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Conformationally Restricted Analogs of Histamine H₁ Receptor Antagonists: trans- and cis-1-Benzyl-3-dimethylamino-6-phenylpiperidine[†]

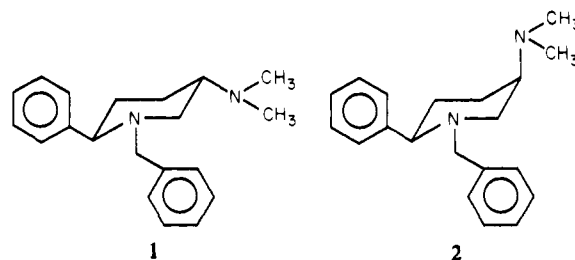
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The syntheses of trans- and cis-1-benzyl-3-dimethylamino-6-phenylpiperidine (1 and 2) are described. Compounds 1 and 2 were found to be inhibitors of histamine, acetylcholine, and barium chloride induced contractions of the isolated guinea pig ileum. 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 H₁ 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 H₁ receptor blockade by ethylenediamine antagonists and that the model proposed by Casey and Ison³ represents a reasonable approximation of the molecular conformation of H₁ receptor-bound histamine antagonists.

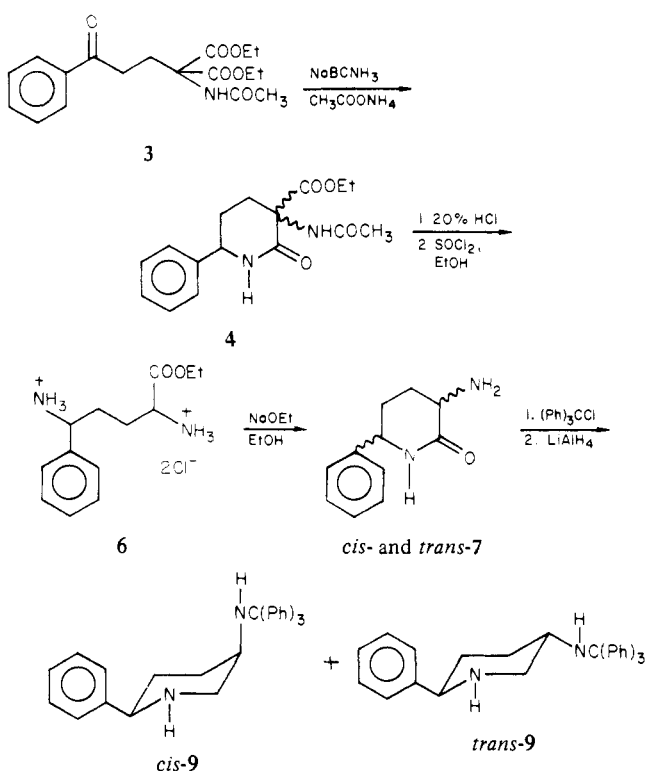
The purpose of the present report is to describe the synthesis and pharmacological evaluation of trans- and cis-1-benzyl-3-dimethylamino-6-phenylpiperidine (1 and 2). These compounds are cyclic analogs of the ethylenediamine histamine antagonists and they contain the essential structural features usually associated with an-



tagonist 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

[†] 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 decarboxy-

lation 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.

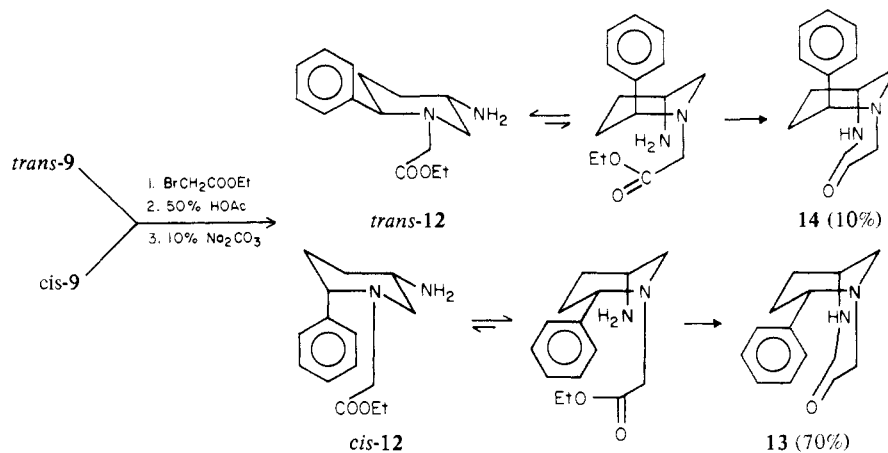
When the diastereoisomeric mixture of *cis*- and *trans*-7 was equilibrated by heating in the presence of sodium ethoxide, the product obtained consisted exclusively of a single isomer (TLC) which was assigned the *trans* configuration (vide infra).

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.

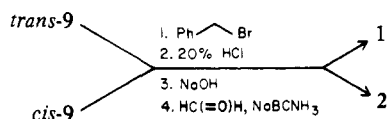
cis- and *trans*-7 were converted to their 3-triphenylmethyl derivatives 8 and this diastereomeric mixture was reduced with lithium aluminum hydride to *cis*- and *trans*-3-triphenylmethylamino-6-phenylpiperidine (9) which were readily separated by dry-column chromatography. When *trans*-7, which had 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 Hassid⁷ 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 ED₅₀ of 6.72 (± 0.66) $\times 10^{-6}$ M in the presence of 4 $\times 10^{-6}$ M histamine, while the *cis* isomer 2 had an ED₅₀ of 1.83 (± 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 H₁ antagonist tripeleminamine (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 $\times 10^{-7}$ M acetylcholine. In this assay, the *trans* isomer 1 had an ED₅₀ of 2.90 (± 0.25) $\times 10^{-6}$ M and the ED₅₀ of 2 was 1.45 (± 0.06) $\times 10^{-6}$ M. The standard antihistamine tripeleminamine (10⁻⁷ M) did not inhibit the response to acetylcholine.

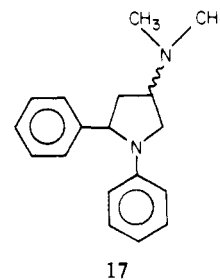
In view of the absence of appreciable stereoselectivity in the inhibition of either histamine or acetylcholine, it was decided to determine the inhibiting effect of 1 and 2 on barium chloride induced contractions of the guinea pig ileum. The *trans* isomer 1 (5 $\times 10^{-6}$ M) caused a 39%

inhibition of the contractions produced by 3.2 $\times 10^{-4}$ M barium chloride while *cis* isomer 2 (2 $\times 10^{-6}$ M) caused a 50% reduction of the contractions produced by 1.6 $\times 10^{-4}$ 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 μ M while *cis* compound 2 had a K_i value of 31.6 \pm 3.8 μ M. 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 ED₅₀ 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 H₁ 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



both a selective interaction with the histamine H₁ receptor as well as stereoselectivity of antagonist activity. Both *cis*- and *trans*-17 are more potent histamine H₁ antagonists than 1 and 2; *cis*-17 (5 $\times 10^{-8}$ M) causes a 45–55% inhibition of the guinea pig ileum contractions produced by 4 $\times 10^{-6}$ M histamine while *trans*-17 (1 $\times 10^{-8}$ 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 H₁ 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 CDCl₃ with Me₄Si as internal standard or in D₂O 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 H₂O and ether to afford 3 (88.3 g, 86%): mp 116–118° (lit.¹² 113–114°). Anal. (C₁₈H₂₃N₂O₆) 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 CHCl₃. The combined CHCl₃ solution was washed with H₂O and dried (Na₂CO₃) and the CHCl₃ 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, CHCl₃–C₆H₆ (1:3)] exhibited two spots (R_f 0.39 and 0.5). Anal. (C₁₆H₂₀N₂O₄) 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 (D₂O) 2.1 (m, CH₂CH₂), 4.15 (m, NCHCO), 4.45 (m, C-5H), 7.5 (s, C₆H₅). Anal. (C₁₁H₁₃N₂O₂Cl₂) 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. (C₁₃H₂₂N₂O₂Cl₂) 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 (CDCl₃) 1.75 (s, NH₂),

2.9 (m, CH₂CH₂), 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, C₆H₅). Anal. (C₁₁H₁₄N₂O) 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 (CDCl₃) 2.05 (s, NH₂), 1.88 (m, CH₂CH₂), 3.3 (m, NCHCO), 4.42 (m, C-6H), 6.23 (s, broadened, NHCO), 7.2 (s, C₆H₅). Anal. (C₁₁H₁₄N₂O) 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 CHCl₃ and to this solution was added 20.2 g (0.2 mol) of distilled triethylamine followed by dropwise addition of a 200-ml CHCl₃ 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. (C₃₀H₂₈N₂O) 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 LiAlH₄ (8.76 g, 231.2 mmol) in 300 ml of dry THF under N₂. 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 LiAlH₄ was destroyed by dropwise addition of 9 ml of H₂O, 27 ml of 15% NaOH, and 9 ml of H₂O. The mixture was stirred for 1 hr and filtered and the solids were washed with two 50-ml portions of THF. The combined THF solutions were evaporated in vacuo. The residue was dissolved in ether, washed with H₂O, dried (MgSO₄), 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 (CDCl₃) 1.16 (m, 4 H, CH₂CH₂), 1.45 (s, 2NH), 2.55 (m, NCH₂CHN), 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. (C₃₀H₃₀N₂) C, H, N.

cis- and trans-3-Triphenylmethylamino-6-phenylpiperidin-2-one (8). To a 500-ml CHCl₃ 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 CHCl₃. 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 (CDCl₃) 1.5 (m, CH₂CH₂), 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. (C₃₀H₂₈N₂O) 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 LiAlH₄ (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 H₂O was added followed by 21 ml of 15% NaOH and an additional 7 ml of H₂O. 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 H₂O, and dried (MgSO₄). 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 H₂O, drying (MgSO₄), and evaporation of the ether followed by drying of the residue under vacuum. Anal. (C₃₀H₃₀N₂) 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% H₂O, 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 (CHCl₃-CH₃OH-NH₃ (90:9:1)) and the extracts were evaporated to dryness. The residues were taken up in benzene, dried (CaSO₄), 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 (CDCl₃) 1.58 (m, 2NH and -CH₂CH₂-), 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. (C₃₀H₃₀N₂) 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. (C₃₀H₃₀N₂) 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 Na₂CO₃ (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 CHCl₃ which were combined, washed with H₂O, and dried (MgSO₄). The viscous residue was purified by dry-column chromatography on silica gel [ethyl acetate-petroleum ether (25:75)] and the compound was extracted with CHCl₃-CH₃OH (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 (CHCl₃) 1740 cm⁻¹. Anal. (C₃₃H₃₆N₂O₂) 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 H₂O. The trityl alcohol was filtered and washed with 10 ml of H₂O 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. (C₁₉H₃₀N₂O₆) 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 CHCl₃, cooled, and stirred with 20 ml of 10% Na₂CO₃ for 10 min. The CHCl₃ layer was separated, washed with H₂O, dried (K₂CO₃), 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 (CDCl₃) 1.15 (t, CH₃), 1.4–2.8 (m, NH₂, C-2, C-4, C-5 methylenes, C-3H), 3.0 (d, J = 5 Hz, NCH₂CO), 3.35 (m, C-6H), 3.95 (q, CH₂), 7.09 (s, C₆H₅).

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 Na₂CO₃ (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 CHCl₃. The combined CHCl₃ extracts were

washed with H₂O, dried (MgSO₄), 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. (C₃₄H₃₆N₂O₂) 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 H₂O. 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. (C₁₉H₃₀N₂O₆) 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 CHCl₃ was added 10 ml of 10% Na₂CO₃ and the mixture was stirred for 10 min; the CHCl₃ layer was separated, washed with water, dried (K₂CO₃), 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. (C₁₅H₂₂N₂O₂) 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 (CDCl₃) 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, C₆H₅), 7.68 (br, NH). Anal. (C₁₃H₁₆N₂O) 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 (CDCl₃) 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, C₆H₅, N-4H). Anal. (C₁₃H₁₆N₂O) 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 Na₂CO₃ (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 CHCl₃. The CHCl₃ extracts were combined, washed with H₂O, dried (MgSO₄), and evaporated to a solid which was recrystallized from ethyl acetate to yield cis-**15** (4.3 g, 84%): mp 208–210°. Anal. (C₃₇H₃₆N₂) 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 Na₂CO₃ (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 CHCl₃. The combined CHCl₃ extracts were washed with H₂O, dried (MgSO₄), 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. (C₃₇H₃₆N₂) 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 CHCl₃. The CHCl₃ was washed with brine, dried (Na₂SO₄), and evaporated to yield cis-**16** which was recrystallized from cyclohexane to afford 2.6 g (77%) of purified product: mp 65–67°. Anal. (C₁₈H₂₂N₂) 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 CHCl₃ which was washed with H₂O, dried (Na₂SO₄), and evaporated. The solid residue was recrystallized from acetonitrile to yield *trans*-16 (2.2 g, 80%): mp 132–133°. Anal. (C₁₈H₂₂N₂) 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 (MgSO₄), 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 (CDCl₃) 2.15 [s, 6 H, N(CH₃)₂]. Anal. (C₂₀H₂₆N₂) 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. (C₂₀H₂₈N₂Cl) 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 (MgSO₄), 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(CH₃)₂]. Anal. (C₂₀H₂₆N₂) 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. (C₂₀H₂₈N₂·Cl·H₂O) 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 ED₅₀ 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 bu-

tyrophenone 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. Smisman.