α-Effect Nucleophiles: A Novel and Convenient Method for the Synthesis of Dibenzo[a,d]cycloheptenimines[1]

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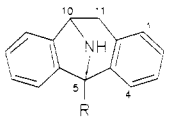
Received June 8, 1987

A new approach to the medicinally important 5-methyl- and 5*H*-dibenzo[*a*,*d*]cycloheptenimines is presented. Through the novel addition to carbinol **3** of various species exhibiting an α-effect, amine equivalents were incorporated at the tertiary C-5 position, giving derivatives **9a–d**. Ritter reactions of carbinol **3** gave a dimerized and rearranged derivative as well as an imine-bridged species [a 5,10-(nitrilomethano) derivative]. Under moderately acidic conditions, high yields of the C-5 derivatives **9a–d** were obtained without competing elimination or dimerization. The rate of ring closure of these compounds to the corresponding heterocycles **10a–d** was greatly enhanced under basic conditions. An increasing reactivity order paralleling an increase in nucleophilicity was observed (**9a** ≥ **9c** > **9b** > **9d** > **9e**). The synthesis of the 5-desmethyl ring-closed hydroxylamine **14** was also expedited by this route. Investigation of the ^{13}C NMR spectral properties of the ring-closed heterocycles showed an equilibration, via inversion at the nitrogen bridge, between syn and anti conformers. Hydrogenolysis of **10a–c** and **14** completed the synthesis of the 5-methyl- and 5*H*-dibenzo[*a*,*d*]cycloheptenimines **1a** and **1b**, respectively.

The dibenzo[*a*,*d*]cycloheptenimine MK-801 (**1a**)[2] has drawn considerable recent attention[3] as an anticonvulsant and neuroprotective agent that is a noncompetitive *N*-methyl-D-aspartate receptor antagonist.[4] The previous synthesis of **1a** from the readily available tricyclic ketone **2** proceeds in satisfactory yield, but it requires nine steps.[2] This approach involves formation of an oxime at C-10, reduction to a hydroxylamine, and then ring closure into an exocyclic double bond at C-5. We describe here a shorter (four-step) and higher yielding synthesis that reverses the order of imine bridge formation by employing direct addition of highly reactive amine nucleophiles to the tertiary C-5 position of carbinol **3**, followed by ring closure into the C-10, C-11 double bond.



1a, R = CH_3 (MK-801)

1b, R = H

The possibility of direct introduction of nitrogen nucleophiles at C-5 of the dibenzocycloheptene skeleton had been previously considered.[2] However, it was not pursued with 5-methyl-substituted substrates, due to the strong tendency both of heteroatom-substituted diarylmethanes to undergo solvolysis and of alkylated derivatives to undergo elimination to, in this case, compound **4**.[5] Particularly lacking was any precedent for converting alkyl diarylmethyl compounds to nitrogen derivatives by using acid catalysis. Two challenges were thus presented: (1) direct introduction of an amine equivalent at the tertiary C-5 position and (2) transannular ring closure into the unactivated endocyclic C-10, C-11 double bond.

We investigated whether direct nitrogen incorporation could be accomplished at C-5[6] by initially employing the classical method for preparing tertiary carbinamines, the Ritter reaction.[7] While this study was not expected to lead directly to a new synthesis of **1a**, it established that direct incorporation of nitrogen at C-5 was indeed possible, provided that the nucleophile was sufficiently reactive. It also demonstrated that carbinol **3** was a more suitable substrate than the methylene derivative **4**. Thus, we began a study of the reaction of carbinol **3** with more suitable nitrogen nucleophiles.

The resulting new synthesis of **1a** (Scheme III) requires the use of α-effect[8] amine nucleophiles as well as carefully controlled acidic conditions for the addition at C-5. Intrinsic to the success of this reaction and the subsequent ring closure is the enhanced nucleophilicity of the nitrogen species.

This paper describes this short and practical synthesis of **1a** as well as its extension to the 5-desmethyl analogue **1b**.[6a] Also included are a description of the Ritter reactions of carbinol **3** and a discussion of the inversion barriers at the bridging nitrogen of the 12-substituted heterocycles **10a–d**.

Ritter Reaction Products from Carbinol 3. The Ritter reaction[7] provided a unique opportunity for assessing the possibility of nitrogen incorporation at C-5 without having to consider the tendency of the product to eliminate. That is, the nitrilium salt intermediate of the Ritter reaction could potentially react with the transannular C-10, C-11 double bond of the dibenzocycloheptene system (e.g., Scheme II),[9] thus providing a

(1) (a) Presented in part at the 184th National Meeting of the American Chemical Society, Kansas City, MO, Sept 1982; paper ORGN 212. (b) Bender, D. R.; Karady, S.; Rothauser, T. U.S. Patent 4 477 668.

(2) Christy, M. E.; Anderson, P. S.; Britcher, S. F.; Colton, C. D.; Evans, B. E.; Remy, D. C.; Engelhardt, E. L. *J. Org. Chem.* **1979**, *44*, 3117.

(3) (a) Dagani, R. *Chem. Eng. News* **1986**, *64*, 23. (b) Barnes, D. M. *Science (Washington, D.C.)* **1987**, *235*, 632.

(4) Wong, H. F.; Kemp, J. A.; Priestly, T.; Knight, A. R.; Woodruff, G. N.; Iverson, L. K. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 7104.

(5) Reference 2 and references cited therein.

(6) Methods used to incorporate nitrogen directly at C-5 of 5*H*-dibenzo[*a*,*d*]cycloheptene and related skeletons vary depending on whether the skeleton is substituted at C-5 with an alkyl or aryl group. Unsubstituted derivatives have been prepared by displacement of halides or sulfonate by amines or azide[6a-c] and by reduction of imines.[6d,e] A 5-methyl derivative was prepared by converting the 5-keto compound to an *N*-sulfonyl imine followed by reaction with methyllithium.[6f] 5-Aryl-5-azido derivatives were prepared by heating NaN_3 with the isolated fluoroborate salts of the C-5 carbonium ions, which were in turn prepared from C-5 carbinols.[6c] (a) Nedelec, L.; Frechet, D. (Roussel Uclaf) U.S. Patent 3 892 756, 1975. (b) Kyburz, E.; Spiegelberg, H. (Hoffman-LaRoche) Netherlands Patent 6 600 093, 1966. (c) Looker, J. J. *J. Org. Chem.* **1971**, *36*, 1045. (d) Halczenko, W.; Shepard, K. L. *J. Heterocycl. Chem.* **1982**, *19*, 967. (e) Brenner, D. G.; Halczenko, W.; Shepard, K. L. *J. Heterocycl. Chem.* **1982**, *19*, 897. Shepard, K. L.; Brenner, D. G. *U.S. Patent* 4 256 889, March 17, 1981. (f) Brenner, D. G.; Shepard, K. L. U.S. Patent 4 232 158, Nov 4, 1980.

(7) The Ritter and related reactions have been reviewed: (a) Krimen, L. I.; Cota, D. J. *Org. React. (N.Y.)* **1969**, *17*, 213. (b) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279.

(8) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16.

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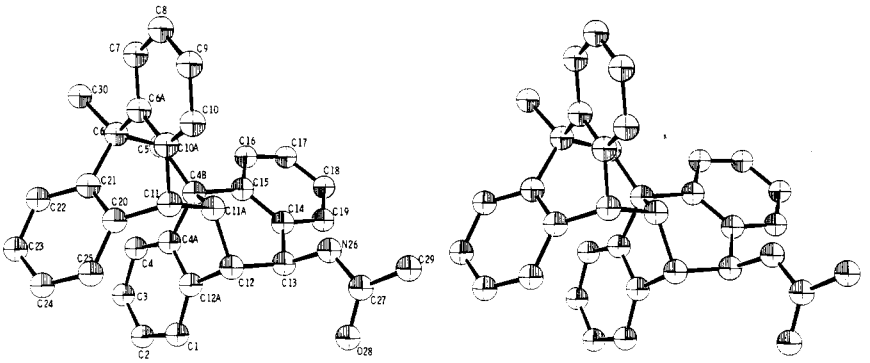
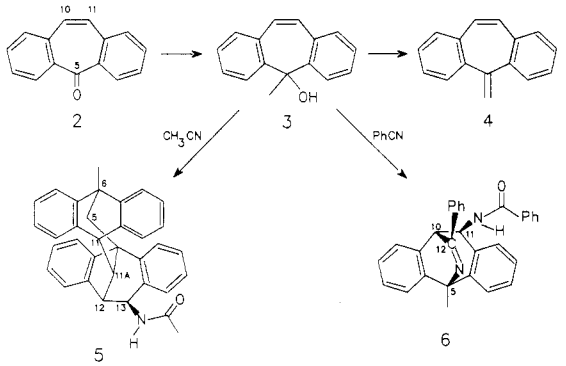


Figure 1. Stereo ORTEP view[11] of structure **5** with the Chemical Abstracts numbering system.

trapping option that would not be available to products from other nitrogen nucleophiles. For this study, we used the C-5 hydroxyl derivative **3** instead of the extensively conjugated methylene derivative **4**, since the carbinol could be expected to undergo substitution more readily.[10]

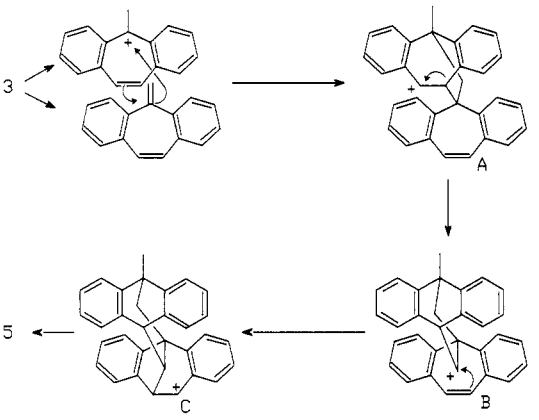


Reaction of **3** in sulfuric acid with acetonitrile eventually gave the dimerized and rearranged derivative **5** as sole product. However, it was evident from monitoring by TLC that **3** was first rapidly converted to a mixture of **5** and the C-5 methylene derivative **4**, and then **4** was slowly converted to **5**. A separate reaction starting with **4** confirmed its conversion to **5** at a rate much slower than the nearly instantaneous direct conversion of carbinol **3** to **5**. These results confirmed our expectation that the C-5 hydroxy derivative would be more reactive than the methylene derivative.

The mass spectrum of **5** indicated a dimeric structure, IR showed the presence of an amide, ^{13}C and ^{1}H NMR suggested cyclodimerization, and X-ray crystallographic data indicated the rearranged structure **5** (Figure 1).

A reasonable mechanism for the formation of **5** begins with cyclodimerization to intermediate A of Scheme I. This step is analogous to the conversion of diphenylmethylcarbinol to a hydrindene derivative.[12] Conversion

Scheme I. Proposed Mechanism for the Formation of 5



to **5** is then completed via Wagner–Meerwein rearrangement to B,[13] trapping of the nonstabilized secondary carbocation by the remaining cycloheptene vinyl group to give C, and then reaction with acetonitrile to give the amide.

In contrast with the behavior of carbinol **3**, reaction of CH_3CN/H_2SO_4 with 10,11-dihydrocarbinol **7** (for which cyclodimerization or internal trapping is not possible) immediately gave the methylene derivative **8**, which underwent no further reaction. This behavior is analogous to that of other diarylmethylcarbinols.[12,14,15]

When nitrile reactivity was varied by treating carbinol **3** with benzonitrile instead of acetonitrile, the imine-bridged derivative **6** was formed in modest yield.[9b] Its structure was confirmed by its mass spectrum (molecular weight equals that of **3** plus two molecules of benzonitrile), by its IR spectrum (presence of amide and imine absorptions), and by the following NMR experiments.

Carbon-13 NMR showed two sp^2 carbons at 169.1 and 167.0 ppm, consistent with the imine and amide carbons.

(9) (a) Two-atom bridges readily form in the dibenzo[a,d]cycloheptene series (for example, see: Dobson, T. A.; Davis, M. A.; Hartung, A. M.; Manson, J. M. *Tetrahedron Lett.* **1967**, 4139), and there is precedent for intramolecular trapping of a nitrilium salt by a vinyl group (ref 7a). (b) This reaction has been independently demonstrated on an analogous tricyclic carbinol: Reamer, R. A.; Brenner, D. G.; Shepard, K. L. *J. Heterocycl. Chem.* **1986**, *23*, 961.

(10) When a vinyl group is an integral part of an extensively conjugated system, it is usually less reactive in the Ritter reaction than the corresponding carbinol.[7a] For example, we were unable to induce stilbene to undergo a Ritter reaction, yet the corresponding carbinol (1,2-diphenyl-1-hydroxyethane) is readily converted to the amide (Mousseron, M.; Christol, H.; Laurent, A. *C. R. Hebd. Seances Acad. Sci.* **1959**, *248*, 1904; see also ref 7b).

(11) Johnson, C. A. ORTEP-II: *A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations*, 2nd rev., with supplemental instructions; U.S. Atomic Energy Commission, Oak Ridge National Laboratory, Oak Ridge, TN, 1979; ORNL-3794.

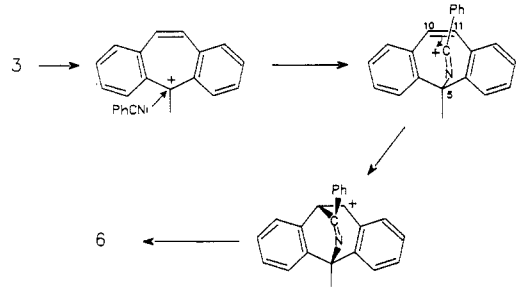
(12) Kaluszyner, A.; Blum, S.; Bergmann, E. D. *J. Org. Chem.* **1963**, *28*, 3588.

(13) Similar rearrangements in the dibenzo[a,d]cycloheptene series have been noted under both acidic[13a,b] and thermal[6c] conditions. (a) Christy, M. E.; Boland, C. C.; Williams, J. G.; Englehardt, E. L. *J. Med. Chem.* **1970**, *13*, 191. (b) Buchanan, G. L.; Jhaveri, D. B. *J. Org. Chem.* **1961**, *26*, 4295.

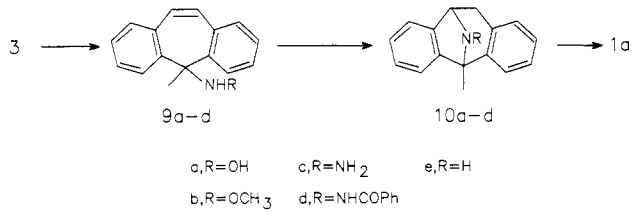
(14) Christol, H.; Laurent, A.; Solladis, G. *Bull. Soc. Chim. Fr.* **1963**, 877.

(15) The only carbinol of this type known to give the normal Ritter product is diphenyl(difluoromethyl)carbinol.[12]

Scheme II. Proposed Mechanism for the Formation of 6



Scheme III. Synthesis of MK-801 (1a)



A coupled spectrum would not permit unequivocal assignment of these carbons or the direction of the imine bond, so the following experiments were run. Low-power irradiation of the ortho aromatic protons (C-12 phenyl) while a coupled carbon spectrum was being obtained showed the imine carbon (169.1 ppm) to be a doublet of doublets (J = 4.2 and 6.5 Hz). These splittings are due to long-range spin–spin coupling to the protons on C-10 and C-11 respectively. These assignments were further verified by two-dimensional heteronuclear correlation experiments (HETCOR) using J-modulation delays optimized for the two different long-range couplings and thereby unequivocally establishing these coupling pathways.[16] This confirms the imine bond orientation because the 6.5-Hz coupling between H-11 and the imine carbon (C-12) must be over three bonds, thus precluding a reversed imine bond orientation.

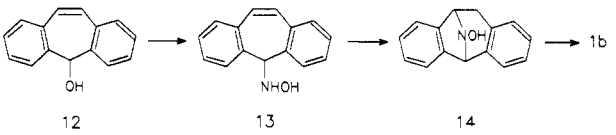
A Dreiding model indicates that the dihedral angle between H-10 and H-11 would be the same regardless of the stereochemistry of the benzamide group, and therefore, their vicinal ^1H–^1H coupling constant contains no information about stereochemistry at C-11. However, the three-bond coupling of 6.5 Hz from H-11 to the imine carbon (C-12) indicates a trans diaxial pathway between these nuclei, thus defining the stereochemistry as indicated at C-11.

A reasonable mechanism for the formation of **6** (Scheme II) begins with the desired nucleophilic attack by nitrogen on the C-5 dibenzotropylium cation to give a nitrilium salt intermediate, which is then trapped by the C-10, C-11 vinyl group to give a benzyl carbocation. Reaction with another molecule of benzonitrile gives the amide **6**.

The ring systems corresponding to **5** and **6** are new, although 12,13-dihydro analogues of **6** [10,5-(iminomethano) derivatives], which are isomers of the isopavine alkaloids, are common.

Reactions of α-Effect Nitrogen Nucleophiles with Carbinol 3. Successful introduction of a useful amine equivalent to C-5 of carbinol **3** required the use of both α-effect nucleophiles and a carefully controlled, moderately acidic medium. To illustrate the latter point, when **3** was added at room temperature to an equilibrated mixture of dichloroacetic acid (pK_a 1.49),[17a] methylene chloride, sodium acetate, and hydroxylamine hydrochloride, an 86% yield of the 5-methyl-5-hydroxamino **9a** was realized (Scheme III). However, trifluoroacetic acid (pK_a 0.23)[17a] deactivated the nucleophile, leading instead to formation of elimination product **4**. Acetic acid (pK_a 4.75),[17b] on the other hand, did not promote the reaction.

Scheme IV. Synthesis of 1b



Not only was the acidity of the medium important but only nucleophiles with an α-effect gave the desired reaction.[18] Attempted addition to **3** of benzylamine, formamide, ethyl carbamate, urea, cynamide, or benzamidine (all non α-effect nucleophiles) gave **4** exclusively. In addition to hydroxylamine, other α-effect nucleophiles added to **3** under similar reaction conditions. Methoxyamine, hydrazine, and benzoyl hydrazide gave the corresponding products **9b**, **9c**, and **9d** in 82%, near quantitative, and 93% yields respectively. Equilibration of the hydrochloride salts of hydroxylamine and methoxyamine with a mixture of sodium acetate in dichloroacetic acid and methylene chloride was necessary for optimum results, presumably due to slow dissolution of the hydrochloride salts and/or slow formation of the more soluble dichloroacetate salts. Premature addition of **3** gave increased amounts of elimination product **4**.

The addition of hydroxylamine to the 5-desmethyl carbinol **12** also required a controlled acidic medium and gave the desired 5-desmethyl-5-hydroxamino **13** in 85% yield[19] (Scheme IV). By incorporating the amine equivalent at C-5, the route to **1b** first established by Nedelec and Frechet[6a] was shortened considerably while greatly enhancing the overall yield of the 5-desmethyldibenzocycloheptenimine **1b**.

Hydroxylamines are known to disproportionate in solution and upon standing.[20] Compounds **9a**, **9b**, and **13** were no exception and were therefore stored below 0 °C with time in solution held at a minimum. The 5-methyl-5-hydrazino **9c** is particularly unstable and even at room temperature is rapidly converted to **4**. Consequently **9c** was directly transformed to the more stable ring-closed product.

Transannular Ring Closure. Initial attempts at thermal ring closure of the 5-methyl-5-hydroxamino **9a** gave inconsistent yields of **10a** and produced the byproducts **9e**,[21] **4**, and **11** (see Experimental Section). The analogous compounds **9b–d** were either unreactive or eliminated the nitrogen group to give **4**. Additionally, under the same reaction conditions, the 5-desmethyl-5-hydroxamino **13** failed to ring close, which may be attributed to the Thorpe–Ingold effect.[22] The ability of alkyl

(16) Freeman, R.; Morris, G. A. *J. Chem. Soc., Chem. Commun.* **1978**, 684.

(17) (a) *Handbook of Chemistry and Physics*, 50th ed.; Weast, R. C., Ed.; The Chemical Rubber Co.: Cleveland, OH, 1969. (b) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972.

(18) For a review of α-effect nucleophilic substitution reactions, see: Grehov, A. P.; Veselov, V. Y. *Russ. Chem. Rev. (Engl. Transl.)* **1978**, *47*, 631.

(19) Early attempts at increasing the solubility of hydroxylamine hydrochloride and derived salts involved the addition of hindered alcohols, such as 2-propanol. A procedure of this type is illustrated in the preparation of **13**. It was later found that the reaction proceeded in similar yields without the presence of a cosolvent.

(20) Smith, P. A. S. *Open Chain Nitrogen Compounds*; W. A. Benjamin: New York, 1966; Vol. 2.

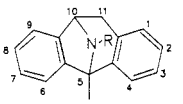
(21) **9e** was identified by comparison with authentic material prepared from the corresponding 5-azido compound, which was in turn prepared from **3**[1b].

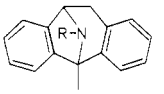
Table I. Relative Rates of Ring Closure of 9a–e

substrate	conditions[a]	time[b]	product	yield, %
RNHOH (**9a**)	10% DMSO/toluene, 55–60 °C	5 min	**10a**	85[c]
$RNHNH_2$ (**9c**)	10% DMSO/toluene, 55–60 °C	5 min	**10c**	95[d]
$RNHOCH_3$ (**9b**)	10% DMSO/toluene, 55–60 °C	15 min	**10b**	65[c]
RNHNHCOPh (**9d**)	DMSO, 110 °C[e]	18 h	**10d**	84[c]
RNH_2 (**9e**)[1b]	DMSO, 125 °C	18 h	**1a**[f]	80[g]

[a] Reactions were carried out by using 100 mol % of potassium *tert*-butoxide with 1 g of substrate/10 mL of solvent. [b] Time required to complete the reaction. [c] Isolated yield after crystallization. [d] Yield of crude product. [e] Using 120 mol % of potassium *tert*-butoxide. [f] Spectral data and melting point are in agreement with literature values.[2] [g] Yield after chromatography.

Table II. Selected ^{13}C NMR Chemical Shifts for 1a and 10a–d

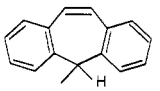




compound	temp, °C	syn/anti ratio		^{13}C chemical shifts[a] C-5	5-CH_3	C-10	C-11
1a, R = H	35	one conformer		63.9	19.9	58.2	34.3
10a, R = OH	35	2/1	syn	68.7	17.7	63.8	28.5
			anti	74.1	15.2	70.2	34.7
10b, R = OCH_3	35	3/2	syn	68.3	18.3	60.8	28.6
			anti	74.0	14.9	67.8	35.3
10c, R = NH_2	−30	9/1	syn	68.0	17.1	63.1	27.4
			anti	73.2	obscured	69.9	35.0
10d, R = NHCOPh	−60	9/1	syn	68.0	17.2	61.7	27.5
			anti	72.8	15.4	68.6	34.5

[a] Spectra were obtained in $CDCl_3$ (internal TMS reference) except **10c**, which was run in 1/1 CD_2Cl_2/CH_2Cl_2.

substituents to facilitate ring closure has been previously noted.[23]



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In order to circumvent the problems associated with thermal ring closure, we sought a more reactive intermediate. In previous studies of thermal ring closures of alkenylhydroxylamines (which were postulated to proceed via a radical chain), House et al.[23b,24] had noted an increase in the ease of oxidation of hydroxylamines in the presence of base. Since the radical chain was purported to be initiated by a nitroxide compound which arose via ionization and subsequent oxidation, ring closure should be greatly facilitated under basic conditions.

Conversion of **9a** in 10% DMSO–toluene with potassium *tert*-butoxide at 55–60 °C to the desired ring-closed hydroxylamine **10a** proceeded in 5 min (versus 15 h under thermal conditions[25]) without disproportionation or other side-product formation. The ring closure could also be accomplished with a variety of other bases (potassium carbonate, sodium hydride, and *n*-butyl lithium) in numerous solvents (DMF, DMSO, DMF/toluene, DMSO/THF, and toluene). The 5-desmethyl-5-hydroxamino **13** also ring-closed to the desired compound **14** (78% yield).

As seen in Table I, , all of the analogous α-effect "open-chain" compounds ring-closed in good yields, but at varying rates. The increase in the reaction times appeared to be concurrent with decreased nucleophilicity of the α-effect group [where the reactivity order is RNHOH (**9a**) ≥ $RNHNH_2$ (**9c**) > $RNHOCH_3$ (**9b**) > RNHNHCOPh (**9d**) > RNH_2 (**9e**)[1b]]. The same reactivity order was also observed when sodium hydride was used. Ritchie[26] and Bruice[27] have observed similar reactivity orders for the reactions of nonionized α-effect nitrogen species with esters and highly stable cations.

These results clearly show that ionization of the α-effect groups greatly enhanced reactivity relative to the corresponding nonionized species and the analogous 5-methyl-5-amino compound **9e**. Steric hindrance and/or resonance stabilization by the benzoyl group of **9d** are possible causes of its radically reduced rate of ring closure.

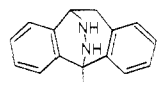
The synthesis of **1a** could now be completed by hydrogenolysis of any of the ring-closed compounds **10a–c**. For example, hydrogenolysis of a solution of hydroxylamine **10a** in 1:1 (v/v) 1.2 M HCl/acetic acid (from the ring-closure reaction) with sodium acetate and 5% palladium on carbon gave the desired 5-methyldibenzocycloheptenimine **1a** in 90% yield over two steps (ring closure and hydrogenolysis). It was not necessary to isolate **10a** prior to hydrogenolysis since ring closure of **9a** gave a clean conversion to the desired ring-closed product. Under similar reaction conditions, methoxyamine **10b** and hydrazine **10c** also gave **1a**, and the 5-desmethyl hydroxylamine **14** gave **1b**, all in high yield.

Spectral Properties of the Syn and Anti Conformers of Heterocycles 10a–d. Proton and ^{13}C NMR of the heterocycles **10a–d** indicated the presence of syn and anti forms (inversion at the nitrogen bridge) with the syn conformer predominating (Table II). For **10a** and **10b**, ambient-temperature ^{13}C NMR permitted assignment of the syn conformer to the higher field resonance of C-11, due to shielding from the "cis" γ oxygen.

(22) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley-Interscience: New York, 1966; p 191.
(23) (a) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2778. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.
(24) House, H. O.; Manning, D. T.; Melillo, D. G.; Fel, L. F.; Haymes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855.
(25) The use of 10% (v/v) DMSO/toluene did not significantly increase the rate of thermal ring closure.
(26) Ritchie, C. D. *J. Am. Chem. Soc.* **1975**, *97*, 1170.
(27) Dixon, J. E.; Bruice, T. C. *J. Am. Chem. Soc.* **1971**, *93*, 3248.

Since **10a** and **10b** are two distinct conformers at ambient temperature, two experiments were done to demonstrate an equilibrium between the conformers. High-temperature ^1H NMR studies of **10a**, up to 145 °C in DMSO-d_6, showed broadening of resonances; but the coalescence temperature appeared to be higher. Proton NMR measurements in $CDCl_3$ (obtained within 10 min of dissolution) showed a syn/anti ratio of 3/1. After overnight aging at room temperature, this ratio changed to 2/1, indicating that nitrogen inversion occurs.

For compounds **10c** and **10d**, ambient-temperature ^{13}C NMR showed only one set of peaks; however, some line broadening was observed. Low temperature (−30 °C for **10c** and −60 °C for **10d**) slowed the inversion at nitrogen, and the syn and anti conformers could be assigned by using the same chemical shift arguments presented for **10a** and **10b**. It is apparent from this data that a lower barrier for inversion exists for compounds **10c** and **10d** (N–N bond) relative to **10a** and **10b** (N–O bond). This is in accord with the general principle that increasing the electronegativity of adjacent atoms increases the barrier to inversion.[28]



15

When the ring closure of **9c** was first examined, ^{15}N and ^{13}C NMR were used to distinguish between the two structures **10c**, a mononitrogen bridge, and **15**, a dinitrogen bridge. The similarity of the ^{13}C NMR chemical shifts for the five compounds **1a** and **10a–d** indicated a mononitrogen bridge. In addition, ^{15}N NMR studies of **10c** at −5 °C showed only one protic nitrogen signal at 30.8 ppm downfield from external NH_4Cl (δ_N 0.0). This is consistent with a primary amino group as seen in alkyl-substituted hydrazines[29] and contrasts with the ^{15}N NMR resonance for the bridged nitrogen in **1a**, which comes at 55.0 ppm.

Summary. A highly efficient synthesis of dibenzo[*a*,*d*]cycloheptenimines, specifically MK-801 (**1a**) and its 5-desmethyl analogue **1b**, has been developed via the addition of α-effect nitrogen nucleophiles to an appropriate C-5 carbinol (e.g., **3**), followed by transannular ring closure under basic conditions.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237B spectrometer in chloroform unless otherwise specified. Nuclear magnetic resonance spectra were obtained on Hitachi Perkin-Elmer R-24A, Varian CFT-20 and XL-100, and Bruker WM-250 spectrometers in $CDCl_3$ using Me_4Si as internal standard unless otherwise specified. Coupling constants are in hertz. Mass spectra were obtained on Finnigan/MAT, Model 212 and Finnigan 4500 GC/MS spectrometers. Microanalyses were carried out on a Perkin-Elmer 240 elemental analyzer. TLC was performed on Analtech silica gel GF 250 and 2000 plates. Reactions were run under nitrogen. Melting points are uncorrected.

5-Hydroxy-5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (3). The reported procedure[30,31] was slightly modified. Ketone **2** (876 g, 4.25 mol) in tetrahydrofuran (THF, 2.37 L) was added to a solution of THF (1.42 L) and MeMgBr in ether (2.28 M, 5.96 mol) at 15–20 °C and stirred for 2 h. Aqueous NH_4Cl (3.6 L, 5.0 M) was carefully added while the temperature was kept at less than 30 °C. The phases were separated, and the aqueous phase (with NaCl added as necessary to break emulsions) was extracted with EtOAc (3 × 1.8 L). The combined extracts were dried and evaporated to a thick slurry (1.75 L). EtOAc (0.25 L) was added, and the mixture was warmed enough (65 °C) to give a solution and then cooled to just under 50 °C. Hexane (10 L) was added in portions, giving a white fluffy precipitate. The mixture was cooled to 5 °C, aged 0.5 h, and filtered. The solids were washed with cold hexane (2 × 1 L) and dried (air, 50–55 °C) to give 783 g (83%) of **3**: mp 113.5–115 °C (lit.[30] mp 112–115 °C); ^1H NMR δ 1.60 (3 H, s), 2.45 (1 H, s, exchanges with D_2O), 6.85 (2 H, s), 7.15 (8 H, m).

5-Methylene-5*H*-dibenzo[*a*,*d*]cycloheptene (4). A slight modification of a procedure using acid catalysis[31,32] was used. A solution of MeOH saturated with HCl (1.0 mL) was added over 1 min to carbinol **3** (222 mg, 1.0 mmol) dissolved in MeOH (1 mL). The solution was stirred for 0.5 h and then evaporated. A solution of the residue in CH_2Cl_2 (10 mL) was washed with saturated aqueous $NaHCO_3$ (10 mL), dried, and evaporated to a residue (202 mg, 99%), which was essentially pure by TLC. Recrystallization from ethanol gave **4** (146 mg, 72%): mp 119–121 °C (lit.[31] mp 119 °C); ^1H NMR δ 5.17 (2 H, s), 6.71 (2 H, s), 7.2 (8 H, m).

10,11-Dihydro-5-hydroxy-5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (7). 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (20.8 g, 0.1 mol) was treated with MeMgBr as described for the preparation of **3** except that ether was used for the reaction and extractions. The combined extracts were dried ($MgSO_4$), the $MgSO_4$ was thoroughly washed with CH_2Cl_2, and the filtrate was evaporated to a crude residue (20.6 g, 92%), which was recrystallized from ethanol (5 mL/g) to give **7** (14.95 g, 67%): mp 143.5–145.5 °C (lit.[32] mp 142–143 °C); ^1H NMR δ 1.85 (3 H, s), 2.20 (1 H, s), 3.15 (4 H, m), 7.0–8.0 (8 H, m).

10,11-Dihydro-5-methylene-5*H*-dibenzo[*a*,*d*]cycloheptene (8). A solution of MeOH/HCl (5 mL) was added over 5 min to carbinol **7** (4.0 g, 17.9 mmol) in CH_2Cl_2 (40 mL) at 30 °C. The solution was stirred for 0.5 h, cold water (25 mL) was added, and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL), dried, and evaporated to a residue (3.3 g), which was essentially pure by TLC. Recrystallization from petroleum ether gave **8** (2.21 g, 60%): mp 65–67 °C (lit.[32] mp 67–68 °C); ^1H NMR δ 3.07 (4 H, s), 5.32 (2 H, s), 7.1 (8 H, m).

***N*-[6,11,11a,12-Tetrahydro-6-methyl-5*H*-6,11-[1′,2′]benzeno-4b,12-([1,2]benzenomethano)dibenz[*a*,*f*]azulen-13-yl]acetamide (5).** Carbinol **3** (222 mg, 1.0 mmol) dissolved in CH_3CN (1.5 mL) was added over 10 min to CH_3CN/H_2SO_4 (1:1 v/v, 1 mL) at 10 °C. The solution was stirred at 10 °C for 10 min and then at room temperature for 2 h. The solution was added to cold water (15 mL), and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (10 mL), dried, and evaporated to give **5** (226 mg, 97%), which gave a single spot on TLC. A portion was recrystallized from ethanol: mp >320 °C; IR (Nujol) 1635, 3260 cm^{-1}; mass spectrum, m/z 467 (M^+), 408, 393, 263; ^1H NMR (selected data) δ 2.06, 2.10 (2 × 3 H, s, 6-CH_3, $COCH_3$), 2.45, 2.97 (2 H, AB quartet, ^2J = 13.9, 5-CH_2), 2.67 (1 H, s, 11a-H), 3.74 (1 H, d, 1.5, 12-H), 4.01 (1 H, s, 11-H), 4.89 (1 H, d of d, 7.5, 1.5, 13-H), 5.94 (1 H, d, 7.5, NH). Anal. Calcd for $C_{34}H_{29}NO$: C, 87.3; H, 6.2; N, 3.0. Found: C, 87.4; H, 6.2; N, 2.9.

***N*-[10,11-Dihydro-5-methyl-12-phenyl-5,10-(nitrilometheno)-5*H*-dibenzo[*a*,*d*]cyclohepten-11-yl]benzamide (6).** Carbinol **3** (222 mg, 1 mmol) was added to a solution of concentrated H_2SO_4 (1 mL) and benzonitrile (1 mL) at 15 °C and stirred at room temperature for 2.5 days (reaction is complete in 1 h). The solution was added to cold water (15 mL) and extracted with $CHCl_3$ (3 × 20 mL). Insoluble material was removed by filtration. The combined extracts were washed with saturated aqueous $NaHCO_3$ (15 mL), dried, and evaporated to a residue (150 mg, 35%), which appeared by NMR to be about 75% pure **6**. Crystallization from $CHCl_3$/hexanes gave **6** (51 mg, 12%): mp 226–227 °C; IR (CH_2Cl_2) 3425, 1660, 1625, 1600 cm^{-1}; ^{13}C NMR (selected data) δ 25.3 (5-CH_3), 45.5 (C-10), 51.4 (C-11), 64.1 (C-5), 167.0 (NHCO), 169.1 (C-12); ^1H NMR (selected data)

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(32) Triebs, W.; Klinkhammer, H.-J. *Chem. Ber.* **1950**, *83*, 367.

δ 2.47 (3 H, s, 5-CH_3), 5.35 (1 H, d, 4.4, 10-H), 5.53 (1 H, d of d, 8.1, 4.4, 11-H), 6.16 (1 H, d, 8.1, NH), 8.07 (2 H, br d, 7, ortho proton on C-12 phenyl); mass spectrum, m/z 428 (M^+), 413, 323, 307. Anal. Calcd for $C_{30}H_{24}N_2O$: C, 84.1; H, 5.6; N, 6.5. Found: C, 83.8; H, 5.5; N, 6.2.

X-ray Analysis of 5. An X-ray diffraction experiment on a single crystal of **5** grown in ethanol at approximately 6 °C was used to determine its crystal structure. The unit cell parameters are a = 16.882 (7) Å, b = 9.718 (3) Å, c = 15.872 (5) Å, β = 102.97 (3)°, V = 2537 (1) Å^3, and calculated density = 1.224 g/cm^3 in the centrosymmetric space group $P2_1/c$ (Z = 4). Intensities were measured on a fully automated Syntex $P2_1$ diffractometer using Cu Kα radiation (λ = 1.5418 Å) at 50 kV/30 mA to a maximum 2θ of 115° using a $2\theta/\omega$ scan. Of the 3214 symmetry independent reflections, 1117 (34.8%) were considered observed at the level $I \geq 3\sigma(I)$. Data reduction, least-squares refinement procedures, and various electron density syntheses were performed by the XRAY system of computing programs.[33] Initial phasing was calculated by the direct-methods program MULTAN 78.[34] A 35-atom trial structure obtained from a MULTAN phased E map with the lowest residual figure of merit proved to be correct. A difference electron density synthesis provided the final non-hydrogen atom. Non-hydrogen atoms were refined with anisotropic temperature factors using full-matrix least squares throughout. After sufficient refinement, hydrogen atoms were located by difference electron density syntheses, assigned equivalent isotropic temperature factors of the atoms to which they were bound, and refined for positional parameter variation only. A final difference electron density synthesis was featureless with the highest value of 0.3 e/Å^3. The final residual index (R factor) was 0.059.

5-Methyl-5-hydroxamino-5*H*-dibenzo[*a*,*d*]cycloheptene (9a). To a three-necked flask equipped with an addition funnel, stirrer, and thermometer were added 138 mL of methylene chloride, 138 mL (1.62 mol) of dichloroacetic acid, and 88.61 g (1.08 mol) of sodium acetate. When the solids were in solution, 75.11 g (1.08 mol) of hydroxylamine hydrochloride was added and the reaction mixture stirred for 1.5 h at ambient temperature. An additional 1.36 L of methylene chloride was added, and the suspension was stirred for 1.5 h. To this was added 60.0 g (0.27 mol) of carbinol **3** in 0.60 L of methylene chloride.

After 0.5 h, the reaction was quenched with 0.9 L of ice water and 0.3 L of concentrated ammonium hydroxide (pH 8). The aqueous layer was separated and washed with 0.4 L of methylene chloride, and the combined organic layers were washed with 0.8 L of brine and dried over sodium sulfate. The organic solution was filtered and concentrated under reduced pressure to approximately 0.1 L. To the stirred concentrated filtrate was added 1.1 L of hexane, and the resulting mixture was chilled (0–5 °C) for 1 h. The precipitate was filtered, washed with cold hexane, and dried to give 54.8 g (86%) of a white crystalline solid **9a**: mp 130–133 °C; IR 3578, 3222, 1639 cm^{-1}; ^{1}H NMR δ 2.15 (s, 3 H, CH_3), 6.35 (s, 2 H, NHOH, exchanged by D_2O), 7.02 (s, 2 H, HC=CH), and 6.96–7.74 (m, 8 H, Ar). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.78; H, 6.36; N, 5.66.

5-Methyl-5-(methoxyamino)-5*H*-dibenzo[*a*,*d*]cycloheptene (9b). The reaction of 5.0 g (22.5 mmol) of carbinol **3** with 7.5 g (90 mmol) of methoxyamine hydrochloride, 7.4 g (90 mmol) of sodium acetate, and 11.5 mL (135 mmol) of dichloroacetic acid by the procedure for **9a** gave 4.6 g (82%) of **9b** (after crystallization): mp 118.5–126.0 °C; IR 3232, 1450, 1194 cm^{-1}; ^{1}H NMR δ 2.17 (s, 3 H, CH_3), 3.33 (s, 3 H, OCH_3), 7.15 (s, 2 H, HC=CH), and 6.64–7.85 (m, 9 H, NH and Ar). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.40; H, 6.88; N, 5.39.

5-Hydroxamino-5*H*-dibenzo[*a*,*d*]cycloheptene (13). The reaction of 50.0 g (0.24 mol) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (**12**) with 66.7 g (0.96 mol) of hydroxylamine hydrochloride, 75.6 g (0.96 mol) of sodium acetate, and 204.8 mL (2.40 mol) of dichloroacetic acid in 1.75 L of methylene chloride and 0.10 L of 2-propanol by the procedure for **9a** gave 45.5 g (85%) of **13**: mp 117.5–120.5 °C; IR 3533, 3211 cm^{-1}; ^{1}H NMR δ 4.90 (s, 1 H, CH), 5.87 (s, 2 H, NHOH, exchanged by D_2O), 6.84 (s, 2 H, HC=CH), and 7.26 (m, 8 H, Ar); ^{13}C NMR (at −20 °C) δ 73.0 (C-5), 127.7, 128.6, 129.8, 130.1 and 130.4 (8 H bearing Ar C and C-10, C-11), 135.9 (C-9a and C-11a), and 137.2 (C-4a and C-5a). This material was taken directly to **14**.

5-Methyl-5-hydrazino-5*H*-dibenzo[*a*,*d*]cycloheptene (9c). In a three-necked flask fitted with a thermometer and stirrer were placed 100 mL of methylene chloride, 21.5 mL (0.26 mol) of dichloroacetic acid, and 6.0 mL (0.10 mol) of 85% hydrazine hydrate. The mixture was stirred for 5 min, and then 5.5 g (24.8 mmol) of carbinol **3** in 60 mL of methylene chloride was added. After 1 h at ambient temperature, the reaction was quenched and a methylene chloride solution of **9c** was obtained as described for the preparation of **9a**. The methylene chloride was removed under reduced pressure to give 6.0 g of a crude yellow viscous oil **9c** (which was used without further purification in the subsequent ring closure): IR (neat) 3466, 3332, 1599 cm^{-1}; ^{1}H NMR δ 2.06 (s, 3 H, CH_3), 3.05 (s, 3 H, $NHNH_2$ exchanged by D_2O), 6.95 (s, 2 H, HC=CH), and 6.85–7.81 (m, 8 H, Ar); ^{13}C NMR (at 0 °C) δ 22.9 (CH_3), 64.1 (C-5), 126.7, 126.8, 128.8, 129.8 and 131.1 (8 H bearing Ar C and C-10, C-11), 133.2 (C-9a and C-11a), and 139.2 (C-4a and C-5a).

5-Methyl-5-(benzoylhydrazino)-5*H*-dibenzo[*a*,*d*]cycloheptene (9d). The reaction of 5.0 g (22.5 mmol) of carbinol **3** with 12.24 g (90 mmol) of benzoylhydrazine and 9.64 mL (113 mmol) of dichloroacetic acid by the procedure for **9a** gave 7.15 g (93%) of a yellow viscous oil **9d**. An analytical sample was obtained by crystallization from methylene chloride/hexane: mp 127–131 °C dec; IR 3389, 3278, 1650 cm^{-1}; ^{1}H NMR δ 2.20 (s, 3 H, CH_3), 5.60–7.00 (br s, 2 H, NHNH), and 6.88–8.00 (m, 15 H, HC=CH and Ar). Anal. Calcd for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.06; H, 5.87; N, 8.15.

***syn*- and *anti*-12-Hydroxy-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (10a). Method A.** In a 250-mL three-necked flask equipped with a condenser, addition funnel, and thermometer were placed 4.76 g (42.2 mmol) of potassium *tert*-butoxide and 50 mL of 10% DMSO/toluene. The mixture was heated to 55 °C, and a solution of 10.0 g (42.2 mmol) of hydroxylamine **9a** in 50 mL of 10% DMSO/toluene was added. After the addition was completed, the solution was removed from the heat and the reaction quenched with 50 mL of water. The aqueous layer was separated and back-washed with 20 mL of toluene to which 5 mL of brine had been added. The organic layer was washed with 3 × 50 mL of water and 50 mL of brine. Each successive aqueous layer was back-washed with the initial 20 mL of toluene.[35] The two organic layers were combined and extracted with 3 × 33 mL of a 1:1 (v/v) solution of 1.2 M hydrochloric acid/glacial acetic acid. The acid layers were combined, treated with charcoal, and filtered. The acidic solution of **10a** was used in the subsequent hydrogenolysis. A sample of **10a** was isolated by basification of a portion of the concentrated acid layer, extraction into methylene chloride, and crystallization of the concentrated extract with hexane to give **10a**: mp 138–141 °C (lit.[2] mp 145–147 °C); ^{1}H NMR (syn conformer) δ 1.98 (s, 3 H, CH_3), 2.80 (d, 1 H, *endo*-CH_2), 3.65 (d of d, 1 H, *exo*-CH_2), 4.65 (d, 1 H, CH), 7.05 (m, 8 H, Ar), and 8.40 (br s, 1 H, NOH), (selected data for the minor anti conformer) δ 2.00 (s, 3 H, CH_3), 2.50 (d, 1 H, *endo*-CH_2), 3.55 (d of d, 1 H, *exo*-CH_2), and 4.75 (d, 1 H, CH).

Method B. In a three-necked flask fitted with a condenser and magnetic stirrer was placed 400 mL of toluene. The solvent was degassed, 10.0 g (0.042 mol) of **9a** was added, and then the solution was refluxed overnight, concentrated in vacuo to one-fourth of its original volume, and extracted with 3 × 50 mL of 1 N HCl. The aqueous layers were combined, made basic (pH 8), and extracted with 3 × 50 mL of methylene chloride. The organic layers were combined and dried over sodium sulfate, and the solvent was removed under reduced pressure. The resulting oil crystallized from methylene chloride/hexane to give 6.9 g (69%) of **10a**. Both ^{1}H NMR data and the melting point were in

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(35) It was essential to remove trace amounts of DMSO to avoid catalyst poisoning in the subsequent step.

agreement with literature values.[2]

Isolation of 5-Methyl-5*H*-dibenzo[*a*,*d*]cycloheptene (11). A portion of the toluene layer after acid extraction from the preceding reaction was chromatographed with 10% ethyl acetate/hexane as eluant, and **11** was isolated as a white crystalline compound. ^{1}H NMR spectral data were in agreement with literature values.[36]

***syn*- and *anti*-12-Methoxy-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (10b).** The reaction of 1.0 g (3.98 mmol) of methoxyamine **9b** with 0.45 g (3.98 mmol) of potassium *tert*-butoxide by method A for preparation of **10a** gave, after heating for 15 min, 0.65 g (65%) of **10b**, a white crystalline solid (isolated from the concentrated toluene extract followed by crystallization from hexane): mp 87–88 °C; IR (neat) 1472, 1450, 1039 cm^{-1}; ^{1}H NMR (syn conformer) δ 1.90 (s, 3 H, CH_3), 2.44 (d, 1 H, J = 17, *endo*-CH_2) 3.24–3.74 (m, 1 H, *exo*-CH_2), 3.62 (s, 3 H, OCH_3), 4.17 (d, 1 H, J = 5 Hz, CH), and 6.54–7.42 (m, 8 H, Ar), (anti conformer) δ 1.94 (s, 3 H, CH_3), 2.74 (d, 1 H, J = 17, *endo*-CH_2), 3.24–3.74 (m, 1 H, *exo*-CH_2), 3.56 (s, 3 H, OCH_3), 4.17 (d, 1 H, J = 5, CH), and 6.54–7.42 (m, 8 H, Ar). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.31; H, 6.92; N, 5.32.

***syn*- and *anti*-12-Amino-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (10c).** The reaction of 4.0 g (16.9 mmol) of hydrazine **9c** with 1.91 g (16.9 mmol) of potassium *tert*-butoxide (method A) gave 4.0 g of **10c** as a crude, yellow viscous oil (isolated from the dried concentrated toluene extract), which was used without further purification in the subsequent conversion to **1a**: IR (neat) 3322, 1597 cm^{-1}; ^{1}H NMR (syn conformer) δ 1.82 (s, 3 H, CH_3), 2.51 (d, 1 H, J = 18, *endo*-CH_2), 3.50 (d of d, 1 H, J = 18, J = 6, *exo*-CH_2), 3.22 (s, 2 H, NH_2, exchanged by D_2O), 4.42 (d, 1 H, J = 6, CH), and 6.63–7.50 (m, 8 H, Ar); ^{15}N NMR (at −5 °C; CH_2Cl_2/CD_2Cl_2, 1/1) δ 30.8 (NH_2); ref NH_4Cl, δ_N 0.

***syn*- and *anti*-12-(Benzoylamino)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (10d).** The reaction of 0.50 g (1.47 mmol) of hydrazide **9d** with 0.20 g (1.77 mmol) of potassium *tert*-butoxide in DMSO at 110 °C for 15 h (method A) gave 0.42 g (84%) of a white crystalline solid **10d** (isolated from the concentrated ethyl acetate/toluene extract and crystallized from hexane/methylene chloride): mp 216–218 °C dec; IR 3306, 1678 cm^{-1}; ^{1}H NMR (syn conformer) δ 1.86 (s, 3 H, CH_3), 2.60 (d, 1 H, J = 17, *endo*-CH_2), 3.43 (d of d, 1 H, J = 17, J = 5, *exo*-CH_2), 4.69 (d, 1 H, J = 5, CH), and 6.64–7.84 (m, 14 H, NHCO and Ar). Anal. Calcd for $C_{23}H_{20}H_2O$: C, 81.23; H, 5.92; N, 8.23. Found: C, 81.14; H, 5.90; N, 8.11.

***syn*- and *anti*-12-Hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (14).** In a three-necked flask equipped with a stirrer, condenser, addition funnel, and thermometer was placed 50.0 g (0.224 mol) of 5*H*-hydroxylamine **13** in 750 mL of dry THF (dried over sodium benzophenone ketyl). The solution was warmed to 60 °C, and 112 mL of 2.4 M *n*-butyllithium in hexane followed by 3.2 mL of DMSO was added dropwise. The solution was refluxed for 2.5 h and then quenched with a solution of 3.5 g of potassium carbonate in 300 mL of water. The organic layer was separated and washed with 300 mL of water. The aqueous layers were combined and washed with 3 × 300 mL of diethyl ether. All organic layers were combined, washed with 300 mL of brine, dried over sodium sulfate, and filtered, and the solvent was removed under reduced pressure. The resulting crude solid was recrystallized from methylene chloride/hexane to give 38.9 g (78%) of **14** as a white crystalline solid: mp 178–180 °C dec; IR 3580, 3128 (br) cm^{-1}; ^{1}H NMR (anti conformer) δ 2.70 (d, 1 H, J = 17, *endo*-CH_2), 3.47 (d of d, 1 H, J = 17, J = 6, *exo*-CH_2), 4.53 (m, 1 H, H-10), 4.90 (s, 1 H, H-5), 6.55–7.40 (m, 8 H, Ar), and 8.05 (s, 1 H, NOH, exchanged by D_2O), (minor syn conformer) δ 2.40 (d, 1 H, J = 17, *endo*-CH_2), 3.47 (d of d, 1 H, J = 17, J = 6, *exo*-CH_2), 4.53 (m, 1 H, H-10), and 4.85 (s, 1 H, H-5); ^{13}C NMR (selected data for anti conformer) δ 34.4 (C-11), 70.5 (C-5), 74.3 (C-10), 130.9, 138.8, 140.1 and 146.5 (substituted aromatic C-4a, C-5a, C-10a, and C-11a), (syn conformer) δ 27.4 (C-11), 64.2 (C-5), 69.4 (C-10), 132.2, 136.6, 139.5 and 144.6 (substituted aromatic C-4a, C-5a, C-10a, and C-11a) (syn/anti = 1/3). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.66; H, 5.84; N, 6.16.

(±)-5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (1a). Method A. The acidic filtered solution of **10a** (42.4 mmol, based on 100% conversion of **9a** to **10a**) was brought to a total volume of 120 mL with 1:1 (v/v) 1.2 M HCl/glacial acetic acid and placed in a Parr shaker bottle. To the solution were added 5.4 g (61 mmol) of sodium acetate and 1.0 g (10% by weight) of 5% palladium on carbon. The mixture was shaken under 40 psi of hydrogen pressure at 60 °C for 3 h. The reaction mixture was degassed and filtered and the filtrate concentrated to one-half its original volume. Ice water was added to the filtrate and the resulting solution made basic with concentrated ammonium hydroxide (pH 8). The basic solution was extracted with 3 × 50 mL of methylene chloride, and the combined extracts were washed with 50 mL of brine, dried over Na_2SO_4, and filtered. Solvent removal from the filtrate under reduced pressure gave 8.4 g (90%) of **1a**: mp 77–85 °C. Spectral and chromatographic data for this material, as well as that produced by the following methods, were in agreement with literature values.[2]

Method B. Methoxyamine **10b** (0.25 g, 1.0 mmol) in 1.0 mL of 1.2 M HCl with 3.5 mL of glacial acetic acid was hydrogenolyzed for 15 h with 5% palladium on carbon (0.05 g, 20% by weight) as described in method A above, to give 0.2 g (94%) of **1a**.

Method C. Hydrazine **10c** (0.5 g, 2.12 mmol) was dissolved in 12 mL of aqueous 8.7 M acetic acid and heated at 65 °C for 15 h under 40 psi of hydrogen with 5% palladium on carbon (0.3 g, 60% by weight). Isolation of the product as described in method A gave 0.3 g (64%) of **1a**.

10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (1b). In a Parr shaker was placed 38.5 g (0.173 mol) of ring-closed 5*H*-hydroxylamine **14** in 400 mL of glacial acetic acid and 10 mL of concentrated HCl. The mixture was charged with 11.55 g (30% by weight) of 5% palladium on carbon and shaken under 40 psi of hydrogen pressure at 60 °C for 1.5 h, and then it was degassed, filtered, and concentrated to one-half its original volume. To the concentrated filtrate was added 150 mL of water, and the filtrate was made strongly basic with concentrated ammonium hydroxide and extracted with 3 × 300 mL of methylene chloride. The combined organic layers were dried over potassium carbonate, filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from CH_2Cl_2/petroleum ether to give 29.5 g (89%) of **1b**: mp 111.5–114 °C (lit.[6a] mp 120 °C). ^{1}H NMR and ^{13}C NMR spectra were in agreement with the assigned structure.

Acknowledgment. We thank Jack L. Smith for the mass spectral measurements, Jane T. Wu for the elemental analyses, Jordan Hirshfield (deceased) for the X-ray analysis of **5**, and Drs. W. Jones and R. Firestone for valuable discussions. The secretarial assistance of M. Spears is gratefully acknowledged.

Supplementary Material Available: Tables showing fractional crystallographic coordinates and temperature factors, bond lengths, and bond angles for **5** (3 pages). Ordering information is given on any current masthead page.

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