according to procedure A, afforded pure *n*-octylamine, 11.4 g (88% yield).

Registry No. I, 14937-45-2; *n*-octyl azide, 7438-05-3; *tert*-butyl 2-chloro-2-phenylacetate, 40058-90-0; *sec*-octyl azide, 22513-48-0; benzyl azide, 622-79-7; phenyl azide, 622-37-7; 1-naphthyl azide, 6921-40-0; toluenesulfonyl azide, 941-55-9; *tert*-butyl 2-azido-2-phenylacetate, 82430-95-3; *n*-octylamine, 111-86-4; *n*-hexadecylamine, 143-27-1; *sec*-octylamine, 693-16-3; benzylamine, 100-46-9; aniline, 62-53-3; 1-naphthylamine, 134-32-7; toluenesulfonamide, 70-55-3; phenylglycine, 69-91-0; *n*-octyl methanesulfonate, 16156-52-8; *n*-octyl bromide, 111-83-1; *n*-hexadecyl bromide, 112-82-3; *sec*-octyl bromide, 557-35-7; benzyl chloride, 100-44-7; *n*-hexadecyl azide, 66143-67-7; sodium borohydride, 16940-66-2; trioctylmethylammonium chloride, 5137-55-3; 2-chloro-2-phenylacetic chloride, 2912-62-1; *tert*-butyl alcohol, 75-65-0; sodium azide, 26628-22-8.

Synthesis and Stereochemistry of 11-Substituted 5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclooctenes

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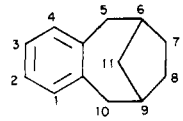
5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclooctene is a ring system where the cyclooctene ring could exist either in a boat or in a chair conformation. Molecular modeling calculations indicated that the boat conformation is the favored conformation when position 11 is substituted by a ketone group, an amino group, or a hydroxy group. NMR shift reagent studies have shown that these same derivatives exist in this boat conformation. The same studies have also demonstrated that chemical modifications of carbon-11 transforming it from a sp^2 to sp^3 (i.e., reduction of carbonyl to alcohol) give rise to endo derivatives exclusively. Attempts to obtain the exo derivatives by displacement reactions of sulfonates or Ritter reactions were unsuccessful. The only exo derivative obtainable was the 11-*exo*-amino-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene, isolated in low yields from the base-catalyzed equilibration of its *N*-benzylidene derivative.

Introduction

The 5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene ring system 1 is a somewhat poorly studied system



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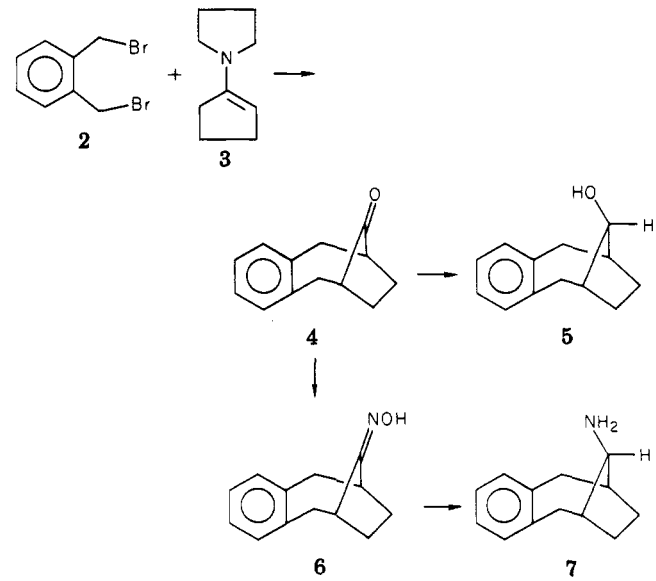
as compared to the other isomeric systems, such as the 5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene (which is the backbone of the benzomorphan analgesics). In our laboratories, we decided to investigate this system for the development of novel analgesics. For this purpose, the stereochemistry of the substituent on the methano part (carbon-11) was of great importance, and great care was taken to ensure the endo orientation of this group. Also, it was imperative that the ring system should adopt a boat conformation, since the distance between substituents at carbon-2 and -11 was critical to our requirements. Should the preferred conformation be a chair, the distance would be completely different, and it is well known that the relative positions of the basic nitrogen and phenol are very critical in potent analgesics.[1,2]

Therefore, we present here the data we have obtained on this system, which extends the observations Hahn and Jatczak[3] have obtained recently on this ring system.

Scheme I



Results and Discussion

A. Preparation of Derivatives of 5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclooctene. We carried out the preparation of 11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (4) according to Opitz and Mildenberger[4] by reacting *o*-xylidene dibromide **2** with the pyrrolidine enamine of cyclopentanone **3** in acetonitrile,

(1) B. Belleau, T. Conway, F. R. Ahmed (*London*) and A. D. Hardy, *J. Med. Chem.*, **17**, 908 (1974).
(2) A. S. Horn and J. R. Rodgers, *Nature* (*London*) **260**, 797 (1976).
(3) W. E. Hahn and M. Jatczak, *Pol. J. Chem.*, **53**, 1221 (1979).
(4) G. Opitz and H. Mildenberger, *Justus Liebigs Ann. Chem.*, **650**, 115 (1961).

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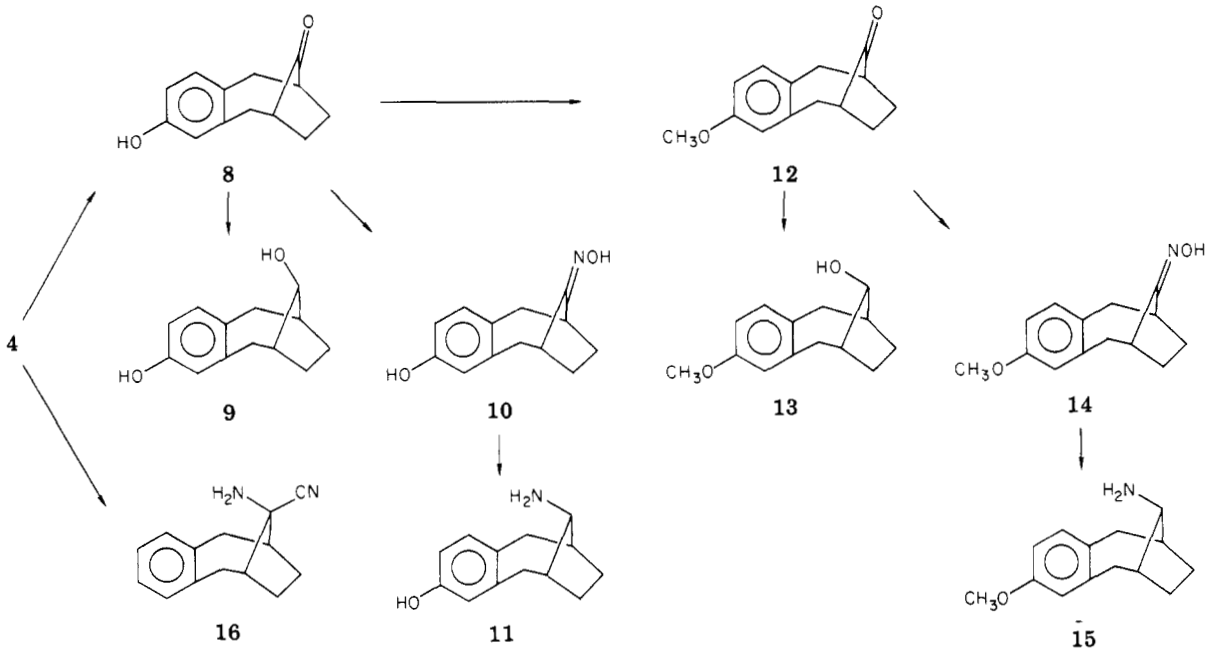
Scheme II



then hydrolyzing the resulting salts according to the method of Stork.[5] This preparation is amenable to large-scale preparations, and, in our hands, the desired ketone **4** could be isolated from the crude reaction mixture by distillation in vacuo.

The resulting ketone **4**, when reduced by sodium borohydride in methanol, gave excellent yields of the *endo*-11-hydroxy-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (**5**). The corresponding amine **7** was prepared by the catalytic hydrogenation of the oxime **6** with Adams' catalyst in acetic acid. Scheme I outlines these preparations.

For the introduction of substituents on the aromatic ring, two different routes have been used. The first involves the direct hydroxylation of the aromatic ring following the experimental conditions developed by Taylor et al.[6] Thus, thallation of **4** was considered as a feasible reaction, since the ketone is not enolisable and, therefore, the oxidative complications arising for enolization of ketones are avoided. Treatment of **4** with thallium trifluoroacetate in trifluoroacetic acid at room temperature for 18 h gave rise to a thallium intermediate, and further oxidation with lead tetraacetate led to a 72% yield of 2-hydroxy-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (**8**). No 1-hydroxy isomer was detected, probably due to its further oxidative degradation by the thallium salts.

This procedure was modified further by following the indications of Campbell et al.,[7] who reported that lead tetraacetate in trifluoroacetic acid can itself hydroxylate aromatic rings, albeit in relatively low yields. However, in our hands, the lead tetraacetate oxidation gave rise to yields of up to 64% of **8** when carried out in trifluoroacetic acid at room temperature for 2–3 days.

When **8** was reacted with sodium borohydride, the corresponding endo alcohol **9** was isolated in 87% yield, and equally the hydrogenation of the oxime of **8** led to an excellent yield of the amine **11**.

The methyl ether of **8** was easily prepared via a dimethyl sulfate/potassium carbonate etherification, and, similarly, $NaBH_4$ reduction and hydrogenation of the oxime gave rise to the corresponding alcohol **13** and amine **15**, again of the same endo stereochemistry.

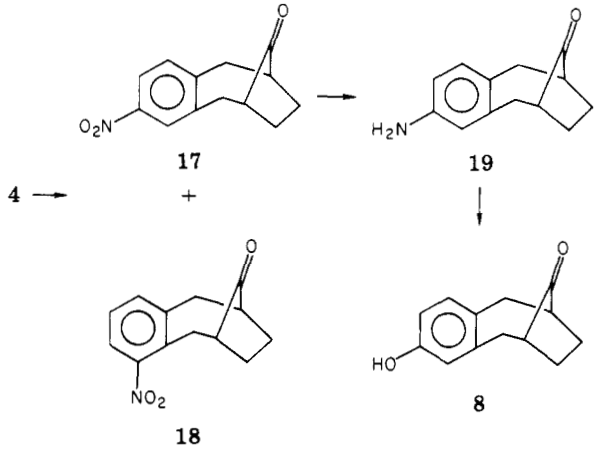
Finally, a Strecker reaction on **4** led to excellent yields of the amino nitrile derivative **16**. Based on the reaction mechanism of the Strecker reaction,[8] the most likely conformation at C-11 is 11-*endo*-amino-11-*exo*-nitrile.

These preparations are listed in Scheme II.

Another method for preparing the 2-hydroxy derivative is described in Scheme III and involves as the key step the nitration of **4**. Thus, when ketone **4** is added to 90% nitric acid cooled at −20 °C, the reaction mixture was found to consist of two isomeric nitration products. Recrystallization of the mixture from methylene chloride–hexane gives rise to 58% of the 2-nitro derivative **17**, readily characterized by its typical NMR absorptions of the aromatic protons.

Chromatography of the mother liquors on silica gel allowed the isolation of 15% of the 1-nitro isomer **18**.

Scheme III



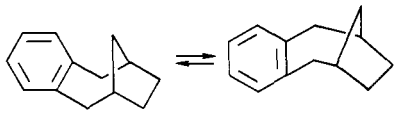
(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).
(6) E. C. Taylor and H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *J. Am. Chem. Soc.*, **92**, 3520 (1970).
(7) J. R. Campbell, J. R. Kalman, J. T. Pinhey, and S. Sternhell, *Tetrahedron Lett.*, 1763 (1972).
(8) D. T. Mowry, *Chem. Rev.*, **42**, 236 (1948).

Table I

compd	ΔE ($E_{boat} - E_{chair}$), kcal/mol: classical	CNDO
4	1.66	2.43
9	3.84	4.00
11	6.38	10.73
11 protonated	7.23	11.93
23	6.19	6.83
23 protonated	6.07	7.87

The nitro derivative, 17, was then converted to its corresponding hydroxy derivative, 8, by reduction of the nitro group to the amine 19, followed by a diazotization reaction and treatment with aqueous sulfuric acid.

B. Stereochemistry of the System. There is a possibility of two conformers for the 5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene system (1), the chair form or the boat form for the cyclooctene ring.



Since the boat form was critical for the design of our target compounds, its relative stability was examined thoroughly with the Merck Molecular Modeling System (MMMS).[9]

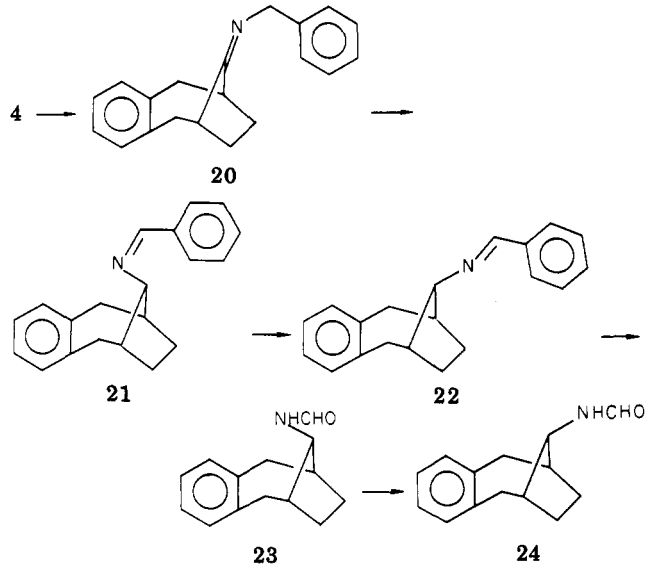
The relative energies of derivatives, such as the ketone 4, the hydroxy derivative 9, or the amine 7, were determined by either the classical method[10] or by the CNDO/2 method.[11] The results are summarized in Table I.

These results, either obtained from the classical calculations or the CNDO calculations, indicate that the boat conformation is favored. ΔE values favoring the boat conformation range from 1.6 to 12. There is a certain discrepancy between the two methods of calculation, but the fact that they both give values of the same direction is considered to be a good indication that the cyclooctene ring should adopt a boat conformation.

C. Stereochemistry of the Functionality at C-11. When sodium borohydride in methanol was used, the reduction of 4 was found to give only one isomer, predicted to be the endo isomer, based on the work of Hahn[3] and of several others.[12-14] Similarly, 2-hydroxy-11-oxo-5,6,7,8,9,10-hexahydrobenzocyclooctene (8) and 2-methoxy-11-oxo-5,6,7,8,9,10-hexahydrobenzocyclooctene (12) led to the corresponding endo alcohols 9 and 13; no epimeric alcohol could be detected in any of these reductions. This is in agreement with the previous work cited above: i.e., reduction of the bridgehead carbonyl in the bicyclo[4.2.1]nonene system always yields almost exclusively the alcohol endo to the 4-chain part of the cycle. This is easily shown on examination of the molecular models, which indicates the hydride attack is nearly impossible from the benzene side or from the 4-carbon part of the ring system.

Several attempts were made to reduce the carbonyl group with reducing agents other than sodium borohydride, and similar results were obtained. Thus, catalytic hydrogenation in ethanol with Adam's catalyst gives exclusively the *endo*-hydroxy isomer. Also reduction by sodium in alcohol, known to favor production of the most stable alcohol products, gave only endo alcohol.

Scheme IV



All three alcohols 5, 9, and 13 have in their NMR spectra a triplet for the hydrogen on carbon-11, again in agreement with Dias and Fulcher[13] for endo alcohols of the bicyclo[4.2.1]nonane system.

Several attempts were made to invert the configuration at C-11. Thus, the mesylate of 9 was prepared, and several attempts to displace it with acetate or azide in DMF at 90 °C overnight showed no reaction at all. Increasing the reaction temperature to 185 °C resulted only in decomposition, as evidenced by the complex TLC.

Attempts using the more reactive triflate of 9 were also unsuccessful, and treatment with azide ion resulted only in hydrolysis to the monotriflate. Similar results were obtained in the Ritter reaction when the alcohol 5 was treated with acetonitrile in sulfuric acid. No displacement could be observed in our hands, and rearrangement of the skeleton was never detected.

The amine derivatives also have the same stereochemistry, since the catalytic reduction of the oxime is subject to similar steric constraints as is the reduction of the ketone to the alcohol. These amines also have in common in their NMR spectrum the triplet for the CH of carbon-11.

However, from the ketone, it is possible to try to equilibrate the amino group via the Schiff's base with benzylamine, by the method of Richer and Perelman[15] (Scheme IV). Despite the fact that this equilibration scheme is reported to not work well on cyclopentane derivatives, we felt that, as in the 4,2,1 system, the bridging position is not enolisable and, also being part of a seven-membered ring, this procedure could be successful. Thus, the equilibration was carried out in Me_2SO with potassium *tert*-butoxide as base. After hydrolytic workup, formylation of the resulting amines, and careful purification of the *N*-formyl derivatives, we were able to isolate a small amount (5%) of the *exo*-*N*-formyl derivative. Its stereochemistry was easily assigned as exo by the NMR absorption for CH on carbon-11 appearing at 4.00 ppm as a singlet. This is in agreement with previous reports[13] and also with the dihedral angle of 90° observed in the molecular model.[16]

(9) P. Gund, J. D. Andose, J. B. Rhodes, and G. M. Smith, *Science*, 208, 1425 (1980).
(10) R. H. Boyd, S. M. Breitlinger, and M. Mansfield, *AIChE J.*, *19*, 1016 (1973).
(11) J. Pople and D. Beveridge, "Approximate Molucular Orbital Theory", McGraww-Hill, New York, 1970.
(12) T. S. Cantrell and H. Shechter, *J. Am. Chem. Soc.*, 85, 3300 (1963).
(13) A. Dias and J. Fulcher, *J. Am. Chem. Soc.*, 98, 798 (1976).
(14) A. Dias and J. Fulcher, *J. Am. Chem. Soc.*, 96, 7954 (1974).
(15) J. C. Richer and D. Perelman, *Can. J. Chem.*, 48, 570 (1970).

Table II

	slope: $\Delta\delta$ vs. g of $Eu(fod)_3$										
compd	H_1	H_2	H_3	H_4	H_{5e}	H_{5a}	H_6	H_7	H_8	H_{11}	OCH_3
4	9.4	9.4	9.4	9.4	17.1	33.6	43.1	16.9	13.8		
5	11.1	11.1	11.1	11.1	32.2	75.6	50.0	19.7	19.7	100.0	
13	22.1		12.7	19.3	40.8	89.2	59.1	27.7	23.4	115.2	7.5
7	10.5	10.5	10.5	10.5	27.5	59.4	49.0	19.6	19.6	84.3	
15	12.0		8.0	12.0	30.5	54.5	50.5	18.0	18.0	84.0	5.5
16	8.0	8.0	8.0	8.0	22.3	29.3	43.7	28.7	16.6		

The exceptional environment around the C-11 carbon appears to be responsible for the results obtained in the course of this work. Thus, when C-11 is an sp^2 carbon, the axial hydrogens on C_5 and C_{10} block the approach of nucleophiles (in the boat conformation), and attack from the least-hindered face gives rise to 11-endo products. If the conformation of the system were a chair, then the aromatic ring would equally block the endo approach of nucleophiles, and attack would occur from the exo face.

In the case of attempted displacement reactions, we consider that the reactions fail due to the development of severe steric interactions in the transition state between the leaving group and the axial 5a and 10a protons, which serves to raise the energy of activation sufficiently to prevent completion of the displacement. Some indications of the degree of steric crowding on the endo face of the system can be derived from the molecular modeling calculations, which show that the endo alcohol **5** has a ground-state energy 3.1 kcal/mol higher than the corresponding exo epimer (33.5 vs. 30.4 kcal/mol). This increase in energy is felt to arise mainly from interactions between the two pseudoaxial benzylic protons and the hydroxy group.

D. Shift Reagent Studies. In order to prove their stereochemistry, we undertook a shift reagent study, using $Eu(fod)_3$, on ketone **4**, on alcohols **5** and **13**, and on amines **7** and **15**, as well as on the amino nitrile **16**. The results are summarized in Table II.

These results are the slopes of the straight lines obtained by plotting $\Delta\delta$ vs. g of $Eu(fod)_3$ added, and the steeper the slope the closer is the proton influenced by the shift reagent.[17,18]

For the ketone **4**, the greatest shifts are observed for protons 6, those bridgehead protons being the closest in this molecule. They are followed very closely by H_{5a}, with a slope of 33.6. The great difference between H_{5e} and H_{5a} clearly indicates that the overall conformation is a boat conformation for the cyclooctene ring. The distance between the oxygen and H_{5a} is 3.0 Å when the conformation is a boat, and the corresponding distance for H_{5e} is 4.1 Å. When the ring is in the chair conformation, the distance O–H_{5e} remains the same, but the distance O–H_{5a} changes to 3.9 Å. Such a conformation would lead to a similar slope for **5a** and **5e**, which is not in agreement with the results obtained on ketone **4**. Thus, the conformation for ketone **4** is a boat conformation, in agreement with the modeling studies.

The alcohols **5** and **13** show a greater ability to complex with the shift reagent, with the slope for the bridgehead protons being 50.0 and 59.1 vs. 43.1 for ketone **4**. Also, with the H_{11} proton being the closest, it has a large slope, 100.0 for **5** and 115.2 for **13**. The large differences between the slopes of H_{5e} and H_{5a} are again an indication that the cyclooctene ring is a boat conformation.

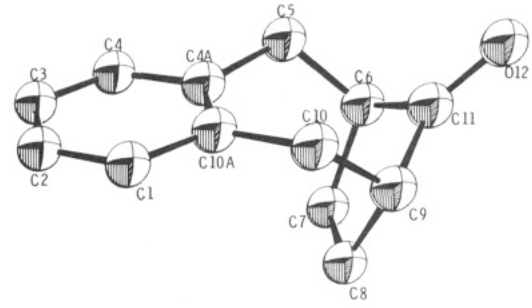


Figure 1. Perspective drawing of compound **4**.

The amines **7** and **15** show a similar pattern and lead to a similar conclusion.

The amino nitrile **16** led to different results when complexed with $Eu(fod)_3$. Good complexation occurs as evidenced by the pronounced shift of the proton H_6. However, the difference between H_{5e} and H_{5a} is small. This could be interpreted to suggest that the molecule adopts a chair conformation. However, based on our previous energy calculations on **11**, this would seem to be unlikely. A more likely explanation of these results is the following: since the amino nitrile **16** is a molecule with two functional groups and can therefore act as a bidendate ligand, the complexation could occur in such a manner that the europium would be in a position different than that found in the previous monofunctional derivatives. Examination of molecular models indicates that in such a complex the distance between the europium atom and H_{5e} and H_{5a} is approximately equal.

E. Single-Crystal X-ray Analysis of 4. A crystal X-ray analysis was obtained on ketone **4**, and Figure 1 contains a perspective drawing of **4** derived from the X-ray results.[19] This X-ray analysis of **4** clearly proves the boat conformation of the cyclooctene ring, and a comparison between this result and the refined structure obtained from the computer work shows an exact fit for the two structures. A similar conformation for the cyclooctene ring was also found in a derivative of amine **11**.[20]

Conclusion

Our results have shown that the 11-substituted 5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctenes exist in a boat conformation, as proven by shift reagent studies, by molecular modeling studies, and by an X-ray analysis of ketone **4**. The unusual reactivity at position 11 in reactions involving addition to an sp^2 center or displacement on an sp^3 center is probably due to the two axial benzylic hydrogens, H_{5a} and H_{10a}. Their position in this rigid system prevents the approach on the endo side and they

(16) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(17) P. Bélanger, C. Freppel, D. Tizane, and J. C. Richer, *Chem. Commun.*, 266 (1971).
(18) P. Bélanger, C. Freppel, D. Tizane, and J. C. Richer, *Can. J. Chem.*, **49**, 1985 (1971).
(19) The following library of crystallographic programs was used: MULTAN 78, University of York, York, England (1978); Structure Determination Package V17.0, Enraf-Nonius Corp., Delft, Holland (1980); ORTEP-II, Oak Ridge National Laboratory, Oak Ridge, TN (1970).
(20) P. Bélanger, J. Scheigetz, C. Dufresne, R. N. Young, and J. P. Springer, unpublished results.

also effectively prohibit the departure of leaving groups from the endo side. By equilibration of the Schiff's base in basic dimethyl sulfoxide, a small percentage of the exo amine was isolated, and its exo relationship was proven unambiguously by NMR. In this system, this was the first exo derivative ever reported.

Experimental Section

Melting points were taken on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 267 grating spectrophotometer and were recorded as KBr disks unless otherwise noted. A Varian EM-360 spectrometer was used to record NMR spectra in deuteriochloroform unless indicated otherwise. Proton chemical shifts are relative to tetramethylsilane as internal standard. Elemental analyses were performed by Dr. C. Daesslé of Montreal or by Galbraith and Associates, Knoxville, TN. The low-resolution mass spectral analyses were performed by the Morgan-Schaffer Corp., Montreal.

All reactions, as well as column chromatography, were monitored routinely with the aid of thin-layer chromatography (TLC) with precoated 0.25-mm silica gel plates (Eastman Kodak) or silica gel GF plates (Analtech).

11-Oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (4). was prepared as reported by Opitz et al.[4] and had a mp of 90–91 °C (lit.[4] mp 90–91 °C).

2-Hydroxy-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (8). (a) Thallium Method. 11-Oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (4; 5 g, 26.8 mmol) and thallium trifluoroacetate (19 g, 35 mmol) were dissolved in trifluoroacetic acid (150 mL) (TFA) and stirred overnight under N_2 at room temperature. Lead tetraacetate (15.5 g) in TFA (10 mL) was then added, and the mixture was stirred for 1 h at room temperature and then for 1 h at reflux. Triphenylphosphine (9.5 g) was added, and the mixture was stirred for 15 min. After evaporation of the solvent, 6 N hydrochloric acid (300 mL) was added, and the mixture was stirred for 10 min. The solids were filtered and washed with methylene chloride.

The aqueous layer was further extracted with methylene chloride, and the combined organic layers were extracted several times with 3 N sodium hydroxide. The aqueous layer was acidified with 6 N hydrochloric acid, and the mixture was extracted with methylene chloride, and the organic phase was washed with brine, dried (Na_2SO_4), and evaporated to yield 3.9 g (72%) of 8: mp 183–185 °C; IR 3350 (OH), 1730 (C=O) cm^{-1}; NMR (Me_2SO-d_6) δ 1.25–1.75 (4 H, m, CH_2 of C_7 and C_8), 2.3–3.0 (6 H, m, bridgehead and benzylic protons), 6.67 (2 H, m, H_1, and H_3), 7.03 (1 H, d, J = 8 Hz, H_4), 9.20 (1 H, s, exchanged by D_2O, OH). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.49; H, 7.13.

(b) Lead Tetraacetate Method. Lead tetraacetate (300 g, 0.88 mol) was dissolved in trifluoroacetic acid (2 L) and cooled at 0 °C. The ketone 4 (100 g, 0.54 mol) was added, and the mixture was stirred for 2 days at room temperature. The solution was evaporated to dryness. To the residues were added 1.6 L of 6 N hydrochloric acid and 800 mL of CH_2Cl_2, and the solution was stirred for 15 min. The suspension was filtered, and the solids were washed with methylene chloride. The phases were separated, and the aqueous phase was extracted 3 times with methylene chloride. The organic fractions were combined, dried (Na_2SO_4), and concentrated. The oil was treated as previously described to yield 85 g of crude 8, which after recrystallization from ethyl acetate (10 mL per gram) yielded 70 g (64%) of phenol 8, mp 183–185 °C.

1- and 2-Nitro-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (18 and 17). To 90% nitric acid (328 mL) cooled to −35 °C was added ketone 4 (59 g, 0.32 mol) in portions over 20 min. The mixture was gradually brought up to −20 °C over 1 h. At this point all the material had dissolved. The mixture was poured into ice and water. The precipitate was filtered and washed well with water, and this solid was recrystallized from methylene chloride–hexane to give 38 g of 17, mp 145–146 °C.

The mother liquors (24 g) were chromatographed on silica gel, and elution with ether–hexane (4:6, v/v) yielded 11 g (15%) of the isomeric 18, mp 128–130 °C, as well as 4.7 g of 17, for an overall yield of 58% for 17.

18: IR 1740 (C=O), 1520 (NO_2) cm^{-1}; NMR δ 1.30 (2 H, m, endo H_7 and H_8), 1.93 (2 H, m, exo H_7 and H_8), 2.60 (1 H, d, J = 15 Hz, axial H_{10}), 2.67 (2 H, m, bridgehead H_6 and H_9), 2.93 (1 H, d, J = 15 Hz, axial H_5), 3.13 (1 H, d of d, J = 8 and 15 Hz, equatorial H_5), 3.33 (1 H, d of d, J = 8 and 15 Hz, equatorial H_{10}), 7.40 (2 H, m, H_3 and H_4), 7.63 (1 H, d of d, J = 2 and 8 Hz, H_2); UV λ_{max} 252 nm (log ϵ 3.96).

17: IR 1740 (C=O), 1520 (NO_2) cm^{-1}; NMR δ 1.0–2.0 (4 H, m, CH_2 of C_7 and C_8), 2.60 (2 H, m, bridgehead protons), 3.00 (4 H, m, benzylic CH_2), 7.37 (1 H, d, J = 8 Hz, H_4), 8.03 (1 H, d of d, J = 2 and 8 Hz, H_3), 8.13 (1 H, d, J = 2 Hz, H_1); UV λ_{max} 272 nm (log ϵ 3.78).

2-Amino-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (19). To 2-nitro-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (86 g, 0.37 mol) in tetrahydrofuran (1 L) was added stannous chloride dihydrate (285 g, 1.26 mol) in concentrated hydrochloric acid (950 mL) over a period of 15 min. The reaction mixture almost came to reflux and was then stirred for 1 h at room temperature. Most of the volatiles were removed in vacuo, and the residue, taken up in water, was made basic with 6 N sodium hydroxide. The resulting suspension was filtered through Celite and washed well with chloroform. The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated to yield crude 19, which was used without further purification: IR 3350 (NH_2), 1730 (C=O) cm^{-1}; NMR δ 1.0–2.0 (4 H, m, CH_2 of C_7 and C_8), 2.40–3.00 (6 H, m, bridgehead and benzylic protons), 3.70 (2 H, s, exchanged by D_2O, NH_2), 6.53 (2 H, m, H_1 and H_3), 6.93 (1 H, d, J = 8 Hz, H_4). Its hydrochloride salt melted at 360 °C. Anal. Calcd for $C_{13}H_{15}NO$·HCl: C, 65.68; H, 6.78; N, 5.89; Cl, 14.91. Found: C, 65.63; H, 7.20; N, 6.11; Cl, 14.85.

2-Hydroxy-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (8). 2-Amino-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (106 g, 0.53 mol) dissolved in 40% sulfuric acid (750 mL) was cooled to 0 °C, and sodium nitrite (44.6 g, 0.65 mol) in water (175 mL) was added dropwise over a 10-min period. The resultant solution was stirred for 15 min, and urea was added until all nitrous acid had been eliminated.

This diazonium solution was added to a mixture of sodium sulfate (190 g), sulfuric acid (140 mL), and water (140 mL) kept at 50–60 °C. Nitrogen evolution was abundant, and the phenol precipitated. When nitrogen evolution ceased, the mixture was cooled, and the solid was filtered, washed well with water, and air-dried to yield 91 g of crude 8. Recrystallized from ethyl acetate, 81 g (76%) of 8, mp 184–185 °C, was collected.

2-Methoxy-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (12). To 2-hydroxy-11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene 8 (2 g, 10 mmol) in acetone (50 mL) was added potassium carbonate (2.8 g, 20 mmol) and dimethyl sulfate (2.5 g, 20 mmol), and the mixture was stirred at room temperature overnight. The solids were filtered off and washed well with acetone. The filtrate was evaporated in vacuo, and the residue was purified by preparative HPLC, eluting with 5% ethyl acetate in hexane to yield 1.8 g (83%) of 12 as an oil, which crystallized on standing: mp 50–51 °C; IR 1735 (C=O) cm^{-1}; NMR δ 0.9–2.0 (4 H, m, CH_2 of C_7 and C_8), 2.40 (2 H, m, bridgehead protons), 2.83 (4 H, m, benzylic CH_2), 3.80 (3 H, s, CH_3O), 6.67 (2 H, m, aromatic H_1 and H_3), 7.07 (1 H, d, J = 8 Hz, H_4). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.43.

Preparation of 11-*endo*-Hydroxy Alcohols (5, 9, and 13). These alcohols were prepared by reducing the ketones 4, 8, and 12 with borohydride in methanol according to the procedure used by Hahn for 4.

Compound 5 was isolated in 86% yield and melted at 122–122.5 °C (lit. mp 119–120.5 °C).

Compound 9 was obtained in a 88% yield, and, after recrystallization from methanol–chloroform, melted at 205–210 °C: IR 3350 (OH) cm^{-1}; NMR δ 1.0–1.6 (4 H, m, CH_2 of C_7 and C_8), 2.0–2.5 (4 H, m, H_{5e}, H_6, H_9, H_{10e}), 3.30 (2 H, m, H_{5e}, H_{10e}), 4.17 (1 H, t, J = 6 Hz, H_{11}), 6.43 (2 H, m, H_1, H_3). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.25; H, 7.83.

Compound 13 was obtained in a 77%, and, on recrystallizing from hexane–ether, melted at 103–104 °C: IR 3350 (OH) cm^{-1}; NMR δ 1.0–1.60 (4 H, m, CH_2 of C_7 and C_8), 1.97 (1 H, s, D_2O exchanged, OH), 2.2 (4 H, m, H_{5e}, H_6, H_9, H_{10e}), 3.67 (3 H, s,

CH_3O), 4.13 (1 H, t, J = 6 Hz, H_{11}), 6.50 (2 H, m, H_1, H_3), 6.90 (1 H, d, J = 8 Hz, H_4). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.00; H, 8.45.

11-Oxime Derivatives of Ketones (4, 8, and 12). The oximes were prepared by heating for 15 min 1 g of ketone, 1 g of hydroxylamine hydrochloride in pyridine (4 mL), and ethanol (15 mL). The volatiles were removed in vacuo, and the residue was taken up in water to give a solid, which was recrystallized from methanol–water.

Thus, **6** was prepared in 92% yield and had a mp of 138–139 °C: IR 3300 (OH), 1680 (C=N) cm^{-1}; NMR δ 1.50 (4 H, m, H_7, H_8), 2.80 (6 H, m, H_5, H_6, H_9, H_{10}), 7.00 (4 H, s, aromatic), 9.40 (1 H, s, exchanged by D_2O, OH). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.60; H, 7.69; N, 6.81.

Similarly, **10** was prepared in 96% yield and melted at 90–95 °C: IR 3300 (OH); 1680 (C=N) cm^{-1}; NMR δ 1.37 (2 H, m, endo H_7, H_8), 1.70 (2 H, m, exo H_7, H_8), 2.90 (6 H, m, H_5, H_{10} and H_6, H_9), 5.03 (2 H, s, exchanged by D_2O, OH), 6.58 (2 H, m, H_1 and H_3), 6.97 (2 H, d, J = 8 Hz, H_4). Anal. Calcd for $C_{13}H_{15}NO_2 \cdot 1.5H_2O$: C, 63.91; H, 7.42; N, 5.73. Found: C, 63.44; H, 6.95; N, 5.20.

Oxime **14** was obtained in 95% yield and melted at 92–99 °C: IR 3250 (OH); 1675 (C=N) cm^{-1}; NMR δ 1.30 (2 H, m, endo H_7, H_8), 1.80 (2 H, m, exo H_7, H_8), 2.95 (6 H, m, H_5, H_{10} and H_6, H_9), 3.80 (3 H, s, CH_3O), 6.65 (2 H, m, H_1, H_3), 7.05 (1 H, d, J = 9 Hz, H_4), 10.25 (1 H, s, exchanged by D_2O, OH). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.63; H, 7.51; N, 6.10.

11-*endo*-Amino-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (7). 11-Oximino-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (**6**; 0.9 g, 4.5 mmol) in acetic acid (50 mL) was hydrogenated in a Parr hydrogenator at 20 psi for 2.5 h over platinum oxide (90 mg). The catalyst was filtered off, and the filtrate was evaporated to dryness. The residue was taken up in water, neutralized with sodium bicarbonate, and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4), and concentrated to yield 0.78 g (92.7%) of **7** as an oil: IR 3300 (NH_2) cm^{-1}; NMR δ 1.50 (4 H, m, H_7 and H_8), 2.30 (3 H, m, H_{5e}, H_{10e}, H_{11}), 2.60 (2 H, d, J = 7 Hz, H_{5a}, H_{10a}), 7.00 (4 H, s, aromatic). Its hydrochloride melted at 283–285 °C. Anal. Calcd for $C_{13}H_{17}N \cdot HCl$: C, 69.82; H, 8.11; N, 6.26; Cl, 15.85. Found: C, 69.85; H, 8.12; N, 6.52; Cl, 16.07.

Similarly, oxime **10** gave **11** in 94% yield. The free amine melted at 199–200 °C: IR 3400 (NH_2, OH) cm^{-1}; NMR δ 1.60 (4 H, m, H_7, H_8), 2.80 (6 H, m, H_5, H_6, H_9, H_{10}, H_{11}), 6.63 (2 H, m, H_1, H_3), 7.05 (1 H, d, J = 8 Hz, H_4). The hydrochloride melted at 169–170 °C. Anal. Calcd for $C_{13}H_{17}NO \cdot HCl$: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79. Found: C, 65.39; H, 7.55; N, 5.71; Cl, 14.94.

Oxime **14** yielded 97.6% of **15**: IR 3380 (OH) cm^{-1}; NMR δ 1.50 (4 H, m, H_7, H_8), 2.80 (7 H, m, H_5, H_6, H_9, H_{10}, H_{11}), 3.83 (3 H, s, CH_3O), 6.60 (2 H, m, H_1, H_3), 6.90 (1 H, d, J = 8 Hz, H_4). Its hydrochloride salt melted at 255–257 °C. Anal. Calcd for $C_{14}H_{19}NO \cdot HCl$: C, 66.26; H, 7.94; N, 5.51; Cl, 13.97. Found: C, 66.26; H, 8.07; N, 5.42; Cl, 13.80.

11-*endo*-Amino-11-cyano-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (16). 11-Oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (**4**; 1 g, 5.4 mmol), ammonium chloride (5 g), and sodium cyanide (0.5 g) were added to a mixture of concentrated ammonium hydroxide (10 mL) and methanol saturated with ammonia (150 mL). The mixture was left at 0 °C overnight. The resultant crystals were filtered, washed with water, and air-dried to give 1.2 g (98%) of **16**: mp 121–123 °C; IR 3370 (NH_2), 2220 (CN) cm^{-1}; NMR δ 1.30 (2 H, m, endo H_7, H_8), 2.00 (2 H, m, exo H_7, H_8), 2.50 (6 H, m, H_5, H_{10}, H_6, H_9), 7.00 (4 H, s, aromatic). Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 79.02; H, 7.60; N, 13.14.

11-*endo*-Formamido-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (23). 11-*endo*-Amino-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (**7**; 600 mg, 3 mmol) was dissolved in formic acid (5 mL), and formic acetic anhydride (1 mL) was then added. The mixture was stirred at room temperature for 2.5 h. Water was then added, and the mixture was evaporated to dryness. The residue was taken up in chloroform, washed with dilute HCl and with water, dried (Na_2SO_4), and concentrated in vacuo to yield 580 mg of **23**: mp 182–184 °C after recrystallization from methylene chloride; IR 3240 (NH), 1650 (C=O) cm^{-1}; NMR δ 1.40 (4 H, m, H_7, H_8), 2.60 (6 H, m, H_5, H_6, H_9, H_{10}), 4.27 (1 H, t, J = 5 Hz, 1 H, H_{11}), 7.00 (4 H, s, aromatic), 8.23 (1 H, s, CHO). Anal. Calcd for $C_{14}H_{16}NO$: C, 78.47; H 7.52; N, 6.54. Found: C, 78.31; H, 7.58; N, 6.50.

11-*exo*-Formamido-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (24). 11-Oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (**4**; 2 g, 10.7 mmol) and benzylamine (1.15 g, 10.7 mmol) in benzene (50 mL) were refluxed under a Dean–Stark apparatus for 18 h. The volatiles were removed under vacuum to yield crude 11-(benzylimino)-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (**20**). It was then taken up in dimethyl sulfoxide (10 mL), and a solution of potassium *tert*-butoxide (0.21 g, 0.2 mmol) in Me_2SO (15 mL) was added. The mixture was then stirred under nitrogen at room temperature overnight. The reaction mixture was poured into water and extracted with ether. The organic phase was washed, dried (Na_2SO_4), and evaporated to dryness to yield 630 mg of a mixture of 11-*endo*-amino and 11-*exo*-amino derivatives.

This mixture was then formylated as previously described. Recrystallization from methylene chloride yielded 340 mg of pure **23**, mp 182–184 °C.

The mother liquors were evaporated to dryness and recrystallized from ether–hexane, yielding **24** as needles: mp 205–206 °C; IR 3240 (NH), 1650 (C=O) cm^{-1}; NMR δ 1.40 (4 H, m, H_7, H_8), 2.62 (6 H, m, H_5, H_6, H_9, H_{10}), 4.00 (1 H, s, H_{11}), 7.00 (4 H, s, aromatic). Anal. Calcd for $C_{14}H_{16}NO$: C, 78.47; H, 7.52; N, 6.54. Found: C, 78.52; H, 7.93; N, 6.72.

Single-Crystal X-ray Analysis of 4. Single crystals of **4** formed as thick rods and during data collection were coated with epoxy glue to prevent sublimation. The cell constants determined were a = 6.773 (4), b = 12.767 (5), c = 23.064 (7) Å, and β = 93.28 (4)° with symmetry $P2_1/c$ and Z = 8. Of the 2834 unique reflections measured, 2098 were observed ($I \geq 3\ \sigma I$) and were corrected for Lorentz and polarization effects. Structure solution proceeded routinely by direct methods, and the structure was refined by full-matrix least-squares techniques. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.050. Tables 3, 4, and 5 containing the fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. The two independent molecules in the asymmetric unit are related by a noncrystallographic center of symmetry.

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Registry No. **4**, 54962-18-4; **5**, 71962-68-0; **6**, 82799-22-2; **7**, 77954-86-0; *exo*-**Z**, 82838-33-3; **Z**·HCl, 77983-76-7; **8**, 82799-14-2; **9**, 82799-20-0; **10**, 82799-23-3; **11**, 82838-31-1; **11**·HCl, 82889-94-9; **12**, 82799-19-7; **13**, 82799-21-1; **14**, 82799-24-4; **15**, 82799-25-5; **15**·Hcl, 82838-32-2; **16**, 82799-26-6; **17**, 82799-15-3; **18**, 82799-16-4; **19**, 82799-17-5; **19**·Hcl, 82799-18-6; **20**, 82799-28-8; **23**, 82799-27-7; **24**, 82838-34-4; benzylamine, 100-46-9.

Supplementary Material Available: Tables of atom positional coordinates, thermal parameters, bond distances, and bond angles are available (5 pages). Ordering information is given on any current masthead page.