Structure and Activity of Hydrogenated Derivatives of (+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine (MK-801)

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Several hydrogenated derivatives of the potent NMDA antagonist 1 have been prepared and evaluated as competitive inhibitors of [³H]-1 binding. These compounds were also tested for their ability to act as noncompetitive antagonists of NMDA in vitro. These studies indicate that two aromatic rings are not strictly required for high-affinity binding or NMDA antagonism.
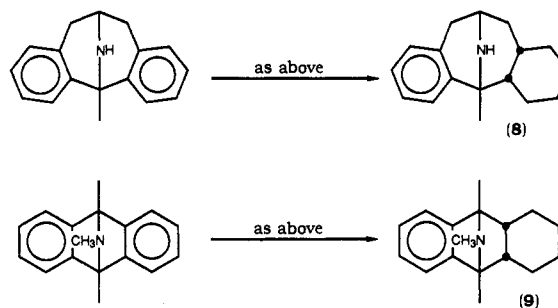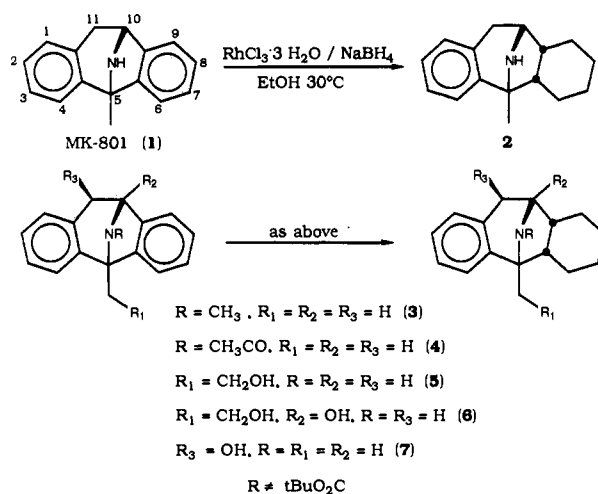
Recent interest in excitatory amino acid receptors in the central nervous system (CNS) has stimulated the search for compounds which interact selectively with these receptors.[1] MK-801 (1) (Scheme I) is one such example from our laboratories. It has been shown to be a potent and selective noncompetitive antagonist of the N-methyl-D-asparate (NMDA) subclass of glutamate receptors.[2] Although numerous compounds have been prepared and evaluated as NMDA antagonists, our laboratories have concentrated on those that incorporate the nitrogen-bridged dibenzocycloalkane ring system exemplified by 1. Initial studies designed to develop the structure–activity profile of 1 focused on an array of substitutions on the parent structure as well as related dibenzocycloalkane ring systems.[3] An important issue not addressed by these studies is the absolute and relative importance of the aromatic rings for antagonist activity. Set forth in this report is an exploration of this question.

Chemistry

Traditionally, reduction of aromatic rings has required rather stringent conditions involving active metal catalysts at high pressures of hydrogen. However, a recent review[4] on metal hydrides described the use of rhodium chloride–sodium borohydride for reduction of arenes at atmospheric pressure without a hydrogen atmosphere. This operationally simple system was reported to give good yields of totally reduced products with predictable stereochemistry.[5] Our initial efforts centered on application of this reaction to 1, with the expectation that a complex mixture of products might result.

Using the literature procedure, we obtained a mixture containing a substantial amount of starting material and one major product (2) (Scheme I). Isolation of this product, followed by examination of its ¹H NMR spectrum indicated that only one of the aromatic rings had been reduced as evidenced by the ratio of aromatic to aliphatic protons. The chemical shift (3.80 ppm) and complex coupling pattern of the proton at position 10 indicated reduction of the ring in the isoindole portion of the molecule (hereafter referred to as the "right-hand ring"). Included in the aliphatic region were two signals between 0 and 1 ppm. The upfield shift of these protons suggested a nearby aromatic residue. These data and inspection of molecular models supported a product with a cis-fused ring juncture. Through use of the Merck Molecular Modeling System,[6] we were able to energy minimize several of the possible conformations accessible to the saturated ring. One boat conformation, which might give rise to shielded protons, was greater than 1.6 kcal/mol lower in energy than either chair conformer. Homonuclear decoupling experiments were used to identify the two upfield shifted res-
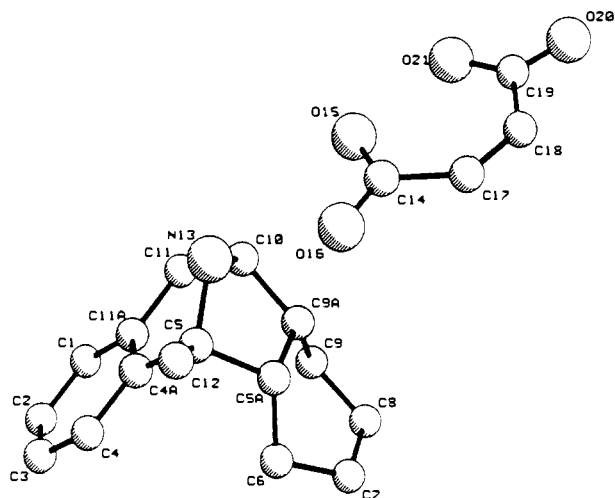
Scheme I

MK-801 (1)

R = CH₃, R₁ = R₂ = R₃ = H (3)

R = CH₃CO, R₁ = R₂ = R₃ = H (4)

R₁ = CH₂OH, R = R₂ = R₃ = H (5)

R₁ = CH₂OH, R₂ = OH, R = R₃ = H (6)

R₃ = OH, R = R₁ = R₂ = H (7)

R ≠ tBuO₂C

onances as $H_{6\alpha}$ and $H_{9\alpha}$. The aforementioned low-energy boat conformation places these protons in the vicinity of
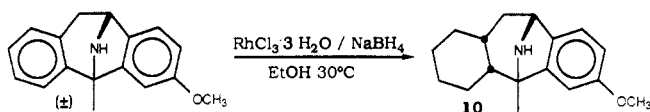
(1) Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2057–2066.

(2) Wong, E. H. F.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104–7108.

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(4) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763–780.

(5) Nishiki, M.; Miyataka, H.; Niino, Y.; Mitsuo, N. and Satoh, T. *Tetrahedron Lett.* **1982**, *23*, 193–196.

(6) (a) Gund, P.; Andose, J. D.; Rhodes, J. B.; Smith, G. M. *Science* **1980**, *208*, 1425. (b) Smith, G. M.; Hangauer, D. G.; Andose, J. D.; Bush, B. L.; Fluder, E. M.; Gund, P.; McIntyre, E. F. *Drug Inf. J.* **1984**, *18*, 167. (c) Halgren, T. A., unpublished work on the development of the force field program OPTIMOL. (d) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

[†] Neuroscience Research Centre.

Figure 1. A computer-generated drawing of the maleate salt of 2 generated from the final X-ray coordinates.

Scheme II

Scheme III

+ N-ethyl derivatives of **2** and **11**

Scheme IV

Figure 2. Stereoview comparison of 2 (dashed) with 1 (solid).

Figure 3. Stereoview comparison of 11 (dashed) with 1 (solid).

the remaining aromatic ring. Later, this conformation was observed in the solid state by X-ray structure determination of the maleate salt of **2** (Figure 1).

Upon further experimentation, the reduction was improved by adding the borohydride solution over an extended period, which enabled the reaction to go to completion. Examination of the crude reaction mixture indicated the presence of a minor isomer having an even higher upfield-shifted proton at −0.4 ppm. It was later identified as compound 11, one of the major products from the catalytic hydrogenation of 1.

In order to examine the generality of this reaction toward other dibenzocycloalkanes, the modified reaction conditions were applied to a number of other analogues as summarized in Scheme I. The reaction tolerates alkylation and acylation of the nitrogen without loss of regiospecificity. However, the Boc derivative of 1 was unreactive, presumably due to steric hindrance. In two cases of attempted reduction of dibenzocyclooctenimines, the reduction was either very sluggish (8) or failed completely.[7] Interestingly, introduction of a phenolic oxygen at carbon 7 gave a more complex mixture with reduction of the other aromatic ring predominating to afford 10 as the major product (Scheme II).

Subsequently other methods were examined for reducing the aromatic rings of 1. High-pressure catalytic hydrogenation over palladium, rhodium, or Raney nickel each provided several reduced analogues which were separable by silica gel chromatography in most cases (Scheme III). Under these reaction conditions either or both rings are reduced. In some cases there is incomplete reduction which results in tetrasubstituted alkene products.

Also of interest were Birch type reductions of 1. From previous analogue work we were aware that 1 was somewhat resistant to dissolving-metal reductions. However, lithium in either ethyl- or propylamine at 0 °C did serve to reduce one of the rings albeit in very poor yield (Scheme IV). For the Birch reductions without the addition of a
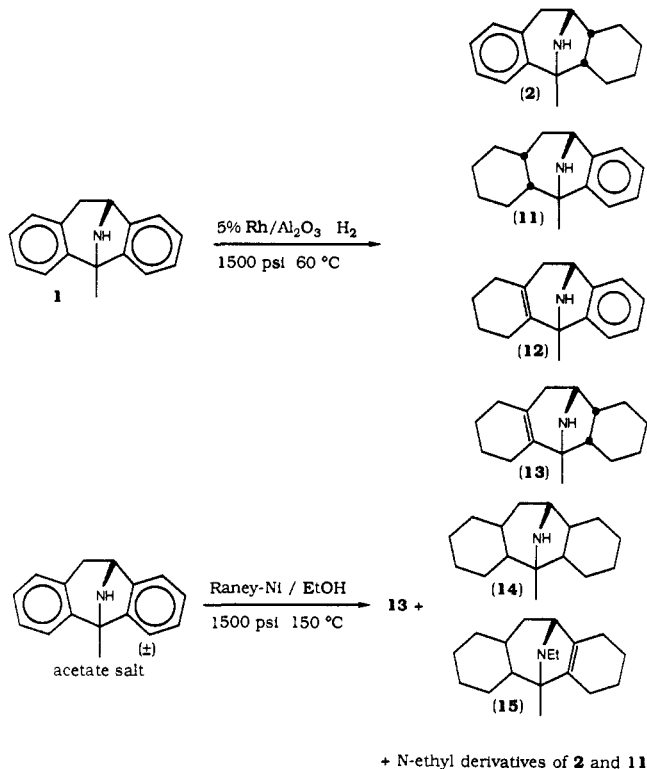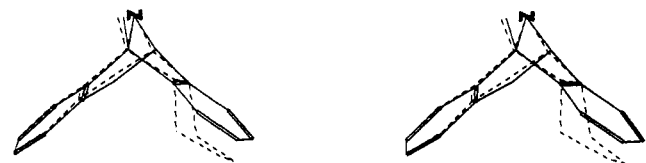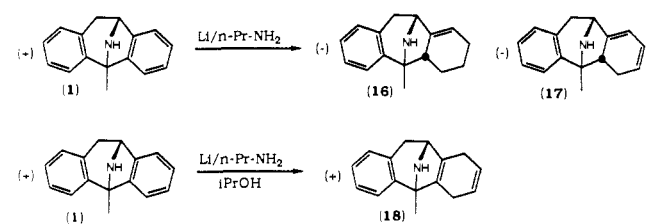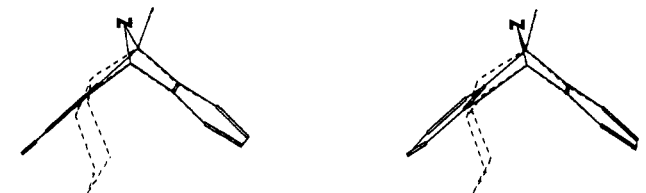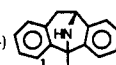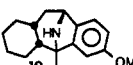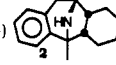
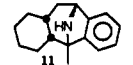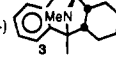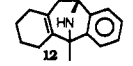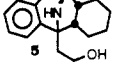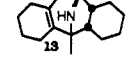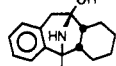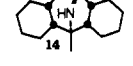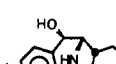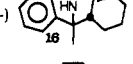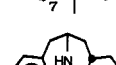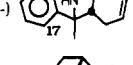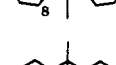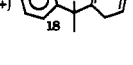proton source, one obtains both alkene 16 and conjugated diene 17. However, when isopropyl alcohol was added, diene 18 was isolated. The dienes were shown to revert slowly to 1 upon standing.

The structures of the reduced products were assigned by proton and carbon NMR. Ring-juncture stereochemistry was assumed to be cis in most cases due to the upfield shift of particular protons and by analogy to 2. For the reduced products having the carbon skeleton of 1, the chemical shift of the proton at C_{10} was indicative of which aromatic ring had been reduced. In general, when this proton is either benzylic or allylic, it appears at or below

(7) Personal communication from Dr. Paul Leeson, MSDRL England.

Table I

compound	IC_{50}, nM (n)	NMDA ant K_b, nM ($n \geq 3$)	compound	IC_{50}, nM (n)	NMDA ant K_b, nM ($n \geq 3$)
1 (+)	30.5 ± 1.5 (>5)	130	**10**	240 (2)	310 ± 110
2 (−)	16 ± 8.2 (4)	230 ± 7	**11**	188 (2)	130 ± 3
3 (+)	96 ± 23 (3)	290 ± 60	**12**	193 ± 15 (3)	270 ± 20
5	220 (2)	240 ± 40	**13**	80 ± 14 (3)	280 ± 30
6	396 (2)	770 ± 50	**14**	35 (2)	800 ± 150
7 (+)	69 (2)	250 ± 6	**16** (−)	60 ± 9.6 (3)	300 ± 80
8	164 (2)	250 ± 10	**17** (−)	21 ± 4 (3)	270 ± 40
9	111 (2)		**18** (+)	20 ± 4 (4)	

4.0 ppm. Energy minimization (using the OPTIMOL program[6c,d]) of potential conformations of the saturated ring of 11 was particularly helpful in proposing the chair conformer shown in Figure 3. This conformer had the lowest energy of those minimized and places the $H_{1\alpha}$ proton within 2.6 Å of the plane of the aromatic ring. In the case of the reduction using Raney nickel, several products were obtained as their N-ethyl derivatives, presumably due to the presence of acetic acid as the salt of the starting material. Reduction to acetaldehyde, followed by reductive amination of the starting material or product, could explain the formation of these byproducts.

Results

All of these compounds were tested to determine their ability to inhibit [³H]-1 binding to rat cortical membranes,[8] and the more active analogues were evaluated as NMDA antagonists by using a rat cortical slice preparation.[2] These data are presented in Table I. Compound 2 was found to inhibit the binding of [³H]-1 to its binding site at an IC_{50} of 16 nM (Table I). This was the first indication that at least one of the aromatic rings of the nitrogen-bridged dibenzocycloalkane series was not required for high affinity at the binding site of compound 1. It should be noted that some of the compounds in the table were tested as racemates.

As shown in the table, several of the reduced analogues retain high binding capability. Some general trends are apparent from the binding data. In general, reduction of the right-hand aromatic ring is well tolerated and in some cases is beneficial. For example, compounds 2, 3, 5, 7–9, 13, 14, 17, and 18 had affinity equal to or better than their aromatic counterparts (see ref 3 and Table I). This implies that the receptor does not require an aromatic interaction

in this region, and will accommodate a simple hydrophobic group. The steric requirements of the saturated ring can be seen in Figure 2, where the dashed structure representing the reduced analogue 2 is compared to 1 (solid figure). In this figure, the common atoms of the left aromatic ring and nitrogen were superimposed. The boat-shaped saturated ring occupies a region of space similar to that occupied by the right-hand aromatic ring of 1 but it lies somewhat below the aromatic plane.

Reduction of the left-hand ring affords analogues with reduced binding affinity. A comparison of the proposed conformation of the saturated analogue 11 to that of 1 is illustrated in Figure 3. The overall shape difference between the two compounds is more pronounced in this case. The fall in binding affinity for 11 may be the result of a loss of an important aromatic interaction with the receptor, or simply an undesirable steric interaction due to the change in molecular shape. This trend holds true for other cases where the left aromatic ring is reduced.

Perhaps most interesting is the fully reduced compound 14, which has a binding affinity equal to that of 1. This would indicate that the loss in affinity exhibited by analogue 11 is compensated by reduction of the remaining aromatic ring.

It is perhaps worth noting that analogue 11 is equipotent to 1 as an NMDA antagonist yet is apparently a much poorer ligand for the receptor. This inconsistent correlation between the binding data and the NMDA assay may reflect the difficulty in comparing competitive binding to a noncompetitive process, a phenomenon which has been observed for other analogues of 1.[3]

In summary, a number of reduced imino-bridged dibenzocycloalkenes have been synthesized and evaluated as receptor ligands as well as NMDA antagonists. Several of these reduced analogues show enhanced affinity for the receptor when compared to their aromatic counterparts.[3] These results indicate that aromatic groups are not strictly

(8) Wong, E. H. F.; Knight, A. R.; Woodruff, G. N. *J. Neurochem.* **1988**, *50*, 274–281.

required for high affinity ligands.

Experimental Section

General. All melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were obtained on a Varian XL-300 or Nicolet 360 MHz instrument using CDCl$_3$ solutions (10 mg/mL) with (CH$_3$)$_4$Si as an internal standard. Chemical shifts are reported in ppm downfield from TMS. Thin-layer chromatography was carried out using E. Merck silica gel plates. Column chromatography was performed with 240-400 mesh silica gel by gravity. Reversed-phase preparative HPLC was carried out on a Waters Prep-500 using a C-18 Prep-Pak cartridge. Starting materials for the following compounds were prepared according to the cited literature references: 1, 2, 11-18;[9] 3-5;[10] 6;[11] 7;[12] 8;[13] 9;[14] 10.[3]

(−)-(5R,5aS,9aR,10R)-5a,6,7,8,9,9a,10,11-Octahydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (2). General Procedure. A suspension of 3.0 g (8.89 mmol) of 1·HCl[9] in 200 mL of CHCl$_3$ was washed with 10% NaHCO$_3$, dried over Na$_2$SO$_4$, and evaporated to give the free base, which was dissolved in 20 mL of EtOH and evaporated twice to remove traces of CHCl$_3$. This free base was dissolved in 200 mL of EtOH, and 2.36 g (8.98 mmol) of RhCl$_3$·3H$_2$O (Aldrich) was added in one portion. After stirring under N$_2$ at 30 °C for 1.5 h, a solution of 3.36 g (88.9 mmol) of NaBH$_4$ in 200 mL of EtOH was added over a period of 3.0 h. After stirring overnight at room temperature, the mixture was filtered through a Celite pad, washed with EtOH, and evaporated to a small volume at reduced pressure. The remaining NaBH$_4$ was carefully quenched by the addition of 200 mL of 2.5% HCl. After basifying with 2.0 M NaOH, the aqueous solution was extracted with 2 × 250 mL of CHCl$_3$, and the combined organics were washed with saturated NaHCO$_3$, H$_2$O, and brine and dried over Na$_2$SO$_4$. The residue remaining after evaporation at reduced pressure was chromatographed on fine SiO$_2$ using 95:5:0.5 CH-Cl$_3$-CH$_3$OH-NH$_4$OH to give 1.25 g (62%) of the title compound as a colorless solid: mp 56-58 °C; ^{1}H NMR (CDCl$_3$) δ 0.41 (dq, 5, 12 Hz, H$_{6\alpha}$), 0.92 (dq, 5, 12 Hz, H$_{9\alpha}$), 1.15-1.55 (m, 6 H), 1.57 (s, H$_3$C), 1.92 (dt, 5.5, 11 Hz, H$_{5a}$), 2.27 (s, HN), 2.35 (dddd, 5, 7, 11, 12 Hz, H$_{9a}$), 2.75 (d, 17 Hz, H$_{11\beta}$), 3.07 (dd, 5.5, 17 Hz, H$_{11\alpha}$), 3.80 (ddd, 5.5, 7, 1 Hz, H$_{10}$), 7.00-7.18 (m, 4 H-arom). Anal. (C$_{16}$H$_{21}$N·C$_4$H$_4$O$_4$) C, H, N.

The free base was dissolved in EtOAc and treated with 1.0 equiv of maleic acid to afford the maleate salt as a colorless solid: mp = 149-150 °C; [α]$_D$ = −5.24° (c = 1.17, CH$_3$OH).

The following compounds were prepared by using the general procedure above.

(+)-(5R,5aS,9aR,10R)-5a,6,7,8,9,9a,10,11-Octahydro-N,5-dimethyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (3) was purified by silica gel chromatography using 95:5:0.5 CHCl$_3$-CH$_3$OH-NH$_4$OH to give the free base as a colorless oil (49%): ^{1}H NMR (CDCl$_3$) δ 0.30-0.47 (m, 1 H), 1.53 (s, H$_3$C), 2.08 (dt, 15, 5 Hz, 1 H), 2.36 (s, H$_3$CN), 2.52 (d, 18 Hz, 1 H), 3.14 (dd, 18, 6 Hz, 1 H), 3.53-3.62 (m, HC$_{10}$). Anal. (C$_{17}$H$_{23}$N·HCl·4H$_2$O) C, H, N.

To a solution of the free base in ether was added ethanolic HCl to give the HCl salt as a colorless solid: mp = 232-235 °C; [α]$_D$ = +12.3° (c = 0.64, CH$_3$OH).

(5R*,5aS*,9aR*,10R*)-5a,6,7,8,9,9a,10,11-Octahydro-5-(2-hydroxyethyl)-5H-dibenzo[a,d]cyclohepten-5,10-imine (5) was purified by silica gel chromatography using 90:10:1.0 CH-Cl$_3$-CH$_3$OH-NH$_4$OH to give the free base as a waxy solid (22%): ^{1}H NMR (CDCl$_3$) δ 0.34-0.51 (m, 1 H), 0.81-0.98 (m, 1 H), 2.73 (d, 16 Hz, 1 H), 3.08 (dd, 18, 6 Hz, 1 H), 3.44 (br s, 2 H), 3.86-3.90 (m, 2 H), 3.94-4.05 (m, 1 H). Anal. (C$_{17}$H$_{23}$NO) C, H, N.

(5R*,5aS*,9aR*,10S*)-5a,6,7,8,9,9a,10,11-Octahydro-10-hydroxy-5-(2-hydroxyethyl)-5H-dibenzo[a,d]cyclohepten-5,10-imine (6) was purified by chromatography on silica gel using 95:5:0.5 CHCl$_3$-CH$_3$OH-NH$_4$OH to give the free base as a colorless oil (31%). An analytical sample was prepared by trituration with 1:1 hexane-acetonitrile: mp = 169-171 °C; ^{1}H NMR (CDCl$_3$) δ 0.27-0.44 (m, 1 H), 0.79-0.96 (m, 1 H), 3.08 (d, 10 Hz, 2 H), 3.69-3.90 (m, 2 H), 4.02-4.12 (m, 1 H). Anal. (C$_{17}$H$_{23}$NO$_2$) C, H, N.

(+)-(5R,5aS,9aR,10S,11R)-5a,6,7,8,9,9a,10,11-Octahydro-11-exo-hydroxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (7) was purified by silica gel chromatography using 90:10:1.0 CHCl$_3$-CH$_3$OH-NH$_4$OH to give the free base as a colorless solid (34%): mp = 171-172 °C; ^{1}H NMR (CDCl$_3$) δ 0.17-0.34 (m, 1 H), 0.62-0.80 (m, 1 H), 1.57 (s, H$_3$C), 1.8-1.93 (m, 1 H), 2.31-2.46 (m, 1 H), 2.86 (br s, 2 H), 3.76 (dd, 9, 3 Hz, HC$_{10}$), 4.34 (d, 3 Hz, HC$_{11}$).

The free base was dissolved in warm EtOAc and 1.0 equiv of maleic acid was added to give the maleate salt: [α]$_D$ = +11.8.° (c = 0.56, CH$_3$OH). Anal. (C$_{16}$H$_{21}$NO·C$_4$H$_4$O$_4$) C, H, N.

(4aS*,6S*,12R*,12aS*)-1,2,3,4,4a,5,6,7,12,12a-Decahydro-12-methyldibenzo[a,d]cycloocten-6,12-imine (8) was purified by chromatography on silica gel using 95:5 CHCl$_3$ (saturated with NH$_3$)-CH$_3$OH: mp = 48-49 °C; ^{1}H NMR (CDCl$_3$) δ 0.92-1.23 (m, 6 H), 1.23-1.34 (m, 1 H), 1.40-1.49 (m, 2 H), 1.50 (s, H$_3$C), 1.67 (br s, HN), 1.82 (q, 7 Hz, 1 H), 1.86-1.95 (m, 1 H), 2.00 (m, 7 Hz, 1 H), 2.65 (d, 17 Hz, HC$_{10}$), 3.22 (dd, 17, 7 Hz, HC$_7$), 3.57 (m, 1 H). Anal. (C$_{17}$H$_{23}$N) C, H, N.

1,2,3,4,4a,9,10,10a-Octahydro-N,9,10-trimethylanthracen-9,10-imine (9) was purified by silica gel chromatography using 95:5:0.5 CHCl$_3$-CH$_3$OH-NH$_4$OH to give the free base as a colorless oil (81%): ^{1}H NMR (CDCl$_3$) δ 0.08-0.26 (m, 2 H), 1.48 (s, 2 H$_3$C), 1.83 (s, H$_3$CN).

To a solution of the free base in ether was added ethanolic HCl which provided the HCl salt as a colorless solid: mp 215 °C dec. Anal. (C$_{17}$H$_{23}$NO·HCl) C, H, N.

(4aR*,5S*,10R*,11aR*)-1,2,3,4,4a,10,11,11a-Octahydro-7-methoxy-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrochloride salt (10) was purified by flash chromatography on silica gel using 95:5:0.5 to 90:10:1 CHCl$_3$-CH$_3$OH-NH$_4$OH to give 2.17 g (32%) of the free base as a colorless oil: ^{1}H NMR (CDCl$_3$) δ −0.82-0.00 (m, 1 H), 0.81-1.56 (m, 7 H), 1.48 (s, H$_3$CN), 1.80-2.00 (m, 2 H), 2.15-2.20 (m, 1 H), 2.25-2.32 (m, 1 H), 2.72 (br s, 1 H), 3.81 (s, H$_3$CO), 4.19 (m, HC$_{10}$), 6.67 (dd, 2, 8 Hz, 1 H), 6.73 (m, 1 H), 7.02 (d, 8 Hz, 1 H). An analytical sample of 10 was prepared by treating a solution of the free base in ether-ethanol with ethanolic HCl: mp 240-242 °C dec. Anal. (C$_{17}$H$_{23}$NO·HCl) C, H, N.

High-Pressure Hydrogenation of (±)-1 (Acetate Salt). A solution of 4.0 g (14.2 mmol) of the title compound in 150 mL of ethanol was hydrogenated over 1.25 g of 5% Rh/Al$_2$O$_3$ at 1500 psi at 60 °C for 18 h. The reaction mixture was filtered, and the solvents were removed at reduced pressure. The brown residue was chromatographed on 400 g of fine silica gel using the following solvent ratios of CHCl$_3$-CH$_3$OH-NH$_4$OH: 95:5:0.5 (2 L), 92.5:7.5:0.75 (1.5 L), 90:10:1 (1.5 L), and 87.5:12.5:1.25 (1 L). The 24-mL fractions were analyzed by TLC (SiO$_2$), combined, and evaporated at reduced pressure.

Fractions 49-52 gave 76 mg (2.4%) of **(5S*,10R*)-1,2,3,4,10,11-hexahydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine (12):** ^{1}H NMR (CDCl$_3$) δ 1.14-2.09 (m, 11 H), 1.50 (s, H$_3$C), 2.10-2.25 (m, 1 H), 2.65 (dm, 17 Hz, H$_{11}$), 4.45 (d, 5.5 Hz, H$_{10}$), 7.0-7.31 (m, 4 H-arom); ^{13}C NMR (CDCl$_3$) δ 118.0 (CH), 123.0 (CH), 125.5, 128.3 (CH), 128.5 (CH), 131.8, 137.5, 145.8.

A solution of the free base in 1:1 ether-pentane was treated with ethanolic HCl to give the HCl salt: mp = 238-239 °C dec. Anal. (C$_{16}$H$_{19}$N·HCl·0.1H$_2$O) C, H, N.

Fractions 70-115 were evaporated to afford 760 mg of a mixture of two compounds which were separated as follows. The mixture was dissolved in 10 mL of CH$_2$Cl$_2$ and treated with 2 mL each of acetic anhydride and pyridine overnight. The reaction mixture

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was poured into 2 M HCl and extracted with CHCl₃. After washing with H₂O, drying over Na₂SO₄, and evaporation, the mixture of acetylated compounds was separated by preparative HPLC using a 70:30 to 35:65 gradient of 0.1% TFA in H₂O–CH₃CN over 1 h. The early eluting peak was collected, evaporated, and extracted with two portions of CHCl₃ to give 300 mg of a pure acetylated compound. Approximately half of this material was dissolved in 10 mL of ethylene glycol and heated to 190 °C with 1.0 g of KOH for 5 h. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, brine, dried over Na₂SO₄, and evaporated. The remaining half of the material was treated in a similar manner, and the products were combined to give a residue which was chromatographed on 25 g of fine SiO₂ using 93:7:0.7 CHCl₃–CH₃OH–NH₄OH to afford 135 mg (4.2%) of 11 as a colorless oil.

(4a*R**,5*S**,10*R**,11a*R**)-1,2,3,4,4a,10,11,11a-Octahydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine (11): ¹H NMR (CDCl₃) δ −0.185 (dq, 4.12 Hz), 1.48 (s, H₃C), 2.18 (m, 1 H), 4.24 (dd, 2.4, 3.9 Hz, H₁₀), 7.0–7.2 (m, 4 H-arom).

Treatment of a solution of the free base in ether with ethanolic HCl afforded the HCl salt as a colorless solid: mp = 290–292 °C dec. Anal. (C₁₆H₂₁N·HCl) C, H, N.

The later eluting HPLC fraction was worked up as above to afford **(5*R**,5a*S**,9a*R**,10*R**)-*N*-acetyl-5a,6,7,8,9,9a,10,11-octahydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine** (4): NMR was identical with that obtained for the reduction product shown in Scheme I.

Fractions 161–171 yielded 62 mg (1.9%) of **(5*R**,5a*S**,9a*R**,10*R**)-1,2,3,4,5a,6,7,8,9,9a,10,11-dodecahydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine** (13): ¹H NMR (CDCl₃) δ 1.1–1.45 (m, 8 H), 1.21 (s, H₃C), 1.6–2.1 (m, 11 H), 2.14–2.26 (m, 2 H), 3.55 (ddd, 2, 5, 7 Hz, H₁₀); ¹³C NMR (DMSO-*d₆*) δ 127.6, 130.1.

To a solution of the free base in 1:1 ether–pentane was added ethanolic HCl to afford the HCl salt as a light tan solid: mp = 241–243 °C dec. Anal. (C₁₆H₂₅N·HCl) C, H, N.

Alternative High-Pressure Hydrogenation of (±)-1 (Acetate Salt). A solution of 4.0 g (14.2 mmol) of the title compound in 150 mL of ethanol was hydrogenated over 1.0 g of Raney nickel at 1500 psi at 150 °C for 18 h. The reaction mixture was filtered, and the solvents were removed at reduced pressure. The brown residue was partitioned between CHCl₃ and 1% NaOH, and the organic layer was washed with water, dried over Na₂SO₄, and evaporated to give 2.51 g of an amber colored oil. This oil was chromatographed on 250 g of fine silica gel using the following solvent ratios of CHCl₃–CH₃OH–NH₄OH: 97:3:0.3 (0.5 L), 95:5:0.5 (0.5 L), 92.5:7.5:0.75 (0.5 L), 90:10:1 (0.5 L), and 87.5:12.5:1.25 (1 L). The 24-mL fractions were analyzed by TLC (SiO₂), combined, and evaporated at reduced pressure.

Fractions 136–145 afforded 450 mg (13.7%) of 13 as a colorless oil.

Fractions 152–162 were evaporated to give 556 mg (16.8%) of **(4a*R**,5*S**,5a*S**,9a*R**,10*R**,11a*R**)-1,2,3,4,4a,5a,6,7,8,9,9a,10,11,11a-tetradecahydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine** (14): ¹H NMR (CDCl₃) δ 1.0–2.2 (m, 23 H), 1.26 (s, H₃C), 3.36 (t, 7 Hz, HC₁₀).

The free base was dissolved in 1:1 ether–pentane and treated with ethanolic HCl to provide the HCl salt as a colorless solid: mp = 230–233 °C. Anal. (C₁₆H₂₇N·HCl) C, H, N.

The earlier-eluting fractions provided compound 15 and the N-ethylated derivatives of compounds 2, 11, and 13, which are presumably a result of reductive amination of the acetic acid associated with the starting material.

Birch Type Reductions of 1. (5*R*,5a*S*,10*R*)-5a,6,7,8,10,11-Hexahydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine Hydrochloride Salt (16). A solution of 1.0 g (4.5 mmol) of the free base of 1 in 50 mL of *n*-propylamine was cooled to 0 °C under N₂, and 144 mg (20.7 g-atom) of Li wire was added in small pieces over 3 h. The residual metal was removed, and the reaction was quenched by the addition of 30 mL of saturated NH₄Cl solution. The reaction mixture was extracted with three portions of ether, and the combined ether layers were washed with two portions of saturated NH₄Cl, water, and brine. After drying over MgSO₄, the solvents were removed at reduced pressure to give a reddish oil, which was chromatographed on 100 g of fine SiO₂ using 98:2:0.2 CHCl₃–CH₃OH–NH₄OH taking 5-mL

fractions. Fractions 50–62 were combined to give 107 mg of an orange oil. This oil was further purified by preparative reversed-phase HPLC using a C-18 column with 0.1% trifluoroacetic acid in water and acetonitrile. The pure fractions were concentrated, basified, extracted, and evaporated to give an oil: ¹H NMR (CDCl₃) δ 0.26–0.42 (m, 1 H), 1.61 (s, H₃C), 2.63 (d, 15 Hz, 1 H), 3.22 (dd, 15, 6 Hz, 1 H), 4.16–4.22 (m, 1 H), 5.47–5.55 (m, 1 H); [α]_D = −48.4° (c = 0.43, CH₃OH). This oil was dissolved in ether and treated with 31 μL of 8.55 M ethanolic HCl to afford 26 mg (2.2%) of 16 as a light brown solid. Anal. (C₁₆H₁₉N·HCl·0.25H₂O) C, H, N.

(5*R*,5a*S*,10*R*)-5a,6,10,11-Tetrahydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine Hydrochloride Salt (17). Fractions 80–126 were combined and purified as described above to give 36 mg (3.1%) of a tan solid: mp = 230 °C dec; ¹H NMR (CDCl₃) (free base) δ 1.21 (m, 1 H), 1.75 (s, H₃C), 2.05 (m, 1 H), 2.24 (br s, 1 H), 2.56 (dd, 12, 6 Hz, 1 H), 2.65 (d, 18 Hz, 1 H), 3.30 (dd, 18, 6 Hz, 1 H), 4.31 (d, 6 Hz, HC₁₀), 5.62 (m, 1 H), 5.80–5.93 (m, 2 H); [α]_D = −129° (c = 0.35, CH₃OH). Anal. (C₁₆H₁₇N·HCl·0.4H₂O) C, H, N.

(5*R*,10*R*)-6,9,10,11-Tetrahydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine Hydrochloride Salt (18). A stirred solution of 1.96 g (8.86 mmol) of 1 (free base) in 100 mL of *n*-propylamine and 2.4 mL of 2-propanol under N₂ was cooled in an ice bath, and 315 mg of Li wire (washed with hexane, ethanol, and ether) was added in small pieces over 2.0 h. After stirring for 3.0 h in the cold, an additional 1.0 mL of 2-propanol was added and the stirring was continued for 45 min. The reaction was quenched by the dropwise addition of saturated NH₄Cl to give a yellow solution. Most of the solvent was removed with a rotovap, and the aqueous residue was extracted with two portions of ether. The combined organic layers were washed twice with water and dried over Na₂SO₄, and the solvents were removed with a rotovap to give a yellow oil, which was chromatographed on 200 g of fine SiO₂ using 98:2:0.2 to 95:5:0.5 CHCl₃–CH₃OH–NH₄OH. Fractions containing the product were combined and rotovaped to give an oil, which was purified by RP-HPLC using a Waters Delta-Pak C18 column and a gradient elution of 100% A to 55% A–45% B over 1 h (A = 0.1% TFA in H₂O, B = 0.1% TFA in CH₃CN). The fractions were assayed by HPLC, combined, and rotovaped to remove the acetonitrile. The aqueous residue was basified with 10% Na₂CO₃, extracted with three portions of CHCl₃, the combined organic layers were washed with water and dried over Na₂SO₄, and the solvents were removed to give 60 mg (3.0%) of a colorless oil: ¹H NMR (CDCl₃) δ 1.56 (s, H₃C), 2.58 (d, 17 Hz, 1 H), 3.12 (dd, 17, 5 Hz, 1 H), 4.05 (d, 5 Hz, HC₁₀), 5.67 (s, 2 H).

This oil was dissolved in ether and treated with ethanolic HCl to give 47 mg of 18 as a colorless solid: [α]_D = +146° (c = 0.42, CH₃OH). Anal. (C₁₆H₁₇N·HCl·0.2H₂O) C, H, N.

Crystal-Structure Determinations. Crystals of the maleate salt of 2 (C₁₆H₂₁N·C₄H₄O₄, FW = 343.424) formed from ethyl acetate in space group $P2_12_12_1$ with a = 10.132 (2) Å, b = 12.722 (3) Å, and c = 14.321 (2) Å for Z = 4 and a calculated density of 1.236 g/cm³. An automatic four-circle diffractometer equipped with CuKα radiation (λ = 1.5418 Å) was used to measure 1430 potential diffraction peaks of which 1362 were observed ($I ≥ 3\sigma I$). Application of a multisolution tangent formula approach to phase solution gave an initial model for the structure[15] which was subsequently refined with least squares and Fourier methods. Anisotropic temperature parameters were refined for the non-hydrogen atoms while isotropic temperature factors were applied to the hydrogens but not refined. The function $\sum \omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized with full-matrix least squares to give an unweighted residual of 0.044. Figure 1 is a computer-generated drawing of the maleate salt of 2 showing its absolute stereochemistry. Tables I–III are included in the supplementary material and contain the final fractional coordinates, temperature parameters, bond distances, and bond angles. All bond distances

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and angles are within chemically reasonable limits.

Supplementary Material Available: Tables containing the fractional coordinates, temperature parameters, bond distances, and bond angles for the maleate salt of **2** (4 pages). Ordering information is given on any current masthead page.

High Potency Dipeptide Sweeteners. 1. L-Aspartyl-D-phenylglycine Esters

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Twenty esters of L-aspartyl-D-phenylglycine, as well as two substituted analogues, an *o*-fluoro and a *p*-hydroxy-phenylglycine ester, were prepared. The L-aspartyl-D-phenylglycine (-)-*α*- and (+)-*β*-fenchyl esters had the highest sweetness potency at 1200 and 3700 times that of sucrose, respectively. The high potency of these sweeteners is surprising as the phenyl group occupies a position previously believed to accommodate only much smaller groups.

Since the accidental discovery of aspartame (1) at the G. D. Searle laboratories in 1965,[1] there has been an enormous amount of work to examine the scope and potential of this promising class of sweeteners.[2] Systematic
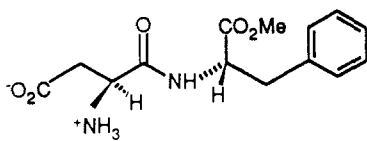
1

variations in the component parts of aspartame have shown that for sweetness the following hold true.
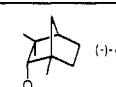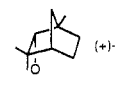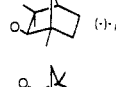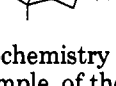
1. Few changes are allowed in the N-terminal aspartic acid. Hydrogen bonding to the sweet receptor with the NH_3^+ group as a donor and the CO_2^- as an acceptor is generally thought to be critical for sweetness.[1,3] The methylene group may be deleted (aminomalonic acid for aspartic acid), but an extra methylene group (glutamic acid for aspartic acid) eliminates sweetness. The curious early observation that the *α*-amino group can be trifluoro-acetylated[5a] has recently been extended to include *N*-(*N'*-formyl)carbamoyl[5b], *N*-4-substituted-phenylcarbamoyl, -thiocarbamoyl, and *N*-cyanoguanidino derivatives,[5c] and amino acid amides.[5d]

2. The peptide bond cannot be inverted, methylated, or replaced by an ester.[6]

3. Proper stereochemistry at the existing chiral centers is critical. For example, of the four possible diastereomers for aspartylphenylalanine methyl ester only the L,L (aspartame) is sweet.[1]

4. Many changes are tolerated in the C-terminal part of the sweetener provided that the small and large R groups occupy the positions shown below.[1c,6a,7]

R_1 = small "upper" group

R_2 = large "lower" group

Table I. Known High Potency Dipeptide Sweeteners

R_1	R_2	sweetener	ref
CH_3	CO_2R	L-aspartyl-D-alanine esters	9a,b
CH_3	CONHR	L-aspartyl-D-alanine amides	10
CH_2OH	CONHR	L-aspartyl-D-serine amides	11
CO_2Me	CO_2R	L-aspartyl-D,L-aminomalonic acid diesters	12a–e
$CONMe_2$	CO_2R	L-aspartyl-D,L-aminomalonic acid ester amides	13

Table II. L-Aspartyl-D,L-aminomalonic acid diesters[12]

2

	R	sweetness potency
a)	(-)-*α*	30000
b)	(+)-*α*	1000
c)	(-)-*β*	5000
d)	(+)-*β*	50000

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