Preparation and stereochemistry of 8- and 9-hydroxy-2,5-ethano-3-benzazocines

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Two isomers of a novel ring system, 1,2,3,4,5,6-hexahydro-2,5-ethano-3-benzazocine, were prepared by a Beckmann rearrangement of *syn*- and *anti*-2-hydroxy-11-oximino-6,9-methano-5,6,7,8,9,10-hexahydrobenzocyclooctene, **4***a* and **4***b* respectively. Because of the similarity in their ir, nmr, and ms, it was impossible to distinguish between the different isomers. To resolve this problem, selective benzylic oxidation and nmr shift reagent studies gave results that determined the structures.

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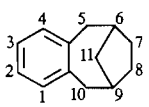
Deux isomères d'un nouveau système polycyclique, l'hexahydro-1,2,3,4,5,6-ethano-2,5-benz-3-azocine ont été préparés en effectuant le réarrangement de Beckmann sur les isomères *syn* et *anti* de l'hydroxy-2-oximino-11-méthano-6,9-hexahydro-5,6,7,8,9,10-benzocyclooctene **4***a* et **4***b* respectivement. La similarité de leur spectre infrarouge, de résonance magnétique nucléaire et de masse a rendu impossible la distinction des isomères. Il a fallu effectuer une oxydation sélective du carbone benzylique *para* au groupe méthoxy. Des études de résonance magnétique nucléaire avec des réactifs de contact ont résolu ce problème et ont permis d'assigner de façon non ambiguë les structures.

Introduction

The benzomorphan ring system has been a popular model for structural modifications in the preparation of analgesics (1). The system is a 3-benzazocine and is further characterized by a 2,6-methano bridge. While preparation and analgesic properties of other methano bridged benzazocines have been reported (2), the corresponding 2,5-ethano bridged 3-benzazocine is a novel system. During our investigation of the chemistry of the 5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (3) system, we found that such a ring system **1** may be used to generate isomeric 3-benzazocines **2** and **3**. The analgesic properties of derivatives of these and related novel systems will be the subject of a future publication. In this paper we wish to report on the preparation and the proof of structure of two isomers of the 3-benzazocine system.



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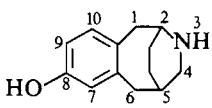

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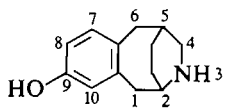
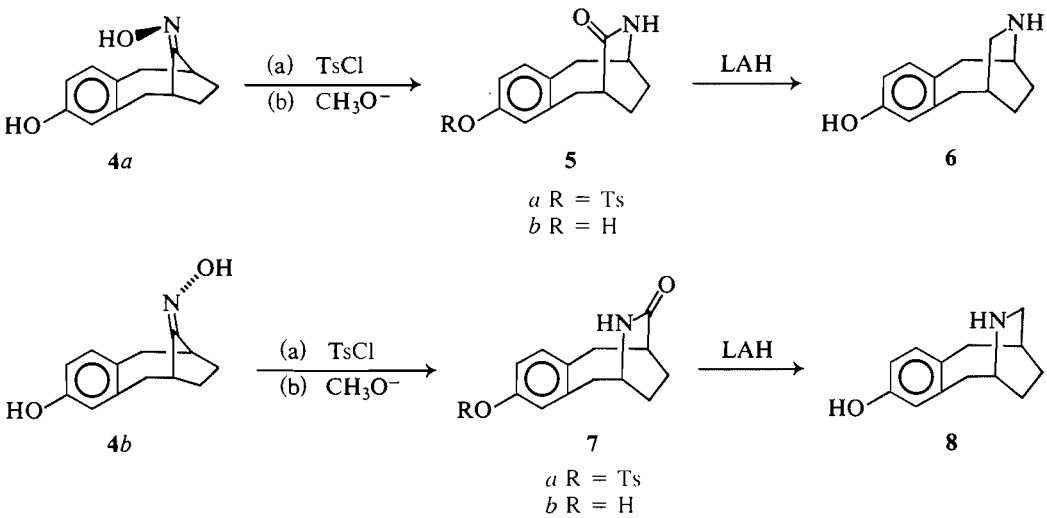


3

Discussion

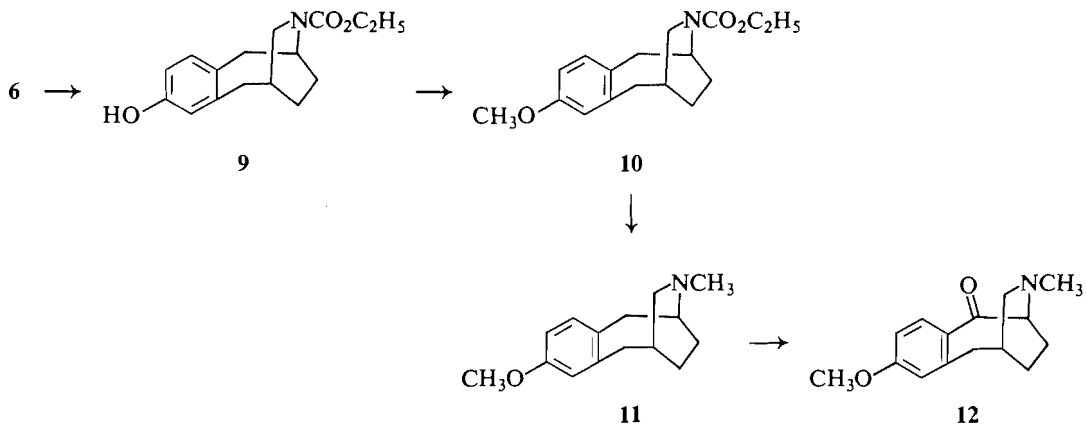
A mixture of *syn*- and *anti*-2-hydroxy-11-oximino-6,9-methano-5,6,7,8,9,10-hexahydrobenzocyclooctene **4***a*, **4***b* was prepared as previously reported (3). The separation of the *syn* and *anti* isomers was easily accomplished by preparative high pressure liquid chromatography (hplc) on silica gel. The definitive assignment of their structures was not possible either by ^{1}H or ^{13}C nmr. Each of the oxime isomers was converted to its corresponding isomeric 3-benzazocine as is outlined in Scheme 1.

The key step in generating this novel 2,5-ethano-3-benzazocine ring system from the 6,9-methanobenzocyclooctene ring system is based on the Beckmann rearrangement (4). Several conditions were tried and the best results for ring expansion to the cyclic amides were obtained by using *p*-toluenesulfonyl chloride in pyridine (5). The product from the Beckmann rearrangement is known to be highly dependent on the stereochemistry of the starting oxime (6). Thus it was expected that the *syn* isomer would lead to only the 8-hydroxy-2,5-ethano-3-benzazocine **6** after hydrolysis of the *p*-toluenesulfonate **5***a* and lithium aluminium hydride reduction of the resulting amide **5***b*. Similarly, the *anti* isomer **4***b*

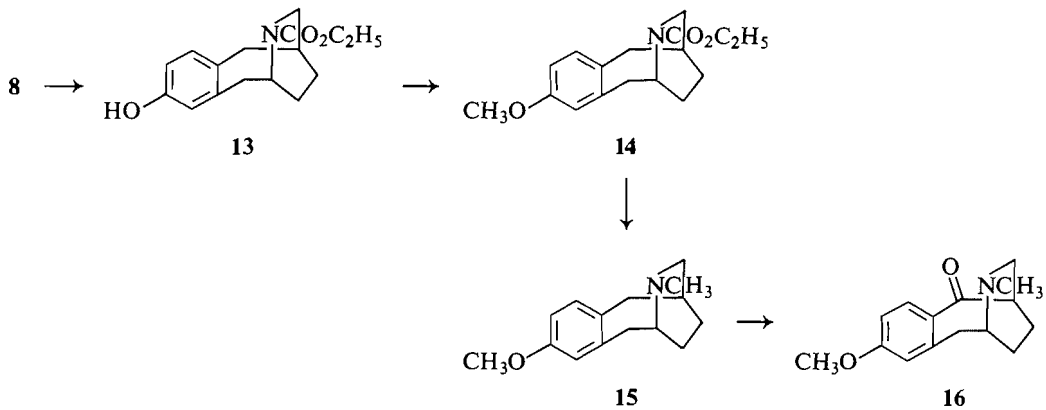


SCHEME 1

[1]Revision received April 29, 1983.



SCHEME 2



SCHEME 3

would be converted to 9-hydroxy-2,5-ethano-3-benzazocine **8**.

The structure assignment of the isomeric Beckmann rearrangement products could not be deduced by conventional methods. Thus, it was decided that the selective oxidation of the benzylic methylene group *para* to the phenolic hydroxyl would produce a β-aminoketone **16** versus an α-aminoketone **12**, therefore permitting better nmr differentiation of the bridgehead protons in **6** and **8**.

Direct oxidation on the free phenolamine **6** or **8** gave only decomposition products. To avoid these complications it was necessary to protect the phenol function as its methyl ether. The synthetic sequence utilized in the preparation of the isomeric ketones **12** and **16** is outlined in Schemes 2 and 3.

Reaction of **7***b* with ethyl chloroformate gave a product in which both the phenol and the amine were protected. On treatment with base, the carbonate was hydrolyzed rapidly. The carbamate **9** was now methylated with dimethylsulfate and potassium carbonate in acetone and the resulting methoxy derivative **10** was reduced with LAH/THF to give the methoxy-*N*-methylamine **11** in an overall yield of 87% from amine **6**. Oxidation with CrO_3/10% H_2SO_4 as reported in the preparation of ethylketocyclazocine (7) gave the desired ketone **12**. The isomer **16** was prepared in a similar manner.

Although the oxidation yields were not optimized, the isomer **15** gave better yields of the corresponding ketone **16** which seemed to be more stable in the oxidation mixture. The ketone **12** obtained from the oxidation of the isomer **11** is an α-aminoketone and as such appears to be much more susceptible to overoxidation. We speculate that the reason for the low yield is due to possible β-elimination, giving a product subject to further degradation.

Nuclear magnetic resonance shift reagent studies

A nmr shift reagent study, using $Eu(fod)_3$, was undertaken on ketones **12** and **16** to prove unambiguously their structure.

In the 90 MHz spectrum of ketone **16**, the bridgehead proton H-5 signal is buried in complex absorptions around 3.1 ppm. The gradual downfield displacement of the absorption due to H-5, using various amounts of shift reagent, can be followed as shown in Table 1. After the addition of 1.0 mmol of $Eu(fod)_3$ to 1.5 mmol of ketone, proton H-5 is shifted to 6.13 ppm and, as can be seen in Fig. 1, it has the characteristics of a poorly resolved multiplet, which is expected from the bridgehead proton of isomer **16** on coupling with three adjacent protons. Somewhat surprisingly (8), the europium appears to complex most strongly with the carbonyl oxygen. This is apparent from the doublet observed for H-7 which is most affected by the shift reagent.

The 90 MHz spectrum of the ketone **12** was in excellent agreement with that expected of isomer **12**. As seen in Fig. 2, the absorption due to the bridgehead proton H-2 is clearly visible at 3.5 ppm without the use of shift reagent and its position corresponds to the expected value from shielding constants (9).

Nevertheless, the addition of $Eu(fod)_3$ was carried out and the results are listed in Table 2. As is the case for isomer **16**, the complexation of europium is with the carbonyl oxygen. Proton H-2 appears as a doublet of doublets with coupling

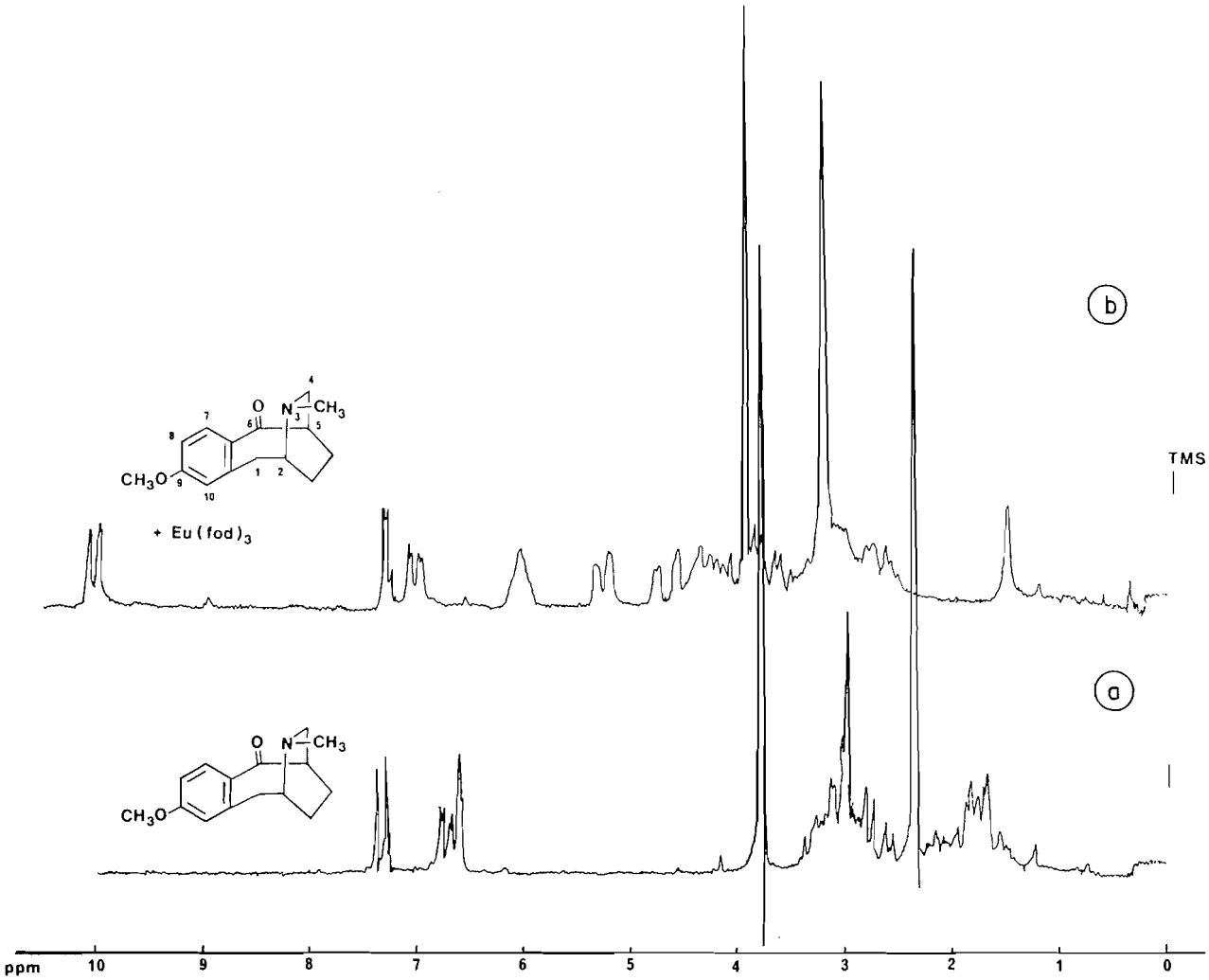


FIG. 1. The ^1H nmr spectra of **16** without shift reagent (spectrum a) and with 0.45 equivalents $Eu(fod)_3$ (spectrum b).

TABLE 1. $Eu(fod)_3$ induced chemical shifts of selected protons of **16**

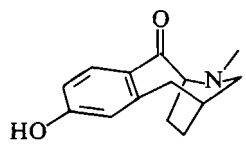
$Eu(fod)_3$ equivalents	H_5	H_{10}	H_8	H_7	H_{11} H_{12}	CH_3O	CH_3N
0	3.1*	6.63	6.77	7.37	1.80	3.83	2.40
0.07	3.3	6.70	6.80	7.60	1.90	3.83	2.50
0.16	3.6	6.80	6.87	8.17	2.10	3.87	2.65
0.23	4.33	6.97	6.93	8.60	2.40	3.93	2.83
0.33	5.10	7.17	7.00	9.23	2.70	4.00	3.03
0.45	6.13	7.37	7.10	10.07	3.00	4.03	3.30
0.61	7.47	7.67	7.23	11.17	3.40	4.10	3.67
0.86	9.33	8.10	7.40	12.73	4.00	4.20	4.20

*Chemical shift expression in ppm downfield from TMS.

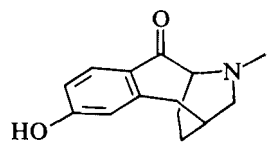
constants of 2 Hz and 7 Hz. Examination of molecular models indicates that the piperidine ring in **12** can exist in two possible conformations. In one conformer (A) the methylene protons at C-11 are bisected by the bridgehead proton H-2 when viewing along the (C_2—C_{11}) bond and one would expect to observe a triplet for H-2 with a coupling constant of about 4 Hz.

In the other conformer (B) the dihedral angles between H-2 and the adjacent methylene protons are about 90° and about 30° giving expected couplings of 1–2 Hz and 7–8 Hz respectively according to Karplus (10). Therefore, the doublet of doublets at 3.5 ppm, having coupling constants of 7 Hz and 2 Hz, appears to correspond to this particular conformer.

This nmr study clearly established the structure of both isomers **12** and **16** and, therefore, their relationship to *syn* and *anti* oximes **4***a* and **4***b*. Compound **16** was obtained from the more polar *syn* isomer **4***a*, whereas **12** originated from the less polar *anti* isomer **4***b*.



A



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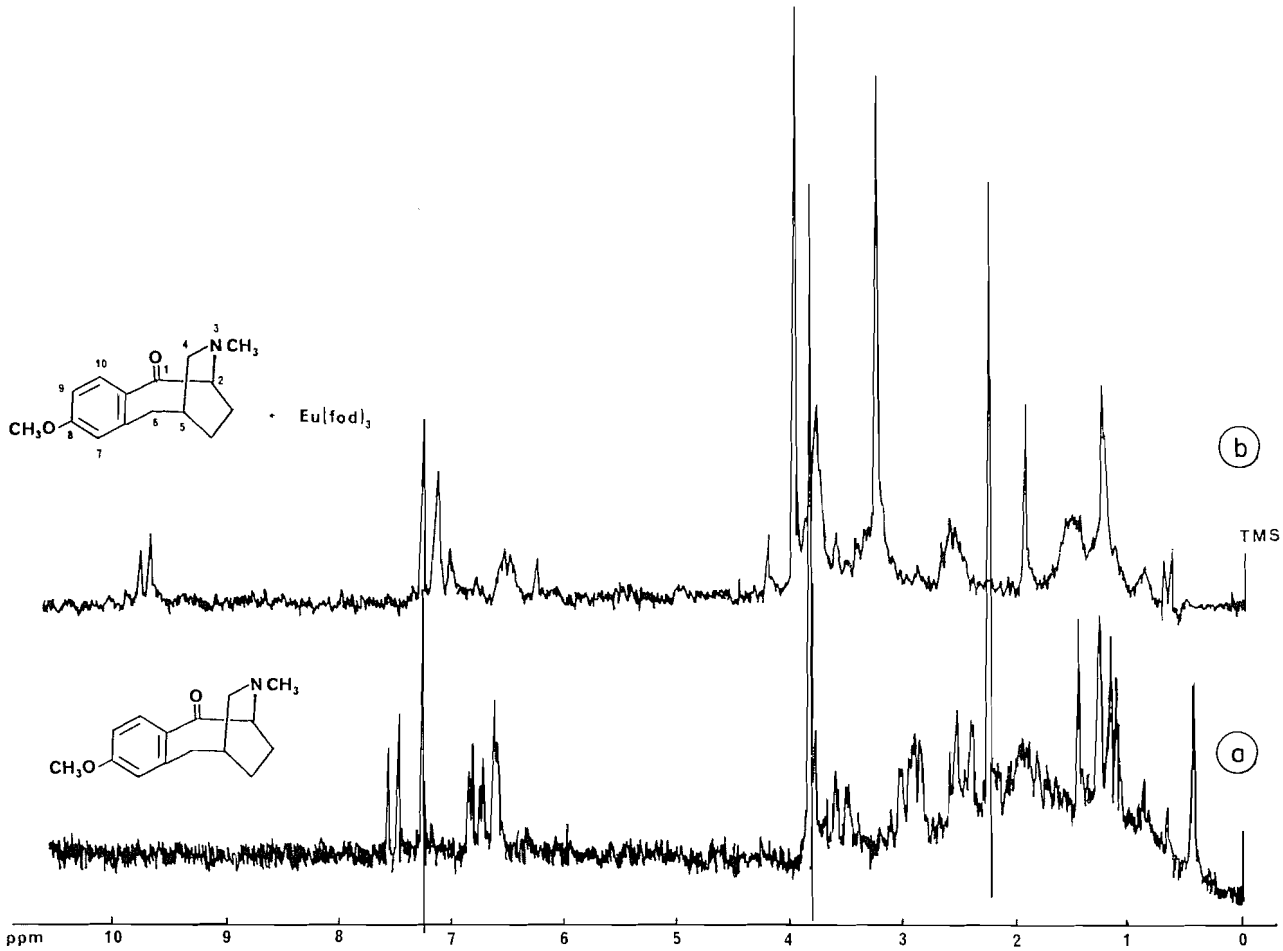

FIG. 2. The ^1H nmr spectra of **12** without shift reagent (spectrum a) and with 0.34 equivalents $Eu(fod)_3$ (spectrum b).

TABLE 2. $Eu(fod)_3$ induced chemical shifts of selected protons of **12**

$Eu(fod)_3$ equivalents	H_2	H_7	H_9	H_{10}	H_{11} H_{12}	CH_3O	CH_3N
0	3.53*	6.67	6.78	7.50	1.83	3.80	2.33
0.04	3.63	6.67	6.80	7.60	1.90	3.83	2.33
0.09	4.13	6.77	6.87	8.03	2.03	3.87	2.50
0.20	5.30	7.00	7.00	8.83	2.20	3.93	2.87
0.34	6.53	7.07	7.13	9.73	2.60	3.97	3.27
0.52	7.63	7.33	7.23	10.50	2.90	4.03	3.63
0.73	9.40	7.70	7.33	11.80	3.43	4.17	4.30

*Chemical shift expression in ppm downfield from TMS.

Mass spectral analyses

The mass spectral analyses of all the 8-hydroxy-2,5-ethano-3-benzazocine analogues, as well as all the 9-hydroxy-2,5-ethano-3-benzazocine analogues, were found to produce similar fragmentation patterns. They all produced as major fragments a dihydropyridinium ion and a *p*-hydroxy or *p*-methoxy-2-methyl tropylium ion. In this series of derivatives there was only one notable exception. The keto derivative **12**, besides giving the above fragmentation, also fragmented the bridge containing the amine as seen by the $M - 57$ peak. The significance of the relative abundance of the $M - 57$ peak (58%) can be interpreted as due to the α-amino ketone nature of this derivative **12**.

Experimental

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. A Varian EM-390 spectrometer was used to record nmr spectra. Proton chemical shifts are relative to tetramethylsilane (TMS) as internal standard. A Waters Prep LC/500 System was used to perform the hplc preparative separations, using one silica gel cartridge with a flow rate of 250 mL/min. Elemental analyses were performed by Galbraith and Associates, Knoxville, TN. The low resolution mass spectral analyses were performed by the Morgan-Schaffer Corporation, Montreal.

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

syn- *and* anti-*2-Hydroxy-11-oximino-6,9-methano-5,6,7,8,9,10-hexahydrobenzocyclooctene (**4**a and **4**b)*

The oxime mixture **4** was prepared as described in ref. 3. Fifteen grams of the mixture were chromatographed on a Waters Prep

LC/500, eluting with hexane/ethyl acetate, 1:1 v/v, to provide 7.3 g of the more polar *syn*-isomer **4***a* and 7.6 g of the less polar *anti*-isomer **4***b*.

Isomer **4**a: mp 190–192°C; (EtOAc/hexane 1:10 v/v); ir (KBr): 3300 (OH^-), 1680 (C=N) cm^{-1}; nmr ($CDCl_3$): 6.4–7.1 (m, 3H), 3.2–3.8 (m, 2H), 2.6–3.0 (m, 4H), 1.1–1.9 (m, 4H). *Anal.* calcd. for $C_{13}H_{15}NO_2$: C 71.86, H 6.95, N 6.44; found: C 71.82, H 6.76, N 6.41.

Isomer **4**b: mp 178–180°C; (EtOAc/hexane 1:1 v/v); ir (KBr): 3320 (OH^-), 1690 (C=N) cm^{-1}; nmr ($CDCl_3$): 6.4–7.1 (m, 3H), 3.2–3.8 (m, 2H), 2.6–3.0 (m, 4H), 1.1–1.9 (m, 4H). *Anal.* calcd. for $C_{13}H_{15}NO_2$: C 71.86, H 6.95, N 6.44; found: C 71.79; H 6.73, N 6.64.

*2,5-Ethano-8-*p*-toluenesulfonyloxy-4-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**5**a)*

syn-2-Hydroxy-11-oximino-6,9-methano-5,6,7,8,9,10-hexahydrobenzocyclooctene (**4***a*) (3.0 g, 13.8 mmol) and *p*-toluenesulfonyl chloride (5.8 g, 30.4 mmol) in pyridine (50 mL) was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* to a residue that was purified by chromatography ($CH_3OH/CHCl_3$, 1:100 v/v) to yield 3.18 g (70%) of the title compound; mp 128–131°C; ir (KBr): 3400 (NH), 1660 (C=O) cm^{-1}; nmr ($CDCl_3$): 6.4–7.8 (m, 7H), 3.5–4.0 (m, 2H), 2.6–3.2 (m, 4H), 2.4 (s, 3H), 1.4–2.1 (m, 4H). *Anal.* calcd. for $C_{20}H_{21}NSO_4$: C 64.66, H 5.69, N 3.77, S 8.63; found: C 64.51, H 5.88, N 3.72, S 8.89.

*2,5-Ethano-9-*p*-toluenesulfonyloxy-4-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**7**a)*

By the same procedure used for the preparation of **5***a*, *anti*-2-hydroxy-11-oximino-6,9-methano-5,6,7,8,9,10-hexahydrobenzocyclooctene (**4***b*) (3.0 g, 13.8 mmol) was converted to 3.13 g (69%) of the title compound, mp 182–186°C; ir (KBr): 3300 (NH), 1670 (C=O) cm^{-1}; nmr ($CDCl_3$): 6.4–7.8 (m, 7H), 3.5–4.0 (m, 2H), 2.6–3.2 (m, 4H), 2.4 (s, 3H), 1.4–2.1 (m, 4H). *Anal.* calcd. for $C_{20}H_{21}NSO_4$: C 64.66, H 5.69, N 3.77, S 8.63; found: C 64.50, H 5.57, N 3.75, S 8.81.

*2,5-Ethano-8-hydroxy-4-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**5**b)*

A solution of 2,5-ethano-8-*p*-toluenesulfonyloxy-4-oxo-1,2,3,4,-5,6-hexahydro-3-benzazocine (**5***a*) (3.55 g, 9.56 mmol) and sodium methoxide (1.9 g, 36.0 mmol) in methanol (17 mL) was stirred at room temperature overnight. Hydrochloric acid (3 *N*; 35 mL) was added and the reaction mixture extracted twice with chloroform. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to yield an oil. After triturating in water, the solid was filtered and dried to yield 1.58 g (76%) of the title compound, mp 241–245°C; ir (KBr): 3400 (OH^-), 3320 (NH), 1650 (C=O) cm^{-1}; nmr (CD_3OD): 6.4–7.0 (m, 3H), 3.6–4.1 (m, 2H), 2.6–3.2 (m, 4H), 1.5–2.1 (s-broad, 4H).

*2,5-Ethano-9-hydroxy-4-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**7**b)*

By the same procedure used for the preparation of **5***b*, 2,5-ethano-9-*p*-toluenesulfonyloxy-4-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**7***b*) (3.25 g, 8.76 mmol) was converted to 1.66 g (87%) of the title compound, mp 305–309°C; ir (KBr): 3400 (OH^-) 3300 (NH), 1650 (C=O) cm^{-1}; nmr (DMSO-d_6): 6.3–7.0 (m, 3H), 3.3–3.9 (m, 2H), 2.7–3.0 (m, 4H), 1.4–1.9 (bs, 4H). *Anal.* calcd. for $C_{13}H_{15}NO_2$: C 71.86, H 6.95, N 6.44; found: C 71.46, H 6.90, N 6.18.

*2,5-Ethano-8-hydroxy-1,2,3,4,5,6-hexahydro-3-benzazocine hydrochloride (**6**)*

To a solution of 2,5-ethano-8-hydroxy-4-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**5***b*) (1.54 g, 7.07 mmol) in tetrahydrofuran (70 mL) was added, in small portions, lithium aluminium hydride (1.34 g, 35 mmol). The mixture was refluxed overnight. The reaction mixture was treated with a saturated ammonium chloride solution (3 mL) and then with 1 *N* sodium bicarbonate (8 mL). The mixture was stirred for 15 min and then filtered. The filtrate was concentrated *in vacuo*. The oil was taken up in methanol, treated with hydrogen chloride, and evaporated to dryness. The residue was triturated in ether to yield 1.04 g (62%) of a solid which, after recrystallization from methanol/chloroform, had mp 234–240°C; ir (KBr): 3400 (OH^-), 3360 (NH) cm^{-1}; nmr (CD_3OD): 6.4–7.1 (m, 3H), 3.7–4.2 (m, 1H), 2.5–3.5 (m, 7H), 1.4–2.2 (m, 4H). *Anal.* calcd. for $C_{13}H_{17}NO \cdot HCl$: C 65.12, H 7.56, N 5.84, Cl 14.78; found: C 64.56, H 7.65, N 5.65, Cl 14.69.

*2,5-Ethano-9-hydroxy-1,2,3,4,5,6-hexahydro-3-benzazocine hydrochloride (**8**)*

Similarly, 2,5-ethano-9-hydroxy-4-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**7***b*) (1.40 g, 6.45 mmol) in tetrahydrofuran (65 mL) was reduced by lithium aluminium hyride (1.2 g, 32 mmol) to yield 1.33 g (87%) of the title compound, mp 275°C; ir (KBr): 3440 (OH^-), 3320 (NH) cm^{-1}; nmr (CD_3OD): 6.4–7.1 (m, 3H), 3.7–4.2 (m, 1H), 2.5–3.5 (m, 7H), 1.4–2.2 (m, 4H). *Anal.* calcd. for $C_{13}H_{17}NO \cdot HCl$: C 65.12, H 7.56, N 5.84, Cl 14.78; found: C 65.09, H 7.60 N 5.77, Cl 15.37.

*N-Ethoxycarbonyl-2,5-ethano-8-hydroxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**9**)*

To a solution of 2,5-ethano-8-hydroxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**6**) (200 mg, 0.98 mmol), 1.0 mL of triethylamine, and 40 mL of THF was added a solution of ethyl chloroformate (122 mg, 1.14 mmol) in 1 mL of THF. The reaction mixture became slightly warm and after stirring for 30 min was concentrated. The residue was partitioned between chloroform and 1 *N* HCl. The chloroform layer was washed with water, dried (Na_2SO_4), and concentrated to yield an oil. An infrared spectrum showed a carbonate band at 1755 cm^{-1} and a carbamate band at 1680 cm^{-1}.

The unpurified *N*-ethoxycarbonyl-2,5-ethano-8-ethoxycarbonyloxy-1,2,3,4,5,6-hexahydro-3-benzazocine was dissolved in 25 mL of methanol and 4 mL of 3 *N* NaOH solution was added. After 5 minutes, the mixture was concentrated and the residue partitioned between 15 mL of 1 *N* HCl and chloroform. The chloroform layer was dried (Na_2SO_4) and concentrated to yield 233 mg (85%) of the title compound, mp 127–131°C; ir (KBr): 3340 (OH^-), 1665 (C=O) cm^{-1}; nmr ($CDCl_3$): 6.3–7.0 (m, 3H), 4.2–4.5 (m, 1H), 3.8–4.2 (q, 2H), 3.4–3.8 (t, 1H), 2.2–3.2 (m, 7H), 0.9–1.9 (m, 7H); *m/e*: 275 (M^+, 67%), 154 (90%), 153 (41%), 122 (100%), 121 (48%). *Anal.* calcd. for $C_{16}H_{21}NO_3$: C 69.79, H 7.68, N 5.08; found: C 69.10, H 7.80, N 4.94.

*N-Ethoxycarbonyl-2,5-ethano-9-hydroxy-1,2,3,4,5,6-hexahydro-3-benzozocine (**13**)*

By the same procedure used for the preparation of **9**, 2,5-ethano-9-hydroxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**13**) (910 mg, 4.48 mol) was converted to 1.1 g (90%) of the title compound. The product was triturated with hexane; mp 103–106°C; ir (KBr): 3340 (OH^-), 1665 (C=O) cm^{-1}; nmr ($CDCl_3$): 6.1–7.0 (m, 3H), 4.2–4.6 (m, 1H), 3.75–4.2 (q, 2H), 3.3–3.75 (t, 1H), 2.2–2.3 (m, 7H), 0.9–2.0 (m, 7H); *m/e*: 275 (M^+, 81%), 154 (83%), 121 (100%). *Anal.* calcd. for $C_{16}H_{21}NO_3$: C 69.79, H 7.68, N 5.08; found: C 69.68, H 7.68, N 5.12.

*N-Ethoxycarbonyl-2,5-ethano-8-methoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**10**)*

A mixture of *N*-ethoxycarbonyl-2,5-ethano-8-hydroxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**9**) (233 mg, 0.84 mmol), dimethyl sulfate (0.23 g; 8.0 mmol), and anhydrous potassium carbonate (0.47 g, 1.7 mmol) in acetone (20 mL) was stirred at room temperature for 3 days. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was taken up in chloroform and washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield 227 mg (93%) of the title compound as an oil; ir (thin film): 1690 (C=O) cm^{-1}; nmr ($CDCl_3$): 6.5–7.0 (m, 3H), 4.2–4.6 (m, 1H), 3.8–4.2 (q, 2H), 3.75 (s, 3H), 3.4–3.8 (m, 1H), 2.2–3.2 (m, 7H), 1.0–1.9 (m, 7H); *m/e*: 289 (M^+, 37%), 154 (25%), 153 (12%), 136 (100%), 135 (24%).

Anal. calcd. for $C_{17}H_{23}NO_3 \cdot \frac{1}{2}H_2O$: C 68.43, H 8.10, N 4.69; found: C 68.08, H 8.02, N 4.57.

N-*Ethoxycarbonyl-2,5-ethano-9-methoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**14**)*

By the same procedure used for the preparation of **10**, *N*-ethoxycarbonyl-2,5-ethano-9-hydroxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**13**) (1.0 g, 3.6 mmol) was converted to 1.04 g (96%) of the title compound as an oil; ir (thin film): 1690 (C=O) cm^{-1}; nmr ($CDCl_3$): 6.5−7.0 (m, 3H), 4.2−4.6 (m, 1H), 3.8−4.2 (q, 2H), 3.75 (s, 3H), 3.4−3.8 (m, 1H), 2.2−3.2 (m, 1H), 2.2−3.2 (m, 7H), 1.0−1.9 (m, 7H); *m/e*: 289 (M^+, 9%), 154 (26%), 135 (100%). *Anal.* calcd. for $C_{17}H_{23}NO_3$: C 70.56, H 8.01, N 4.84; found: C 69.97, H 8.13, N 4.68.

N-*Methyl-2,5-ethano-8-methoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**11**)*

To a solution of *N*-ethoxycarbonyl-2,5-ethano-8-methoxy-1,2,3,4,-5,6-hexahydro-3-benzazocine (**10**) (277 mg, 0.768 mmol) in 10 mL of THF was added lithium aluminum hydride (175 mg, 4.6 mmol) under a nitrogen atmosphere. The mixture was refluxed for 1 hour. After cooling to room temperature, the mixture was treated with a saturated NH_4Cl solution (2.1 mL) followed by 1 *N* $NaHCO_3$ (5.7 mL). The mixture was filtered and the salts washed with THF. The filtrate was concentrated *in vacuo*. The residue was dissolved in chloroform, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield 200 mg (85%) of the title compound as an oil. The hydrochloride melted at 160°C; ir (KBr): 1605, 1580, 1260, 1040 cm^{-1}; nmr ($CDCl_3$): 6.5−7.1 (m, 3H), 3.8 (s, 3H), 2.5−3.4 (m, 8H), 2.4 (s, 3H), 1.1−2.0 (m, 4H); *m/e*: 231 (M^+, 14%), 96 (100%), 94 (25%).

N-*Methyl-2,5-ethano-9-methoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**15**)*

By the same procedure used for the preparation of **11**, *N*-ethoxycarbonyl-2,5-ethano-9-methoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**14**) (703 mg, 18.5 mmol) was reduced to 831 mg (90%) of the title compound as an oil. The hydrochloride melted at 255−258°C; ir (thin film): 1610, 1585, 1270, 1050 cm^{-1}; nmr ($CDCl_3$): 6.5−7.1 (m, 3H), 3.8 (s, 3H), 2.5−3.4 (m, 8H), 2.4 (s, 3H), 1.1−2.0 (m, 4H); *m/e*: 231 (M^+, 21%), 135 (11%), 96 (100%). *Anal.* calcd. for $C_{15}H_{21}NO \cdot H_2O$: C 72.25, H 9.29, N 5.61; found: C 72.19, H 8.67, N 5.78.

N-*Methyl-2,5-ethano-8-methoxy-1-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**12**)*

To a mixture of *N*-methyl-2,5-ethano-8-methoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**11**) (200 mg, 0.86 mmol) in 5 mL of 10% H_2SO_4 was added, in one portion, a solution of chromium trioxide (135 mg, 1.35 mmol) in 5 mL of 10% H_2SO_4. The resultant mixture was heated in an oil bath at 65°C for 1 hour. The mixture was brought to room temperature and basified with NH_4OH. After diluting with THF and stirring for 5−10 minutes, the salts were filtered off and washed with THF. The THF layer was separated and concentrated *in vacuo*. The residue was dissolved in chloroform, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to an oil, which was purified on a silica gel preparative plate, developing with 2% $CH_3OH/CHCl_3$ plus NH_3 vapour to yield 10 mg (5%) of the ketone (**12**): ir (thin film): 1665 (C=O), 1600, 1260 cm^{-1}; nmr ($CDCl_3$): 7.4−8.6 (d, 1H), 6.5−6.8 (m, 2H), 3.8 (s, 3H), 3.4−3.6 (d, 1H), 2.2−3.1 (m, 5H), 2.2 (s, 3H), 1.0−2.2 (m, 4H); *m/e*: 245 (M^+, 50%), 188 (58%), 96 (100%), 94 (68%).

N-*Methyl-2,5-ethano-9-methoxy-6-oxo-1,2,3,4,5,6-hexahydro-3-benzazocine (**16**)*

By the same procedure used for the preparation of **12**, *N*-methyl-2,5-ethano-9-methoxy-1,2,3,4,5,6-hexahydro-3-benzazocine (**15**) (231 mg, 1.0 mmol) was oxidized to 204 mg (83%) of the title compound as an oil. The hydrochloride melted at 233−235°C; ir (thin film): 1670 (C=O), 1260, 1050 cm^{-1}; nmr ($CDCl_3$): 7.2−7.4 (d, 1H), 6.5−6.8 (m, 2H), 3.8 (s, 3H), 2.5−3.4 (m, 6H), 2.4 (s, 3H), 1.4−2.4 (m, 4H); *m/e*: 245 (M^+, 14%), 149 (23%), 96 (100%). *Anal.* calcd. for $C_{15}H_{19}NO_2 \cdot H_2O$: C 68.41, H 8.03, N 5.31; found: C 69.22, H 7.56, N 5.65.

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