relative R_f values of *cis*- and *trans*-9, the following experiments were carried out. *cis*- and *trans*-9 were converted to the *N*-carboethoxymethyl esters 10 by N-alkylation with ethyl bromoacetate (Scheme II). *cis*- and *trans*-10 were detritylated with 50% acetic acid to afford the diacetate salts 11 which were converted to their free bases (*cis*- and *trans*-12) and allowed to undergo intramolecular cyclization to the bicyclic lactams 13 and 14. It was reasoned that *cis*-12 would more readily undergo cyclization than *trans*-12 because in the conformer of *cis*-12 in which the amino group and the ester are in the cis-diaxial orientation required for cyclization, the 6-phenyl group is equatorial. On the other hand, in order for *trans*-12 to undergo cyclization all three substituents must attain an axial orientation or, alternatively, the cyclization

Scheme II



Scheme III



must take place via a boat conformation. Both of the latter conformations are thermodynamically less favorable than the conformation required for cyclization of *cis*-**12**.

When *cis*-**12** was heated at 165° for 48 hr in a stainless steel bomb, the expected lactam **13** was isolated in 70% yield. The NMR spectrum of **13** exhibited a doublet of doublets at 4.0 ppm which was assigned to the axial C-8 benzylic proton. The coupling constants of the C-8 proton were 4 and 11 Hz which are typical of axial-equatorial and axial-axial interactions, respectively.[6] A five-proton singlet at 7.30 ppm was assigned to the equatorial 8-phenyl group and the bridgehead C-9 methylene protons appeared at 3.25 ppm as a multiplet. The C-6 and C-7 methylene protons appeared as a narrow multiplet at 1.95 ppm.

Treatment of *trans*-**12** under the conditions described for the cyclization of *cis*-**12** resulted in the formation of bicyclic lactam **14** in 10% yield. The equatorial C-8 benzylic proton of **14** appeared as a band ($W_{1/2}$ = 9 Hz) at 4.04 ppm. The C-8 phenyl protons were present as a multiplet at 7.45 ppm. The appearance of the aromatic protons as a multiplet rather than as a singlet as seen for **13** is attributed to the restricted rotation of the axial phenyl ring in **14**. The C-9 methylene protons appeared as a three-peak multiplet at 2.83 ppm, which is 0.42 ppm further upfield than the C-9 methylene multiplet of **13**. This difference is apparently due to a shielding effect by the axial phenyl group in **14**. The C-6 and C-7 methylene protons which appeared as a single narrow multiplet in **13** are present as two distinct multiplets at 1.82 and 2.17 ppm in **14**. The differences in the yields of the bicyclic lactams **13** and **14** taken together with the differences in their NMR spectra described above and in the Experimental Section provide further evidence for the stereochemical assignments of *cis*- and *trans*-**9**.

The target compounds **1** and **2** were then prepared from *cis*- and *trans*-**9** as illustrated in Scheme III. N-Alkylation with benzyl bromide followed by detritylation in aqueous acid and N,N-dimethylation according to the procedure of Borch and Hassid[7] afforded **1** and **2** which were converted to their respective dihydrochlorides for biological testing.

Biological Results. Compounds **1** and **2** were evaluated for histamine antagonist activity on the isolated guinea pig ileum.[8] The trans isomer **1** had an ED_{50} of 6.72 ($\pm$0.66) $\times 10^{-6}$ *M* in the presence of 4×10^{-6} *M* histamine, while the cis isomer **2** had an ED_{50} of 1.83 ($\pm$0.39) $\times 10^{-6}$ *M*. Thus, **1** and **2** exhibited no appreciable degree of stereoselectivity in their inhibition of histamine-induced contractions of the guinea pig ileum. The standard H_1 antagonist tripelennamine (10^{-7} *M*) produced a 66–76% inhibition of histamine-induced contractions.

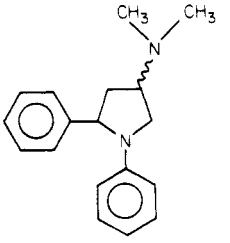
Compounds **1** and **2** were also tested for their ability to inhibit the contractions of the guinea pig ileum elicited by 4×10^{-7} *M* acetylcholine. In this assay, the trans isomer **1** had an ED_{50} of 2.90 ($\pm$0.25) $\times 10^{-6}$ *M* and the ED_{50} of **2** was 1.45 ($\pm$0.06) $\times 10^{-6}$ *M*. The standard antihistamine tripelennamine (10^{-7} *M*) did not inhibit the response to acetylcholine.

In view of the absence of appreciable stereoselectivity in the inhibition of either histamine or acetylcholine, it was decided to determine the inhibiting effect of **1** and **2** on barium chloride induced contractions of the guinea pig ileum. The trans isomer **1** (5×10^{-6} *M*) caused a 39% inhibition of the contractions produced by 3.2×10^{-4} *M* barium chloride while cis isomer **2** (2×10^{-6} *M*) caused a 50% reduction of the contractions produced by 1.6×10^{-4} *M* barium chloride. These data indicate that compounds **1** and **2** are nonspecific inhibitors of smooth muscle contractions.

Compounds **1** and **2** were tested for their abilities to inhibit histamine *N*-methyltransferase (HMT) (E.C. 2.1.1.6) as previously described.[9] The trans isomer **1** had an inhibition constant (K_i) of 247 $\pm$ 67 μM while cis compound **2** had a K_i value of 31.6 $\pm$ 3.8 μM. These results differ from those obtained with *trans*- and *cis*-1,5-diphenyl-3-dimethylaminopyrrolidine where the trans isomer was found to be a more effective inhibitor. Also at variance with the previous results is the tendency of the trans isomer **1** to have a greater potentiating effect on HMT than the cis isomer **2**.

Discussion

The above-described results indicate that compounds **1** and **2** are inhibitors of histamine, acetylcholine, and barium chloride induced smooth muscle contractions. Although the ED_{50} values vs. histamine and acetylcholine are not strictly comparable because of the somewhat different agonist concentrations used in this study, it is apparent that the structural changes brought about by incorporation of the N–C–C–N unit of ethylenediamine histamine antagonists into the molecular framework described by compounds **1** and **2** result in not only minimal stereoselectivity at histamine receptors but a loss of receptor selectivity as well. The structural features usually associated with histamine H_1 receptor antagonist activity are well known[4,10,11] and our previous studies demonstrated that the N–C–C–N unit can be embodied in a conformationally restricted molecule (**17**) which exhibits



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both a selective interaction with the histamine H_1 receptor as well as stereoselectivity of antagonist activity. Both *cis*- and *trans*-**17** are more potent histamine H_1 antagonists than **1** and **2**; *cis*-**17** (5×10^{-8} *M*) causes a 45–55% inhibition of the guinea pig ileum contractions produced by 4×10^{-6} *M* histamine while *trans*-**17** (1×10^{-8} *M*) gives an inhibition of 85%. The additional methylene units of the piperidine ring and the 1-benzyl group and the increased basicity of the ring nitrogens of **1** and **2** over **17** cause steric, spatial, and solubility differences which could contribute to the loss of receptor selectivity and stereoselectivity. It is not known which of these factors or which combination of these factors may be primarily responsible for the relatively nonselective antagonist effects of compounds **1** and **2** on the receptors of the guinea pig ileum.

The stereoselective inhibition of HMT observed with compounds **1** and **2** is at variance with that observed in our previous studies with the substituted pyrrolidines (**17**) where the trans isomer was found to be the more effective inhibitor.[9] However, in view of the nonspecific effects of **1** and **2** discussed above, it would be unwarranted to draw conclusions from the present results regarding similarities

between the antagonist binding site of HMT and the H_1 antagonist receptor.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237B spectrophotometer and a Beckman IR-9 spectrophotometer. NMR samples (10–15% in $CDCl_3$ with Me_4Si as internal standard or in D_2O with DSS as internal standard) were recorded on a Varian A-60D spectrometer; results are expressed in parts per million. Compounds were routinely subjected to TLC analysis using Analtech precoated silica gel GF or alumina plates. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich., and agreed with theoretical values to within 0.4%. The petroleum ether used was that fraction which boils between 60 and 70°C.

Ethyl 2-Acetamido-4-benzoyl-2-carboethoxybutyrate (3). Sodium metal (7.2 g, 0.296 g-atom) was dissolved in 1 l. of super-dry ethanol. The sodium ethoxide solution was cooled in an ice bath and diethyl acetamidomalonate (64.0 g, 0.296 mol) was added in one portion. After a clear solution had formed, β-chloropropiophenone (50.0 g, 0.296 mol) was added in one portion and the resulting mixture was stirred vigorously with cooling for 6 hr. Stirring was continued at room temperature for 16 hr, 30 ml of water was added, and the mixture was stirred an additional hour. Ethanol was removed in vacuo, and the residue was suspended in 300 ml of water, filtered, and washed with H_2O and ether to afford **3** (88.3 g, 86%): mp 116–118° (lit.[12] 113–114°). Anal. ($C_{18}H_{23}NO_6$) C, H, N, O.

cis- **and** *trans*-**3-Acetamido-3-carboethoxy-6-phenylpiperidin-2-one (4).** To a stirred solution of **3** (87.3 g, 0.25 mol) in 1 l. of super-dry methanol was added solid ammonium acetate (192.5 g, 2.5 mol) followed by sodium cyanoborohydride (15.75 g, 0.25 mol). The resulting brown solution was stirred at room temperature for 48 hr. Concentrated HCl was added to pH 3, the solvent was removed in vacuo, and the solid residue was extracted with three 350-ml portions of $CHCl_3$. The combined $CHCl_3$ solution was washed with H_2O and dried (Na_2CO_3) and the $CHCl_3$ was removed under reduced pressure. Trituration of the oily residue with ether yielded **4** as a white solid (54.5 g, 71%): mp 170–186°; ir (KBr) 1730, 1690, 1660 cm^{-1}; TLC [silica gel GF, $CHCl_3$–C_6H_6 (1:3)] exhibited two spots (R_f 0.39 and 0.5). Anal. ($C_{16}H_{20}N_2O_4$) C, H, N, O.

erythro- **and** *threo*-**5-Phenylornithine Dihydrochloride (5).** The diastereomeric piperidone mixture **4** (60.8 g, 0.2 mol) was refluxed in 600 ml of 6 *N* HCl for 24 hr, cooled, and washed with two 50-ml portions of ether, and the aqueous acidic portion was evaporated under vacuum. The residue was triturated with THF to yield 54 g (96%) of **5** as a white solid which melted at 110° with foaming after being dried under vacuum at 110°: ir (KBr) 1740 cm^{-1}; NMR (D_2O) 2.1 (m, CH_2CH_2), 4.15 (m, NCHCO), 4.45 (m, C-5H), 7.5 (s, C_6H_5). Anal. ($C_{11}H_{18}N_2O_2Cl_2$) C, H, N, O.

erythro- **and** *threo*-**Ethyl 5-Phenylornithinate Dihydrochloride (6).** 5-Phenylornithine dihydrochloride (**5**) (60 g, 0.21 mol) was dissolved in 750 ml of super-dry ethanol and cooled in an ice bath. Thionyl chloride (53 g, 0.4 mol) was added dropwise during a period of 2 hr. After addition was completed, the solution was refluxed for 6 hr and stirred at room temperature for 48 hr and the ethanol was removed in vacuo. The residue, upon trituration with ether, afforded 53.3 g (82%) of **6** which was recrystallized from ethanol: mp 225–230°; ir (KBr) 1750 cm^{-1}. Anal. ($C_{13}H_{22}N_2O_2Cl_2$) C, H, N, O.

cis- **and** *trans*-**3-Amino-6-phenylpiperidin-2-one (7).** Ethyl 5-phenylornithinate dihydrochloride (**6**) (61.79 g, 0.2 mol) was dissolved in 500 ml of super-dry ethanol and cooled in an ice bath. A solution of Na (9.2 g, 0.4 g-atom) in 250 ml of super dry ethanol was added dropwise over a period of 2 hr. After the addition was complete, the mixture was stirred 17 hr at room temperature and evaporated to dryness in vacuo and the solid residue was divided into six portions. Each portion was extracted with three 100-ml portions of benzene at room temperature and the benzene extracts were combined and evaporated to yield 33.86 g of **7** (89%) as a solid residue: mp 95–105°; TLC [silica gel GF, pyridine–ethyl acetate (1:1)] showed two spots of approximately equal intensity when sprayed with 50% sulfuric acid and heated on a hot plate (R_f 0.12 and 0.2); ir (KBr) 1675 cm^{-1}; NMR ($CDCl_3$) 1.75 (s, NH_2), 2.9 (m, CH_2CH_2), 3.3 (m, NCHCO), 4.52 (m, C-6H), 6.28 (s, 0.5 H, NHCO), 6.6 (s, 0.5 H, NHCO), 7.24 (s, C_6H_5). Anal. ($C_{11}H_{14}N_2O$) C, H, N, O.

trans-**3-Amino-6-phenylpiperidin-2-one (*trans*-7).** The diastereomeric mixture **6** (30.90 g, 0.1 mol) was dissolved in 250 ml of super-dry ethanol and was cooled in an ice bath. A 150-ml solution of Na (4.6 g, 0.2 g-atom) in super-dry ethanol was added over a period of 2 hr. After the addition was completed, the mixture was stirred at room temperature for 17 hr and evaporated in vacuo at room temperature and the solid residue was boiled with three 300-ml portions of benzene. The combined benzene extracts were evaporated to yield a solid residue, mp 148–151°, which was recrystallized from ethanol to yield *trans*-**7** (13.2 g, 69%): mp 152–153°; TLC as described above for **7** showed one spot, R_f 0.12; ir (KBr) 1675 cm^{-1}; NMR ($CDCl_3$) 2.05 (s, NH_2), 1.88 (m, CH_2CH_2), 3.3 (m, NCHCO), 4.42 (m, C-6H), 6.23 (s, broadened, NHCO), 7.2 (s, C_6H_5). Anal. ($C_{11}H_{14}N_2O$) C, H, N, O.

trans-**3-Triphenylmethylamino-6-phenylpiperidin-2-one (*trans*-8).** *trans*-3-Amino-6-phenylpiperidin-2-one (19.0 g, 0.1 mol) was dissolved in 300 ml of alcohol-free $CHCl_3$ and to this solution was added 20.2 g (0.2 mol) of distilled triethylamine followed by dropwise addition of a 200-ml $CHCl_3$ solution of recrystallized triphenylmethyl chloride (27.8 g, 0.1 mol). The mixture was heated under reflux for 24 hr, cooled, and evaporated to dryness and the solid residue was extracted with boiling THF. The THF extract was evaporated to dryness to give 39.79 g (92%) of a solid residue, mp 172–177°, which was recrystallized from ethanol to give analytically pure *trans*-**8**: mp 178–180°; ir (KBr) 1655 cm^{-1}. Anal. ($C_{30}H_{28}N_2O$) C, H, N, O.

trans-**3-Triphenylmethylamino-6-phenylpiperidine (*trans*-9).** A solution of *trans*-**8** (20.0 g, 46.24 mmol) in 250 ml of dry THF was added over a period of 2 hr to a cold stirring suspension of $LiAlH_4$ (8.76 g, 231.2 mmol) in 300 ml of dry THF under N_2. The mixture was heated under reflux for 72 hr, during which time its color changed from grey to red. After cooling in an ice bath, excess $LiAlH_4$ was destroyed by dropwise addition of 9 ml of H_2O, 27 ml of 15% NaOH, and 9 ml of H_2O. The mixture was stirred for 1 hr and filtered and the solids were washed with two 50-ml poritions of THF. The combined THF solutions were evaporated in vacuo. The residue was dissolved in ether, washed with H_2O, dried ($MgSO_4$), and evaporated to yield 17.8 g (92%) of *trans*-**9** as gelatinous substance: TLC [silica gel GF, THF-petroleum ether (2:8)] showed one spot (R_f 0.41); ir (liquid film) indicated the absence of carbonyl absorption; NMR ($CDCl_3$) 1.16 (m, 4 H, CH_2CH_2), 1.45 (s, 2NH), 2.55 (m, NCH_2CHN), 3.33 (m, C-6H), 7.32 (m, 20 H, aromatic). An analytical sample of *trans*-**9** was prepared by dry-column chromatography on silica gel [petroleum ether–THF (8:2)]. Anal. ($C_{30}H_{30}N_2$) C, H, N.

cis- **and** *trans*-**3-Triphenylmethylamino-6-phenylpiperidin-2-one (8).** To a 500-ml $CHCl_3$ solution of 28.5 g (0.15 mol) of the diastereomeric mixture **7** and 30.36 g (0.3 mol) of distilled triethylamine was added dropwise a solution of triphenylmethyl chloride (41.7 g, 0.15 mol) in 300 ml of $CHCl_3$. The mixture was heated under reflux for 24 hr, cooled, and evaporated to dryness in vacuo and the residue was extracted with boiling THF. Evaporation of the THF extracts yielded 61.43 g (95%) of **8**, mp 170–200°, which was not recrystallized: ir (KBr) 1655 cm^{-1}; NMR ($CDCl_3$) 1.5 (m, CH_2CH_2), 3.0 (m, NCHCO), 3.85 (m, C-6H), 5.85 (broadened s, 0.5 H, NHCO), 6.02 (broadened s, 0.5 H, NHCO), 7.25 (m, 20 H, aromatic). Anal. ($C_{30}H_{28}N_2O$) C, H, N, O.

cis- **and** *trans*-**3-Triphenylmethylamino-6-phenylpiperidine (9).** The mixture of isomers **8** (15.5 g, 0.36 mol) was dissolved in 250 ml of dry THF and added dropwise to a cold mixture of $LiAlH_4$ (6.8 g, 0.18 mol) in 500 ml of THF with stirring. After the addition was complete, the mixture was refluxed for 72 hr during which time the color changed from grey to red. The reaction mixture was cooled in an ice bath, and 7 ml of H_2O was added followed by 21 ml of 15% NaOH and an additional 7 ml of H_2O. The inorganic solids were removed by filtration and washed with THF. The combined THF solutions were evaporated to dryness and the residue was dissolved in 400 ml of ether, washed with two 50-ml portions of H_2O, and dried ($MgSO_4$). Evaporation of the ether afforded a gelatinous residue (14 g, 94%). TLC [silica

gel GF, THF–petroleum ether (2:8)] showed two major spots (R_f 0.41 and 0.66) when the plate was sprayed with 0.2% ninhydrin solution and heated on a hot plate; the spots were of approximately equal intensity. An analytical sample of **9** was prepared by washing an ether solution of the compounds with 10% NaOH and H_2O, drying ($MgSO_4$), and evaporation of the ether followed by drying of the residue under vacuum. Anal. ($C_{30}H_{30}N_2$) C, H, N.

Separation of *cis*- and *trans*-3-Triphenylmethylamino-6-phenylpiperidine (9) by Dry Column Chromatography. Silica gel 60 (1:1 mixture of EM Laboratories No. 7734, particle size 0.063–0.2 mm, 70–230 mesh, and No. 9385, particle size 0.04–0.063 mm, 230–400 mesh) adjusted to activity III was used for the separation. The activity was adjusted according to the directions of Loev and Goodman.[13] The silica (400 g) was conditioned by mixing it overnight on a rotary evaporator with 5% H_2O, 0.5% fluorescent indicator, and 10% of the solvent mixture [THF–petroleum ether (2:8)]. The silica gel was packed in a 2.5-in. diameter sealed nylon tubing to give a column of approximately 2.5 ft in length. The mixture of *cis*- and *trans*-**9** (4.0 g) was mixed with 20 g of silica gel, applied to the top of the column, and covered with an additional 20 g of silica gel. The solvent [THF–petroleum ether (2:8)] was allowed to pass through the column under a pressure of 10 in. of solvent. The isomer bands (R_f 0.34 and 0.59) were extracted [$CHCl_3$–CH_3OH–NH_3 (90:9:1)] and the extracts were evaporated to dryness. The residues were taken up in benzene, dried ($CaSO_4$), and evaporated to dryness in vacuo.

The material of higher R_f consisted of 1.9 g of solid, mp 162–166, which was recrystallized from 95% ethanol to yield *cis*-**9**: 1.7 g; mp 164–166°; NMR ($CDCl_3$) 1.58 (m, 2NH and $-CH_2CH_2-$), 2.2 (d, J = 11 Hz, C-2 methylene), 2.8 (br, C-3H), 3.38 (m, C-6H), 7.3 (m, 20 aromatic H). Anal. ($C_{30}H_{30}N_2$) C, H, N.

The material of lower R_f consisted of 1.80 g of *trans*-**9**. It was a gelatinous material whose ir and NMR spectra were identical in all respects with those of the *trans*-**9** prepared by reduction of *trans*-**8**. Anal. ($C_{30}H_{30}N_2$) C, H, N.

***trans*-3-Triphenylmethylamino-6-phenyl-1-carboethoxymethylpiperidine (*trans*-10).** Ethyl bromoacetate (2.84 g, 0.017 mol) in 20 ml of acetonitrile was added dropwise to a mixture of *trans*-**9** (7.1 g, 0.017 mol) and Na_2CO_3 (3.6 g, 0.034 mol) in 50 ml of acetonitrile and the reaction mixture was stirred under nitrogen at room temperature for 36 hr. After evaporation of the solvent, the residue was extracted with three 50-ml portions of $CHCl_3$ which were combined, washed with H_2O, and dried ($MgSO_4$). The viscous residue was purified by dry-column chromatography on silica gel [ethyl acetate–petroleum ether (25:75)] and the compound was extracted with $CHCl_3$–CH_3OH (9:1). The solvent was evaporated and the residue was dried under vacuum to yield *trans*-**10** (7.2 g, 84%) as a glassy solid: ir ($CHCl_3$) 1740 cm^{-1}. Anal. ($C_{33}H_{36}N_4O_2$) C, H, N, O.

***trans*-3-Amino-6-phenyl-1-carboethoxymethylpiperidine Diacetate (*trans*-11).** *trans*-**10** (6.0 g, 0.0119 mol) was stirred with 40 ml of 50% acetic acid for 24 hr at room temperature. The solvent was removed in vacuo and the residue was triturated with 20 ml of H_2O. The trityl alcohol was filtered and washed with 10 ml of H_2O and the combined aqueous fractions were evaporated to dryness. The solid residue (3.89 g) was recrystallized from ethanol to yield *trans*-**11** (3.21 g, 70%): mp 123–124°; ir (KBr) 1740, 1715 cm^{-1}. Anal. ($C_{19}H_{30}N_2O_6$) C, H, N, O.

***trans*-3-Amino-6-phenyl-1-carboethoxymethylpiperidine (*trans*-12).** The *trans*-diacetate **11** (3.0 g, 0.0078 mol) was dissolved in 20 ml of $CHCl_3$, cooled, and stirred with 20 ml of 10% Na_2CO_3 for 10 min. The $CHCl_3$ layer was separated, washed with H_2O, dried (K_2CO_3), and evaporated to yield *trans*-**12** as a colorless oil (1.94 g, 95%) which was used without further purification: ir (liquid film) 1740 cm^{-1}; NMR ($CDCl_3$) 1.15 (t, CH_3), 1.4–2.8 (m, NH_2, C-2, C-4, C-5 methylenes, C-3H), 3.0 (d, J = 5 Hz, NCH_2CO), 3.35 (m, C-6H), 3.95 (q, CH_2), 7.09 (s, C_6H_5).

***cis*-3-Triphenylmethylamino-6-phenyl-1-carboethoxymethylpiperidine (*cis*-10).** Ethyl bromoacetate (1.67 g, 0.01 mol) in 20 ml of acetonitrile was added during a period of 30 min to a mixture of *cis*-**9** (4.18 g, 0.01 mol) and Na_2CO_3 (2.12 g, 0.02 mol) in 70 ml of acetonitrile–THF (5:1). The reaction mixture was stirred under nitrogen at room temperature for 48 hr, the solvent was evaporated, and the solid residue was extracted with three 50-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to afford *cis*-**10** which was recrystallized from isopropyl alcohol: yield 4.01 g (79%); mp 144–145°; ir (KBr) 1740 cm^{-1}. Anal. ($C_{34}H_{36}N_2O_2$) C, H, N, O.

***cis*-3-Amino-6-phenyl-1-carboethoxymethylpiperidine Diacetate (*cis*-11).** *cis*-**10** (4.0 g, 0.0079 mol) was stirred at room temperature for 24 hr in 30 ml of 50% acetic acid. The reaction mixture was evaporated under reduced pressure and the residue was triturated with 30 ml of H_2O. Trityl alcohol was removed by filtration and the filtrate was evaporated to dryness. The residual solid (2.7 g) was recrystallized from isopropyl alcohol to yield *cis*-**11** (2.5 g, 83%): mp 115–117°; ir (KBr) 1740, 1715 cm^{-1}. Anal. ($C_{19}H_{30}N_2O_6$) C, H, N, O.

***cis*-3-Amino-6-phenyl-1-carboethoxymethylpiperidine (*cis*-12).** To a cold solution of the *cis*-diacetate **11** (2.0 g, 0.005 mol) in 20 ml of $CHCl_3$ was added 10 ml of 10% Na_2CO_3 and the mixture was stirred for 10 min; the $CHCl_3$ layer was separated, washed with water, dried (K_2CO_3), and evaporated. The oily product (1.30 g, 96%) solidified upon cooling the flask in an ice bath and analytically pure *cis*-**12** was collected: mp 38–40°; ir (KBr) 1740 cm^{-1}. Anal. ($C_{15}H_{22}N_2O_2$) C, H, N, O.

***endo*-8-Phenyl-1,4-diazabicyclo[3.3.1]nonan-3-one (13).** *cis*-**12** (0.524 g, 0.002 mol) was dissolved in 25 ml of 1,2-dimethoxyethane and heated in a 45-ml stainless steel bomb at 165° for 48 hr. The reaction solution was evaporated to a brown solid residue which was washed with 10 ml of ether and recrystallized from ethanol–ether (1:2) to afford 0.303 g (70%) of crystalline solid: mp 205°; ir (KBr) 1675 cm^{-1}; NMR ($CDCl_3$) 1.95 (narrow m, C-6 and C-7 protons), 3.25 (overlapping AB q, C-9 methylene), 3.12 (overlapping AB q, C-2 methylene) 3.50 (m, C-5H), 4.0 (d of d, J = 11, 4 Hz, C-8H), 7.3 (s, C_6H_5), 7.68 (br, NH). Anal. ($C_{13}H_{16}N_2O$) C, H, N, O.

***exo*-8-Phenyl-1,4-diazabicyclo[3.3.1]nonan-3-one (14).** A solution of *trans*-**12** (0.524 g, 0.002 mol) in 25 ml of 1,2-dimethoxyethane was heated at 165° for 48 hr in a 45-ml stainless steel reaction bomb. The clear yellow solution was evaporated to dryness in vacuo and the viscous residue was triturated with ether to yield 0.053 g of solid, mp 162–170°, which was recrystallized from THF–petroleum ether (3:1) to yield 0.043 g of **14** (10%): mp 168–170°; ir (KBr) 1665 cm^{-1}; NMR ($CDCl_3$) 1.82 (m, C-6 or C-7 protons), 2.17 (m, C-6 or C-7 protons), 2.83 (AB q, C-9 methylene), 3.37 (m, C-5H), 3.47 (d, J = 18 Hz, C-2H), 4.04 (m, exo C-8H), 4.07 (d, J = 18 Hz, C-2H), 7.45 (m, C_6H_5, N-4H). Anal. ($C_{13}H_{16}N_2O$) C, H, N, O.

***cis*-3-Triphenylmethylamino-6-phenyl-1-benzylpiperidine (*cis*-15).** To *cis*-**9** (4.18 g, 0.01 mol) in 70 ml of acetonitrile–THF (1:1) was added Na_2CO_3 (1.6 g, 0.015 mol) followed by slow dropwise addition of benzyl bromide (1.71 g, 0.01 mol) in 20 ml of acetonitrile–THF (1:1). The reaction mixture was stirred under nitrogen at room temperature for 48 hr and evaporated to dryness and the residue was extracted with three 50-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, washed with H_2O, dried ($MgSO_4$), and evaporated to a solid which was recrystallized from ethyl acetate to yield *cis*-**15** (4.3 g, 84%): mp 208–210°. Anal. ($C_{37}H_{36}N_2$) C, H, N.

***trans*-3-Triphenylmethylamino-6-phenyl-1-benzylpiperidine (*trans*-15).** To a stirred mixture of *trans*-**9** (4.18 g, 0.01 mol) and Na_2CO_3 (1.6 g, 0.015 mol) in 60 ml of THF–ethanol (2:1) was added benzyl bromide (1.71 g, 0.01 mol) in 20 ml of THF during a period of 1 hr. The reaction mixture was stirred at room temperature in a nitrogen atmosphere for 48 hr, evaporated to dryness, and extracted with three 50-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to give a residue which was triturated with 95% ethanol. The solid was collected and recrystallized from 95% ethanol to yield 3.9 g (75%) of *trans*-**15**: mp 173–175°. Anal. ($C_{37}H_{36}N_2$) C, H, N.

***cis*-3-Amino-6-phenyl-1-benzylpiperidine (*cis*-16).** To *cis*-**15** (6.42 g, 0.0126 mol) was added 30 ml of 6 *N* HCl. The mixture was heated on a steam bath for 25 min, cooled in ice, and extracted with three 50-ml portions of ether. The aqueous acidic solution was rendered alkaline with 15% NaOH and extracted with $CHCl_3$. The $CHCl_3$ was washed with brine, dried (Na_2SO_4), and evaporated to yield *cis*-**16** which was recrystallized from cyclohexane to afford 2.6 g (77%) of purified product: mp 65–67°. Anal. ($C_{18}H_{22}N_2$) C, H, N.

trans-3-**Amino-6-phenyl-1-benzylpiperidine** (*trans*-**16**). *trans*-**15** (5.08 g, 0.01 mol) was added to 25 ml of 6 *N* HCl and the mixture was heated on a steam bath for 20 min, cooled in ice, and extracted with three 50-ml portions of ether. The aqueous acidic solution was made basic with 6 *N* NaOH and extracted with $CHCl_3$ which was washed with H_2O, dried (Na_2SO_4), and evaporated. The solid residue was recrystallized from acetonitrile to yield *trans*-**16** (2.2 g, 80%): mp 132–133°. Anal. ($C_{18}H_{22}N_2$) C, H, N.

trans-1-**Benzyl-3-dimethylamino-6-phenylpiperidine** (**1**). Sodium cyanoborohydride (0.600 g, 0.0096 mol) was added to a cold stirred solution of *trans*-**16** (1.0 g, 0.0037 mol) and 4 ml (0.049 mol) of 37% formaldehyde in 30 ml of acetonitrile. A slight evolution of heat occurred followed by the separation of an oily layer. After 15 min of stirring, a few drops of glacial acetic acid were added until the mixture exhibited a pH of 7. Stirring was continued for 48 hr during which time the pH was maintained near neutrality by the occasional addition of a few drops of glacial acetic acid. The solvent was evaporated, 20 ml of 20% NaOH was added to the residue, and the basic mixture was extracted with three 50-ml portions of ether. The combined ether extracts were washed with 20 ml of 0.5 *N* KOH and extracted with three 20-ml portions of 15% HCl. The acidic extracts were combined, made basic with solid KOH, and extracted with three 50-ml portions of ether which were combined, dried ($MgSO_4$), and evaporated to afford crude **1** which was recrystallized from petroleum ether–ether to yield 0.60 g (55%) of **1** as a white crystalline solid: mp 58–60°; NMR ($CDCl_3$) 2.15 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{20}H_{26}N_2$) C, H, N.

The dihydrochloride of **1** was prepared for biological testing by addition of ethanolic HCl to an ether solution of **1**. Solvent was evaporated in vacuo and the product was recrystallized from ethanol–ether to afford **1** dihydrochloride: mp 248–250°. Anal. ($C_{20}H_{28}N_2Cl$) C, H, N.

cis-1-**Benzyl-3-dimethylamino-6-phenylpiperidine** (**2**). To a solution of *cis*-**16** (1.50 g, 0.0056 mol) in 20 ml of acetonitrile was added 5.0 ml (0.06 mol) of 37% formaldehyde. The solution was cooled and stirred vigorously and 0.700 g (0.011 mol) of sodium cyanoborohydride was added in one portion. The pH was adjusted to 7 by the addition of a few drops of glacial acetic acid and was stirred at room temperature for 48 hr. Acetonitrile was removed by evaporation in vacuo and the residue was triturated with 20% NaOH followed by extraction with three 50-ml portions of ether. The combined ether extracts were extracted with three 20-ml portions of 15% HCl which were combined, made basic with solid NaOH, and extracted with three 50-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and evaporated to yield an oil which slowly solidified. The solid was recrystallized from petroleum ether–cyclohexane to afford **2** (1:1 g, 67%): mp 39–40°; NMR 2.15 [s, 6 H, $N(CH_3)_2$]. Anal. ($C_{20}H_{26}N_2$) C, H, N.

The dihydrochloride of **2** was prepared for biological testing by adding ethanolic HCl to an ether solution of **2**. Evaporation of the solvent in vacuo and recrystallization from ethanol–ether afforded **2** dihydrochloride: mp 153–156°. Anal. ($C_{20}H_{28}N_2Cl \cdot H_2O$) C, H, N, O.

Pharmacology. Testing was carried out on the isolated guinea pig ileum which was prepared according to a standard method.[8] The ileum was bathed in Tyrodes solution at 37° and bubbled with air. Tissues were allowed to stabilize for a minimum of 15 min before introduction of agonists. Histamine and acetylcholine were then added at 3-min intervals until reproducible contractions were obtained. Antagonists were allowed to remain in contact with the ileal tissue for 15 min prior to the addition of 4×10^{-6} *M* histamine or 4×10^{-7} *M* acetylcholine. The ED_{50} values cited in the discussion are the results of three determinations at three dose levels. The values in parentheses are standard errors.

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Synthesis and Biological Actions of 2-Substituted Quinolizidines†,[1]

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A series of 2-substituted quinolizidines was synthesized and tested for their effects on motor activity in mice. In the 2-aryl-2-hydroxyquinolizidines (**5** and **6**) a difference was noted in potency between the axial and equatorial aryl analogs. A significant difference in activity was also found between the epimeric 2-(4-fluorobenzoyl)quinolizidines (**10c** and **11c**).

The structure–activity relationship (SAR) of haloperidol (**1**) has been studied in great detail since the utility of this drug as a major tranquilizer was affirmed.[2] The stereochemical requirements for biological activity of the butyrophenone series have not been as well defined.[3] Considering the quinolizidine ring as a semirigid nucleus to which appropriate substituents are added, the compounds **2** could be considered as haloperidol analogs with two fixed stereochemical centers. Before attempting the synthesis of **2**, several model chemical systems, **3** and **4**,

† Dedicated to the memory of Professor Edward E. Smissman.