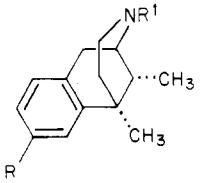
Synthesis and Pharmacology of 8-Amino-3-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocine and Related Compounds[1]

Mark P. Wentland,* Noel F. Albertson, and Anne K. Pierson

Sterling-Winthrop Research Institute, Rensselaer, New York 12144. *Received July 30, 1979*

The title compound **1a** has been prepared and was found to be a strong, orally active analgesic agonist with narcotic–antagonist properties. **1a** was prepared by two independent routes: (a) nitration of volazocine and subsequent reduction and (b) a sequence involving dissolving metal reduction of cyclazocine methyl ether, followed by oximination and Semmler–Wolff rearrangement. Several analogues were prepared and tested.

A possible mode of metabolic inactivation of benzomorphans containing a phenolic hydroxyl is conjugation of that hydroxyl with glucuronic acid.[2] It was anticipated that replacement of the hydroxyl group in benzomorphans by an amino group would give an analgesic less subject to this type of metabolic inactivation and thus be longer acting. An investigation directed toward the syntheses of these derivatives was undertaken, with the amino analogue (**1a**) of cyclazocine (**1b**) chosen first.

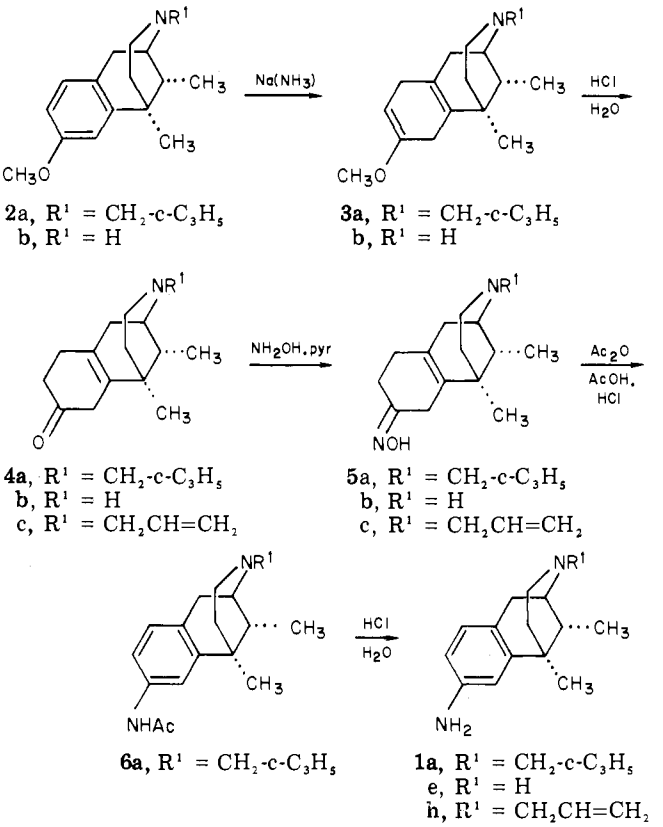


1a, R = NH_2; R^1 = CH_2-c-C_3H_5
b, R = OH; R^1 = CH_2-c-C_3H_5
c, R = H; R^1 = CH_2-c-C_3H_5
d, R = NO_2; R^1 = CH_2-c-C_3H_5
e, R = NH_2; R^1 = H

Chemistry. The nitration of some benzomorphan derivatives had been previously done by May.[3] We used a similar nitration condition with volazocine[4] (**1c**), and an excellent yield of nitro-containing material was obtained. Subsequent reduction with iron and HCl gave the desired amino compound, **1a**, obtained pure in 39% yield after one recrystallization of its dihydrochloride salt. In order to definitively demonstrate that **1a** was indeed the correct regioisomer (8 position), an alternative synthesis (Scheme I) of **1a** was undertaken using cyclazocine methyl ether[5] (**2a**) as starting material.

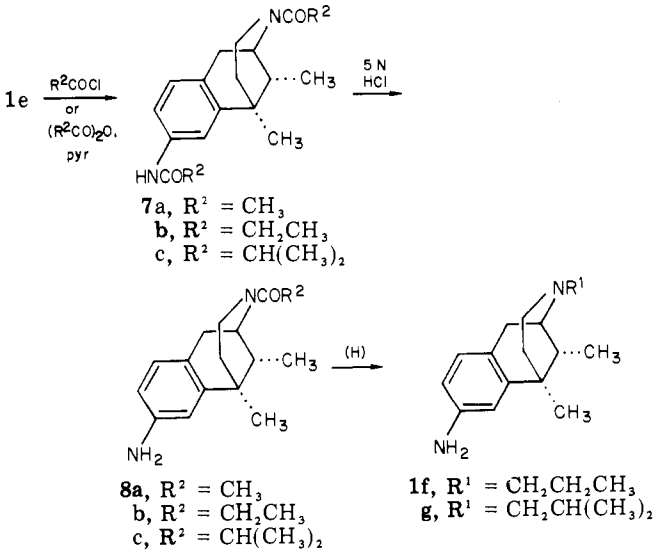
Dissolving metal reduction[6] of **2a** gave a crude enol ether, **3a**, which upon treatment with acetone containing a small amount of aqueous HCl gave the hydrochloride salt of **4a**. The yield of **4a** from **2a** was 76%. Oximination of **4a** with NH_2OH·HCl/pyridine gave **5a** in 90% yield. Semmler–Wolff[7] dehydration of **5a** in Ac_2O/AcOH/HCl gave acetanilide **6a** which, without isolation, was hydrolyzed in 2 N HCl to give a 70% yield of the desired aminobenzomorphan, **1a**, isolated and characterized as its dihydrochloride salt. This salt was in every aspect identical with the dihydrochloride of **1a** made by the nitration/reduction sequence. This scheme constitutes an efficient and potentially general method[8] for the conversion ArOH to $ArNH_2$.

Scheme I



2a, R^1 = CH_2-c-C_3H_5; **b**, R^1 = H
3a, R^1 = CH_2-c-C_3H_5; **b**, R^1 = H
4a, R^1 = CH_2-c-C_3H_5; **b**, R^1 = H; **c**, R^1 = $CH_2CH{=}CH_2$
5a, R^1 = CH_2-c-C_3H_5; **b**, R^1 = H; **c**, R^1 = $CH_2CH{=}CH_2$
6a, R^1 = CH_2-c-C_3H_5
1a, R^1 = CH_2-c-C_3H_5; **e**, R^1 = H; **h**, R^1 = $CH_2CH{=}CH_2$

Scheme II



7a, R^2 = CH_3; **b**, R^2 = CH_2CH_3; **c**, R^2 = $CH(CH_3)_2$
8a, R^2 = CH_3; **b**, R^2 = CH_2CH_3; **c**, R^2 = $CH(CH_3)_2$
1f, R^1 = $CH_2CH_2CH_3$; **g**, R^1 = $CH_2CH(CH_3)_2$

(1) Presented in part at the 7th Northeast Regional Meeting of the American Chemical Society, Albany, New York, Aug 1976.
(2) Dr. L. Shargel, Department of Drug Metabolism, Sterling-Winthrop Research Institute, unpublished results.
(3) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).
(4) N. F. Albertson, U.S. Patent 4108857.
(5) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, 7, 123 (1964).
(6) We thank Dr. Paul A. Bartlett for first performing this transformation.
(7) For a review, see: R. T. Conley and S. Ghosh, *Mech. Mol. Migr.*, 4, 251 (1971).

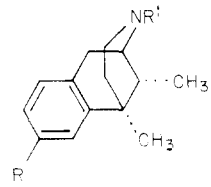
0022-2623/80/1823-0071$01.00/0

Table I. Comparison of the Agonist and Narcotic Antagonist Activities of 1a, Cyclazocine, and Pentazocine

test[a]	route	1a[b]	cyclazocine[c]	pentazocine[c]
phenylquinone, ED_{50}	sc	1.4 (1.1-1.6)	0.04 (0.03-0.07)	3.8 (2.1-6.8)
	po	7.2 (5.6-8.7)	3.6 (2.9-5.1)	95 (73-114)
acetylcholine, ED_{50}	sc	0.80 (0.60-1.0)	0.15 (0.10-0.20)	2.2 (1.7-2.7)
	po	3.2 (2.3-4.8)	5.3 (4.1-7.1)	51 (40-65)
rat bradykinin, ED_{50}	sc	1.2 (0.56-1.9)	0.04 (0.02-0.07)	2.6 (1.7-3.3)
	po	8.1 (4.5-14)	3.7 (2.5-4.5)	40%[d] at 300
rat tail flick, ED_{50}	sc	I[e] at 120	I[e] at 120	I[e] at 120
AD_{50} vs. phenazocine	sc	2.7 (1.7-4.2)	0.028 (0.018-0.043)	6.3 (5.0-7.9)
	po	10 (6.7-15)	3.1 (2.1-4.5)	76 (51-114)
AD_{50} vs. morphine	sc	3.7 (2.4-5.7)	0.029 (0.020-0.042)	9.0 (5.6-14)
	po	15 (10-22)	4.3 (2.5-7.3)	140 (87-224)
AD_{50} vs. meperidine	sc	2.0 (1.2-3.3)	0.019 (0.015-0.024)	3.9 (2.1-7.4)
	po	8.8 (6.1-13)	4.2 (3.0-5.9)	68 (49-95)

[a] Test results in mg/kg (95% confidence limits), calculated as the free base. [b] Tested in aqueous solution as the dihydrochloride salt. [c] See ref 5. [d] 40% protection. [e] Inactive.

Table II. Molecular Formulas and Pharmacological Activities of 8-Amino-2,6-methano-3-benzazocine Derivatives



1

no.	R	R^1	formula	ED_{50}[a]	AD_{50}[b]
1a	NH_2	CH_2-c-C_3H_5	$C_{18}H_{26}N_2 \cdot 2HCl$	0.80 (0.60-1.0)	2.7 (1.7-4.2)
1d	NO_2	CH_2-c-C_3H_5	$C_{18}H_{24}N_2O_2 \cdot HCl$	24 (19-30)[c]	9.6 (6.1-15)[d]
1e	NH_2	H	$C_{14}H_{20}N_2 \cdot 2HCl \cdot H_2O$	6.1 (2.8-11)	I[e] at 80
1f	NH_2	$CH_2CH_2CH_3$	$C_{17}H_{26}N_2 \cdot 2HCl \cdot 1.5H_2O$	5.6 (3.8-8.3)	2.0 (1.2-3.4)
1g	NH_2	$CH_2CH(CH_3)_2$	$C_{18}H_{28}N_2 \cdot 2HCl$	1.5 (0.57-2.7)	9.4 (6.5-14)
1h	NH_2	$CH_2CH=CH_2$	$C_{17}H_{24}N_2 \cdot 2HCl$	2.5 (1.7-3.7)	1.5 (1.0-2.2)
1i	CH_3NH	CH_2-c-C_3H_5	$C_{19}H_{28}N_2 \cdot 2HCl \cdot C_2H_6O \cdot H_2O$	0.44 (0.24-1.4)	1.35 (0.87-2.1)
1j	CH_3CH_2NH	CH_2-c-C_3H_5	$C_{20}H_{30}N_2$	1.3 (0.80-1.8)	I[e] at 80
1k	$CH_3(CH_2)_2NH$	CH_2-c-C_3H_5	$C_{21}H_{32}N_2$	1.2 (0.87-1.5)	?[f] at 40
1l	$CH_3(CH_2)_3NH$	CH_2-c-C_3H_5	$C_{22}H_{34}N_2$	1.0 (0.59-1.6)	I[e] at 40
1m	$C_6H_5CH_2NH$	CH_2-c-C_3H_5	$C_{25}H_{32}N_2 \cdot 2HCl$	1.6 (1.2-2.1)	1.0 (0.53-1.9)
1n	$(CH_3)_2N$	CH_2-c-C_3H_5	$C_{20}H_{30}N_2 \cdot 2HCl$	0.79 (0.38-1.4)	?[f] at 80
1o	c-$C_3H_5CH_2NH$	CH_2-c-C_3H_5	$C_{22}H_{32}N_2 \cdot HCl$	0.70 (0.39-1.2)	8.0 (5.5-12)

[a] Acetylcholine writhing test (mouse), mg/kg sc (95% confidence limits). [b] Phenazocine antagonism (rat), mg/kg sc (95% confidence limits). [c] Phenylquinone writhing data. [d] Narcotic antagonism vs. meperidine. [e] Inactive. [f] Questionable activity.

The same synthetic sequence was implemented using benzomorphan **2b**[9] with similar success. The diamine **1e**, obtained in 52% overall yield from **2b**, was useful in the preparation of derivatives bearing different alkyl substituents on the aliphatic nitrogen (Scheme II). In this sequence it was shown that oxime **5b**·HCl could also be secured in good yield by direct treatment of enol ether **3b** with $NH_2OH \cdot HCl$/pyridine.

Diacylation of **1e** with an appropriate acid chloride or anhydride gave a bisamide **7**. Careful hydrolysis of **7** in 5 N HCl induced selective cleavage of the anilino–carbonyl linkage to give a monoamide **8**, which upon $LiAlH_4$ reduction gave the desired analogues **1f** and **1g**.

An alternative method for the introduction of alkyl substituents on the aliphatic nitrogen of **1e** is exemplified by the synthesis of **1h**. Alkylation of **4b** with allyl bromide gave **4c**, which when subjected to the oximination/dehydration sequence gave **1h**.

Compounds **1i–l** were made by the straightforward procedure of acylation of **1a** with an acid halide or anhydride, followed by hydride reduction. Compound **1m** was prepared by the condensation of **1a** with benzladehyde, followed by sodium borohydride reduction. The methodology described in Scheme III was used in preparing **1n** and, finally, compound **1o** was made by B_2H_6 reduction of bisamide **7** (R^2 = c-C_3H_5).

Pharmacology. **1a** was evaluated in several biological screens. The agonist activity was determined using (a) the modified D'Amour–Smith tail-flick method described by Harris and Pierson;[10] (b) the phenylquinone writhing test of Pearl and Harris;[11] (c) the acetylcholine-induced writhing procedure of Collier;[12] and (d) the rat bradykinin test.[13,14] The procedure of Harris and Pierson[10] was used to determine the narcotic antagonist activity of **1a** vs. phenazocine, morphine, and meperidine. The results are summarized in Table I. Test data are also given for cy-

(8) For two other methods, see: R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **37**, 3570 (1972); R. A. Scherrer and H. R. Beatty, *ibid.*, **37**, 1681 (1972).

(9) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 1435 (1959).

(10) L. S. Harris and A. K. Pierson, *J. Pharmacol. Exp. Ther.*, **143**, 141 (1964).

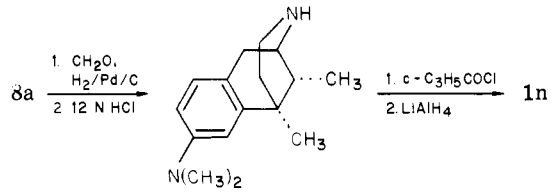
(11) J. Pearl and L. S. Harris, *J. Pharmacol. Exp. Ther.*, **154**, 319 (1966).

(12) H. O. J. Collier, L. C. Dinneen, C. A. Johnson, and C. Schneider, *Br. J. Pharmacol. Chemother.*, **32**, 295 (1968).

(13) G. Deffenu, L. Pegrassi, and B. Lumachi, *J. Pharm. Pharmacol.*, **18**, 135 (1966).

(14) B. A. Berkowitz and E. L. Way, *J. Pharmacol. Exp. Ther.*, **177**, 500 (1971).

Scheme III



9

clazocine (**1b**) and pentazocine. The values for the amino compound **1a** lie between the values of cyclazocine and pentazocine, with one exception: in the acetycholine writhing tests, the amino compound is the most active when given orally.[15]

Perhaps the most significant finding is that, whereas the oral to parenteral ratio for cyclazocine is about 100 or more in all tests in Table I, except the acetylcholine test where it is 35, this ratio is about 5 for the amino analogue. Pentazocine gives intermediate values.

Results in Table II show that substitution on the anilino nitrogen has relatively little effect on the acetylcholine writhing values but generally decreases the antagonist values. Other data summarized in Table II reveal that upon replacement of the cyclopropylmethyl group in **1a** with allyl, *n*-propyl, or isobutyl, agonist activity was sustained. However, these modifications appear to be somewhat less potent than **1a**. The narcotic antagonist activity of the allyl and *n*-propyl derivatives (**1h** and **1f**) was found to be roughly equal to **1a**, while the isobutyl analogue **1g** was less potent than **1a**.

We found the title compound **1a** to have a duration of activity comparable to that of cyclazocine (rat bradykinin test, sc). For **1a**, the mean response scores were reduced by 50% or more for approximately 85 min at a dose of 3.0 mg/kg which is somewhat more than twice the ED_{50}. For cyclazocine, the mean response scores were reduced by 50% or more for approximately 100 min at a dose of 0.1 mg/kg, which again is slightly more than twice the ED_{50}.

In conclusion, we have demonstrated for the first time that analgesic agonist and narcotic antagonist activity can be found in a class of 8-amino-substituted 2,6-methano-3-benzazocine derivatives. The title compound **1a** also has the particular advantage of having a favorable oral/parenteral ratio.

Experimental Section

Combustion data were obtained for all new compounds reported. Analyses are indicated by the symbols of the elements and were within ±0.4% of the theoretical values. Analyses were performed by Instanal Laboratories, Rensselaer, N.Y. The structures of the new compounds were substantiated by NMR (Varian A-60), IR (Perkin-Elmer 21), and mass spectrometry (Joelco JMS-1-OCS). Melting points are not corrected for emergent stem errors. GC data were collected on a Varian 1400 gas chromatograph with a 10% OV-17 column at a column temperature of 270 °C.

3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-8-nitro-2,6-methano-3-benzazocine Hydrochloride (1d). Nitration of 15.1 g of volazocine base,[4] 1c, according to the procedure of May and Fry[3] gave 14.8 g (80%) of crude nitro compound. Conversion to its hydrochloride salt was accomplished by the addition of excess ethereal HCl to an ethanol solution of the nitro compound. Recrystallization of the crude salt from EtOH gave 8.9 g of **1d**·HCl, mp 283–284 °C.

8-Amino-3-(cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocine Dihydrochloride (1a). Method A. Iron powder (13.2 g, 0.236 g-atom) was added in portions to a solution of 11.6 g (0.039 mol) of the nitro compound described above (as the free base after liberation from its recrystallized HCl salt) in 35 mL of water, 60 mL of ethanol, and 3.7 mL of concentrated HCl. The resulting mixture was stirred at reflux for 2.75 h. After the mixture was cooled, 5 g of $NaHCO_3$ was added and the mixture filtered. The filtrate was concentrated at reduced pressure to give 10.4 g of red syrup. Addition of ethereal HCl to an ethanol solution of the crude product gave a salt which had mp 303–306 °C. Recrystallization from methanol–ether gave a pure (TLC, NMR) dihydrochloride salt of **1a**: yield 5.1 g (39%); mp 314–316 °C. This salt proved to be identical (TLC, GC, IR, NMR, MS, and mmp) with a sample of **1a**·2HCl prepared by method B.

3-(Cyclopropylmethyl)-1,2,3,4,5,6,7,8,9,10-decahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-one Hydrochloride (4a). A solution of 50 g of **2a**[5] (0.175 mol), 500 mL of THF, and 500 mL of isopropyl alcohol was added with stirring to 1.5 L of liquid NH_3 supported in a dry ice–acetone bath. Sodium (69.5 g, 3.0 g-atoms) was added in small pieces over 0.5 h. After the blue color disappeared (about 1 h), 200 mL of methanol was added and the ammonia was allowed to evaporate overnight after removal of the cooling bath. The residue was diluted with water and extracted three times with 300 mL of ether. The ether extracts were dried ($MgSO_4$) and concentrated, giving 45.4 g crude **3a**.[16] To an aqueous acetone solution of **3a**, excess ethereal HCl was added. The resulting salt was collected and recrystallized three times from methanol–benzene to give 41.1 g (76% from **2a**) of **4a**·HCl, mp 206–208 °C. Anal. ($C_{18}H_{27}NO$·HCl) C, H, N.

3-(Cyclopropylmethyl)-1,2,3,4,5,6,7,8,9,10-decahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-one Oxime (5a). A solution of 1.0 g (0.0032 mol) of **4a**·HCl and 0.24 g (0.004 mol) NH_2OH·HCl in 5 mL of EtOH and 5 mL of pyridine was refluxed with stirring for 3 h. The mixture was concentrated, dissolved in water, and basified with excess $NaHCO_3$. The organic material was extracted into $CHCl_3$, dried ($MgSO_4$), and concentrated to give a crystalline product. One recrystallization from EtOH afforded **5a**: yield 0.80 g (90%); mp 190–193 °C. Anal. ($C_{18}H_{18}N_2O$) C, H, N.

1a. Method B. Acetic anhydride (41 mL, 0.43 mol) was added to a stirred solution of 59.5 g (0.21 mol) of **5a** in 290 mL of acetic acid. Anhydrous gaseous HCl was slowly passed through the solution until a temperature of 110 °C was attained. The flow of HCl was stopped and the dark red solution stirred at reflux for 1.5 h. The solution was concentrated under reduced pressure and the residue heated on a steam bath in 400 mL of 2 N HCl for 2 h. The resulting solution was concentrated under reduced pressure, and the residue was twice dissolved in methanol and concentrated. This residue was taken up in 200 mL of hot isopropyl alcohol and cooled. Pure **1a**·2HCl (49.0 g, 70%) was filtered and dried, mp 310–312 °C.

1,2,3,4,5,6,7,8,9,10-Decahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-one Hydrochloride (4b). A procedure nearly identical with that for making **4a** was used for converting 77 g of **2b** into **4b**·HCl: yield 61 g (72%); mp 198–201 °C. Anal. ($C_{14}H_{21}NO$·HCl) C, H, N.

1,2,3,4,5,6,7,8,9,10-Decahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzozocin-8-one Oxime Hydrochloride (5b). Method A. **4b**·HCl (2.0 g, 0.0078 mol), NH_2OH·HCl (0.6 g, 0.0085 mol), pyridine (10 mL), and EtOH (20 mL) were refluxed for 2 h with stirring and concentrated. The product was triturated in isopropyl alcohol and dried to give 1.9 g (90%) of **5b**·HCl, mp 237–240 °C. Anal. ($C_{14}H_{22}N_2O$·HCl) C, H, N.

Method B. Crude enol ether **3b** (76 g, 0.326 mol), NH_2OH·HCl (22.8 g, 0.326 mol), pyridine (140 mL), and 95% EtOH (210 mL) were refluxed with stirring for 16 h and concentrated. The residue triturated with 100 mL of isopropyl alcohol and the solid collected to give 64.5 g (72% overall from **2a**) of **5b**·HCl.

8-Amino-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocine Dihydrochloride Hydrate (1e). A

(15) The nitration and subsequent reduction of α- and β-deoxyetazocine has been reported [A. E. Jacobson and E. L. May, *J. Med. Chem.*, 8, 563 (1965)]. Using the hot plate method, the 8-nitro and 8-amino derivatives were found to be less potent as narcotic agonists than etazocine.

(16) The proton NMR of crude **3a** was consistent for the 7,10-dihydro isomer.

procedure nearly identical with method B used in making **1a** was employed to convert 4.0 g of **5b**·HCl into **1e**·2HCl·H_2O (4.0 g, 87%), mp > 280 °C.

3-Acetyl-8-amino-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocine (8a). **1e**·2HCl·H_2O (25 g, 0.08 mol) was heated on a steam bath with 50 mL of acetic anhydride and 250 mL of pyridine for 10 h. The solution was concentrated and taken up in a solution of 50 mL of EtOH and 150 mL of 6 N HCl. After the solution was heated on a steam bath ca. 2 h, TLC ($CHCl_3$–MeOH–isopropylamine, 94:3:3, silica) showed the bisamide **7a** had disappeared and only **8a** was present. The solution was concentrated under reduced pressure and the residue basified with excess 35% NaOH. This mixture was extracted with ether and dried (Na_2SO_4). Upon cooling, 8a crystallized out and 13.9 g (66%) of pure material was collected, mp 208–209 °C. Anal. ($C_{16}H_{22}N_2O$) C, H, N.

8-Amino-*cis*-6,11-dimethyl-1,2,3,4,5,6-hexahydro-3-propyl-2,6-methano-3-benzazocine Dihydrochloride Sesquihydrate (1f). The free base of **1e** (3.0 g, 0.014 mol), propionyl chloride (5.3 g, 0.058 mol), $CHCl_3$ (80 mL), and saturated $NaHCO_3$ (80 mL) were vigorously stirred for 2 h at 25 °C and the layers separated. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated, giving 4.0 g of crude **7b**. Partial hydrolysis of **7b** to **8b** was accomplished by using the procedure for making **8a**. Without purification, **8b** (3.6 g) was reduced with 2.5 g of $LiAlH_4$ in 60 mL of THF (reflux, 1 h). Workup consisted of addition of saturated potassium sodium tartrate solution, followed by filtration and concentration. Three grams (79% from 1e) of crude **1f** was obtained. A dihydrochloride salt was prepared by treatment of the base with ethereal HCl. Recrystallization from MeOH–ether afforded pure **1f**·2HCl·1.5H_2O, mp 202–207 °C.

8-Amino-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-3-(2-methylpropyl)-2,6-methano-3-benzazocine Dihydrochloride (1g). A procedure nearly identical with the one described above (for **1f**) was used to accomplish the formation of **1g**·2HCl from **1e** and isobutyryl chloride, mp >300 °C, 34% overall yield.

1,2,3,4,5,6,7,8,9,10-Decahydro-*cis*-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocin-8-one Hydrochloride (4c). A DMF (50 mL) slurry of **4b**·HCl (5.1 g, 0.02 mol), allyl bromide (2.4 g, 0.02 mol), and $NaHCO_3$ (3.4 g, 0.04 mol) were stirred under N_2 at 140 °C for 1 h and concentrated on the rotary evaporator. The residue was partitioned between ether and saturated $NaHCO_3$. The ether layer was dried (Drierite) and concentrated, and the residue was taken up in EtOH and acidified with ethereal HCl. Recrystallization of this salt from EtOH–ether gave 4.0 g (68%) of **4c**·HCl, mp 163–170 °C dec. Anal. ($C_{17}H_{25}NO$·HCl) H, N; C: calcd, 69.02; found, 68.43.

8-Amino-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-3-(2-propenyl)-2,6-methano-3-benzazocine Dihydrochloride (1h). A procedure nearly identical with that used for the conversion **4a** to **1a** was employed in the preparation of 1h·2HCl (mp >270 °C) from **4c** in 52% overall yield.

3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-8-(methylamino)-2,6-methano-3-benzazocine Dihydrochloride Ethanolate Hydrate (1i). Ten milliliters of HCO_2H was added dropwise to 20 mL of Ac_2O at 0 °C. To this solution, 6.7 g (0.02 mol) of **1a**·2HCl in 20 mL of HCO_2H was added dropwise and kept at 0 °C for 18 h. After concentration and an extractive-basic workup of the solution, 5.0 g of formamide 1 (R = NHCHO; $R^1 = CH_2$-*c*-C_3H_5) was secured. This was treated with 80 mL of B_2H_6 (1 M in THF) at reflux for 3 h. After the mixture was cooled and acidified with 6 N HCl, the THF was stripped and the residue was taken up in water and washed with ether. The aqueous acid solution was basified and extracted with ether. After the solution was dried (Na_2SO_4) and concentrated, 3.5 g (62% from **1a**) of pure **1i** remained. A dihydrochloride salt was recrystallized from EtOH–ether to give **1i**·2HCl·EtOH·H_2O, mp 250 °C dec.

Compounds **1j**, **1k**, and **1l** were similarly prepared. **1j**, boiling range 155–160 °C (0.03 mm), was secured in 38% overall yield by exposure of **1a**·2HCl to Ac_2O/pyridine followed by $LiAlH_4$ reduction. **1k**, boiling range 155–160 °C (0.05 mm), 64%, was made by $(CH_3CH_2CO)_2O$/pyridine treatment of **1a**·2HCl and subsequent $LiAlH_4$ reduction. Finally, **1l**, boiling range 161–165 °C (0.07 mm), 69%, was made by the action of $(CH_3CH_2CH_2CO)_2O$/pyridine on 1a·2HCl and $LiAlH_4$ reduction.

3-(Cyclopropylmethyl)-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-8-[(phenylmethyl)amino]-2,6-methano-3-benzazocine Dihydrochloride (1m). An EtOH (100 mL) solution of **1a** (4.4 g, 0.016 mol) and benzaldehyde (3.2 g, 0.030 mol) was refluxed for 2.5 h and cooled to 25 °C. $NaBH_4$ (1.0 g, 0.026 mol) was added and stirred for 2 h. The solution was concentrated and the residue taken up in 6% HCl and washed with ether. After basification of the aqueous acid solution and extraction with ether, 5.2 g (88%) of pure **1m** was secured after concentration. A dihydrochloride salt was recrystallized from EtOH and had mp 233–237 °C.

8-(Dimethylamino)-*cis*-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (9). A mixture of **8a** (20.0 g), formalin (35–40%, 25 mL), ethanol (180 mL), and 100 mg of 10% palladium on charcoal was hydrogenated at 55 °C on a Parr apparatus until hydrogen uptake ceased. The slurry was filtered and the filtrate concentrated. The residue was made strongly basic with concentrated NH_4OH, and the organic bases were extracted into $CHCl_3$. After drying (Na_2SO_4) and concentration, **9** (ca. 9 g) was secured in a crude state. An oxalate salt which was recrystallized three times from EtOH had mp 165–168 °C. Anal. ($C_{16}H_{24}N_2$·2.5$H_2C_2O_4$) C, H, N.

3-(Cyclopropylmethyl)-8-(dimethylamino)-*cis*-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine Dihydrochloride (1n). To a vigorously stirred mixture of 3.5 g (0.014 mol) of **9**, 100 mL of $CHCl_3$, and 100 mL of 1 N NaOH was added dropwise 4.6 g (0.044 mol) of cyclopropanecarboxylic acid chloride. After the mixture was stirred for 3 h at 25 °C, the layers were separated. The $CHCl_3$ solution was washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated, giving 4.0 g of crude residue. A THF (20 mL) solution of this residue was added to a stirred slurry of 2.0 g (0.05 mol) of $LiAlH_4$ in 70 mL of THF. This was refluxed for 3 h, cooled, and quenched by dropwise addition of saturated potassium sodium tartrate. After filtration, concentration, and an extractive (ether) workup, 3.0 g (70%) of **1n** was obtained. A dihydrochloride salt was prepared and when recrystallized from EtOH had mp 243–246 °C dec.

3-(Cyclopropylmethyl)-8-[(cyclopropylmethyl)amino]-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocine Hydrochloride (1o). To a well-stirred iced mixture of 1.0 g (0.0033 mol) of **1e**·2HCl·H_2O, 5 mL of saturated $NaHCO_3$, and 10 mL of $CHCl_3$ was added 0.73 g (0.007 mol) of cyclopropanecarboxylic acid chloride. After the mixture was stirred for 1 h, the layers were separated and the $CHCl_3$ was dried (Na_2SO_4) and concentrated. The residue was taken up in 20 cm^3 of THF, and 16.5 mL of 1 M BH_3/THF was added. The solution was refluxed for 2 h, cooled, and 20 mL of 5 N HCl was added. The solution was partially concentrated, washed with ether, and basified with 35% NaOH. After an extractive workup of the solution with $CHCl_3$, 0.98 g (82%) of **1o** remained. This product crystallized and was found to be **1o**·HCl, mp 229–232 °C.

Acknowledgment. We thank the Analytical and Physical Chemistry Departments of this Institute for spectral and GC measurements.