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Synthesis and Narcotic Agonist–Antagonist Evaluation of Some 2,6-Methano-3-benzazocine-11-propanols. Analogues of the Ring C Bridged Oripavine-7-methanols[1]

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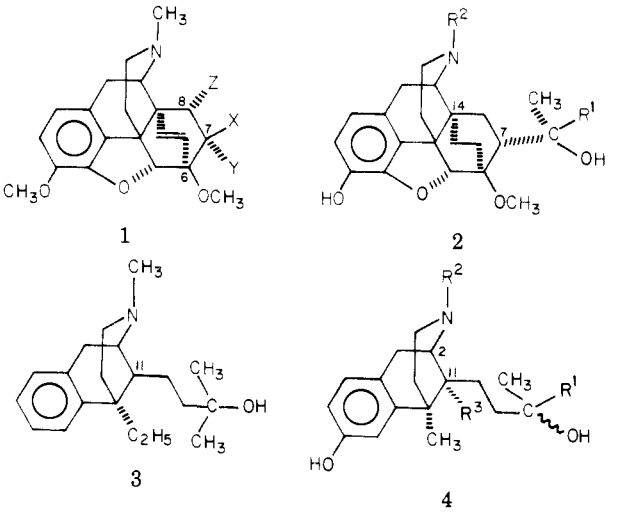
A general synthesis of variously substituted 2,6-methano-3-benzazocine-11-propanols is described. Nine N-CH_3 derivatives and their corresponding N-cyclopropylmethyl counterparts were prepared and studied in the mouse acetylcholine induced writhing and rat phenazocine antagonism tests. The results are compared with literature information on the bridged oripavine methanols. It is concluded that the synthetic analogues have a different structure–activity profile, in general being weak agonists but potent antagonists.

In 1967, Bentley and his colleagues postulated that a separation of some of morphine's pharmacological effects might be achieved by making molecules more rigid and complex than the morphine molecule, thereby rendering the new derivatives less acceptable at some receptor surfaces. To this end, thebaine was condensed with a variety of dienophiles[2-5] to produce ring C bridged adducts of general structure **1**. These rigid molecules possessed functionalities at positions 7 and 8 which were manipulated to produce compounds of still further complexity. In addition, variations at other positions of **1** were made and their effects on biological activity studied. While the hoped for separation of effects may not have been fully realized, compounds of extremely high potency were found. Of particular interest has been the series of ring C bridged oripavines **2** bearing an asymmetric methanol functionality at position 7. The high potency of some of these derivatives, which could not be explained by differences in brain concentrations alone, led to the postulation of a specific receptor interaction. In addition to the anionic, planar, and cavity sites on the analgesic receptor model as proposed by Beckett and Casy,[6] a lipophilic fourth site was proposed to accommodate the group attached to position 7.[7] This proposal was strengthened by the fact that destruction of the aromatic ring of **1** [Z = X = H; Y = C-$(CH_3)(C_3H_7)$OH] by ozonolysis did not result in complete loss of analgesic activity.[8] The extensive chemistry[9] and pharmacology[7,10] of the **1** series have been reviewed.

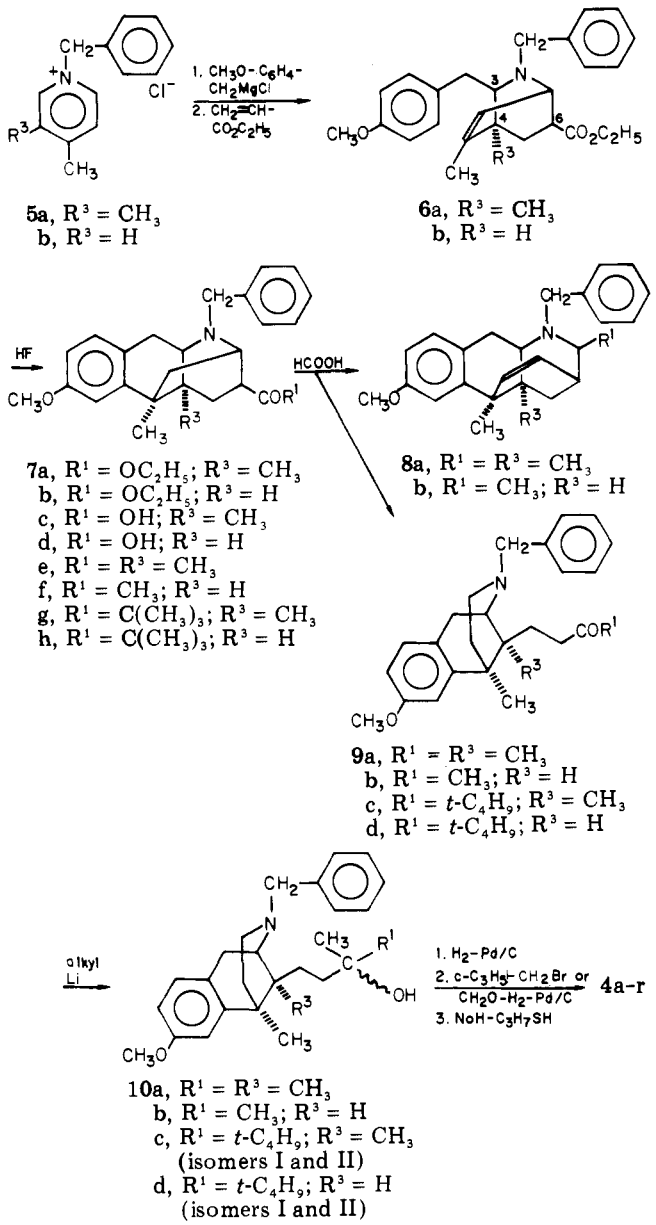
While a few synthetic analogues of the series **2** have been reported,[8,11,12] none are capable of interacting simultaneously with all four of the proposed sites on the analgesic receptor. Synthetic compounds which can so interact might be of value in more precisely defining the structural requirements for narcotic agonist and antagonist activities and may give rise to even better analgesic agents than are currently available. The 2,6-methano-3-benzazocine ring system, a part structure of morphine, can interact with the three original sites proposed by Beckett and Casy. Substitution of this ring system for the morphine skeleton of **2** and attachment of the methanol functionality of **2** to position 11 by a two-carbon chain gives 2,6-methano-3-benzazocine-11-propanols such as **3** which should be capable of a four-point receptor interaction. One of us recently reported[13] the stereospecific synthesis of **3** which



was about 40% as potent as morphine in a conventional rodent test. We have now extended this synthesis to the preparation of a series of compounds **4** which possess a number of structural features found in **2** but not in **3**, namely, (a) a phenolic hydroxyl group; (b) quaternary substitution of position 11 which corresponds to position 14 in **2**; (c) an asymmetrically substituted alcohol bearing carbon atom; and (d) nitrogen substituent R^2 = cyclopropylmethyl (CPM) as well as methyl. All of the compounds prepared have been tested for narcotic agonist and antagonist properties.

Chemistry. 3,4-Dimethyl-1-(phenylmethyl)pyridinium chloride (**5a**, Scheme I) was allowed to react[14] with the Grignard reagent from 4-methoxyphenylmethyl chloride to produce an unstable mixture of dihydropyridines. This crude product was immediately treated with excess ethyl acrylate in refluxing benzene and the adduct **6a** was isolated. The stereochemistry of position 6 is of no consequence since it will be destroyed later in the synthesis.[15] The relative stereochemistry of positions 3 and 4 is exactly that of positions 2 and 11, respectively, in **4** which they are destined to become. The stereochemistry of position 3 follows from the fact that treatment of **6a** with anhydrous hydrogen fluoride results in cyclization to **7a** which, of course, cannot occur with the opposite stereo-

Scheme I



5a, $R^3 = CH_3$
b, $R^3 = H$

6a, $R^3 = CH_3$
b, $R^3 = H$

7a, $R^1 = OC_2H_5$; $R^3 = CH_3$
b, $R^1 = OC_2H_5$; $R^3 = H$
c, $R^1 = OH$; $R^3 = CH_3$
d, $R^1 = OH$; $R^3 = H$
e, $R^1 = R^3 = CH_3$
f, $R^1 = CH_3$; $R^3 = H$
g, $R^1 = C(CH_3)_3$; $R^3 = CH_3$
h, $R^1 = C(CH_3)_3$; $R^3 = H$

8a, $R^1 = R^3 = CH_3$
b, $R^1 = CH_3$; $R^3 = H$

9a, $R^1 = R^3 = CH_3$
b, $R^1 = CH_3$; $R^3 = H$
c, $R^1 = t\text{-}C_4H_9$; $R^3 = CH_3$
d, $R^1 = t\text{-}C_4H_9$; $R^3 = H$

10a, $R^1 = R^3 = CH_3$
b, $R^1 = CH_3$; $R^3 = H$
c, $R^1 = t\text{-}C_4H_9$; $R^3 = CH_3$ (isomers I and II)
d, $R^1 = t\text{-}C_4H_9$; $R^3 = H$ (isomers I and II)

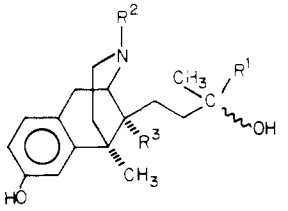
chemistry at this position.[16] The ester **7a** was saponified to the acid **7c** which in turn was treated with methyllithium to give the ketone **7e**. Refluxing a mesitylene solution of **7e** containing excess formic acid gave a mixture of the desired product **9a** and the by-product **8a** from which the former could be separated by crystallization. The ketone **9a** reacted cleanly with methyllithium to give the symmetrical carbinol **10a**. On treatment with *tert*-butyllithium **9a** gave a mixture of **10c** isomers. The major **10c** isomer formed in this reaction was designated as isomer I; isomer II could be isolated but was present in very small quantity. In order to obtain larger quantities of **10c**-II, **7a** was treated with *tert*-butyllithium to give **7g** directly. Ring opening of **7g** with formic acid in mesitylene gave **9c** as the exclusive product. We had speculated[13] that structures such as **8a** arise by a retro-Michael reaction of **7e** which is initiated by base-catalyzed removal of the ring hydrogen α to the carbonyl group. Apparently for **7g** approach by a base is so sterically hindered that α-hydrogen removal does not occur and no by-product is formed. Reaction of **9c** with methyllithium gave **10c**-II as the major isomer although this reaction was not as stereoselective as that of **9a** with *tert*-butyllithium. Since, however, we were interested in having large amounts of both **10c**-I and **10c**-II we elected to use the reaction of **9c** with methyllithium, the isomers being readily separable by crystallization. We repeated the foregoing sequence starting with **5b** to give the structures in Scheme I where $R^3 = H$. Clean ring opening of **7h** and the same stereoselectivity of addition of *tert*-butyl- and methyllithiums to **9b** and **9d**, respectively, were observed in this series also.

At the present time we are unable to assign the relative configurations of the carbinol carbons of the I and II isomers of **10c** and **10d** with certainty. We have, however, made a tentative assignment based on their NMR spectra. The NMR spectra of the two carbinol epimers of 1 [Z = X = H; Y = $C(CH_3)(C_6H_5)OH$] have been reported.[17] In this case, the carbinol methyl group in the epimer corresponding to the more analgesically active configuration occurs at slightly higher field (δ 1.42) than in the other epimer where it occurs at δ 1.52. With **10c**, this signal in the spectrum of isomer I occurs at δ 1.16 while that of isomer II occurs at slightly higher field (δ 1.00). Similarly for **10d**-I this signal occurs at δ 1.12 and for **10d**-II at slightly higher field (δ 1.02). These data suggest that the relative configuration of the carbinol carbon of the II isomers corresponds to the analgesically active configuration of this carbon in the ring C bridged oripavine methanols. If this assignment is correct it is interesting to note that when compared with metal alkyl additions to the carbonyl group of 1 (Z = X = H; Y = COR^1),[18] the corresponding additions to the carbonyl group of **9** are stereoselective in the opposite sense. In the former case, stereoselectivity was proposed to be the result of prior complexation of the metal atom with the carbonyl oxygen and the oxygen of the ether function at position 6. Since **9** does not possess an ether function and the conformationally mobile carbonyl group is at some distance from the ring system, it is difficult to explain the observed stereoselectivity. Compound **9b** was also allowed to react with ethyl-, propyl-, and butyllithiums to give the corresponding structures **10** where R^1 is ethyl, propyl, or butyl, respectively. [These compounds were not isolated as such but were converted directly to compounds **4** (vide infra)]. Therefore, these compounds probably have the same alcohol carbon configuration as the I isomers of **10c,d**.

The final conversion of the alcohols **10** to **4** was carried out using a three-step procedure without isolation of intermediates. The phenylmethyl group was removed by catalytic hydrogenolysis. The nitrogen was methylated reductively with formaldehyde or alkylated with cyclopropylmethyl bromide. Finally, the methyl ether was cleaved using the sodium salt of propanethiol.

Pharmacology. The compounds **4a–r** in aqueous solutions were assayed for agonist activity in the acetylcholine writhing procedure of Collier et al.[19] and for narcotic antagonist activity vs. phenazocine by the method of Harris and Pierson.[20] The results are shown in Table I, along with comparative data for metazocine, cyclazocine, nalorphine, and buprenorphine. Compounds **4a–i** bear an *N*-CH_3 group. The homologous series **4a–d** does not show any dramatic change in agonist potency as a function of chain length R^1, with only a slight increase on going from CH_3 to C_2H_5. Assuming that the carbinol carbon stereochemical assignment is correct, it is interesting that the corresponding homologous series of ring C bridged thebaines shows a decrease in potency on going from CH_3 to C_2H_5, without much further change.[7] The *tert*-butylcarbinols **4e–g,i** are very weak agonists and while **4a–d** are inactive as narcotic antagonists note that **4e** shows weak antagonist activity. These five compounds all have R^3 =

Table I. Physical Properties and Biological Activities of 2,6-Methano-3-benzazocine-11β-propanols



Compd	R^1	R^2	R^3	Isomer	Mp, °C	Formula[a]	ED_{50}[b]	AD_{50}[c]
4a	CH_3	CH_3	H		182-183	$C_{19}H_{29}NO_2$	8.2 (5.7-11)	i[d]
4b	C_2H_5	CH_3	H	I	155-157	$C_{20}H_{31}NO_2 \cdot CH_3SO_3H$	3.3 (2.5-4.2)	i
4c	C_3H_7	CH_3	H	I	144-146	$C_{21}H_{33}NO_2 \cdot CH_3SO_3H$	2.6 (1.9-3.6)	i
4d	C_4H_9	CH_3	H	I	184-186	$C_{22}H_{35}NO_2 \cdot CH_3SO_3H$	2.5 (1.8-3.5)	i
4e	$C(CH_3)_3$	CH_3	H	I	206-208	$C_{22}H_{35}NO_2 \cdot CH_3SO_3H$	>75[e]	?[f]
4f	$C(CH_3)_3$	CH_3	H	II	212-215	$C_{22}H_{35}NO_2 \cdot CH_3SO_3H$	>25[e]	i
4g	CH_3	CH_3	CH_3		179-182	$C_{20}H_{31}NO_2$	3.8 (3.2-4.6)	2.3 (1.5-3.6)
4h	$C(CH_3)_3$	CH_3	CH_3	I	242-247	$C_{23}H_{37}NO_2 \cdot CH_3SO_3H$	>25[e]	0.33 (0.21-0.51)
4i	$C(CH_3)_3$	CH_3	CH_3	II	219-223	$C_{23}H_{37}NO_2$	>25[e]	i
4j	CH_3	CPM[g]	H		138-140	$C_{22}H_{33}NO_2$	16 (13-19)	0.046 (0.030-0.071)
4k	C_2H_5	CPM	H	I	195-196	$C_{23}H_{35}NO_2 \cdot CH_3SO_3H$	7.9 (5.0-12)	0.040 (0.023-0.068)
4l	C_3H_7	CPM	H	I	182-183	$C_{24}H_{37}NO_2 \cdot CH_3SO_3H$	7.6 (5.8-9.3)	0.019 (0.011-0.032)
4m	C_4H_9	CPM	H	I	184-185	$C_{25}H_{39}NO_2 \cdot CH_3SO_3H$	6.5 (5.0-7.9)	0.025 (0.017-0.037)
4n	$C(CH_3)_3$	CPM	H	I	232 dec	$C_{25}H_{39}NO_2 \cdot CH_3SO_3H$	>25[e]	0.27 (0.17-0.41)
4o	$C(CH_3)_3$	CPM	H	II	248-250	$C_{25}H_{39}NO_2 \cdot CH_3SO_3H$	9.0 (6.6-13)	1.1 (0.69-1.8)
4p	CH_3	CPM	CH_3		236-238	$C_{23}H_{35}NO_2 \cdot HCl$	4.5 (2.8-6.6)	0.006 (0.003-0.011)
4q	$C(CH_3)_3$	CPM	CH_3	I	249 dec	$C_{26}H_{41}NO_2 \cdot CH_3SO_3H$	>25[e]	0.022 (0.015-0.033)
4r	$C(CH_3)_3$	CPM	CH_3	II	266-268	$C_{26}H_{41}NO_2 \cdot CH_3SO_3H$	8.9 (6.7-11)	0.71 (0.47-1.1)
						Metazocine	0.54 (0.39-0.91)	i
						Cyclazocine	0.15 (0.10-0.20)	0.007 (0.004-0.011)
						Nalorphine	2.8 (1.5-7.7)	0.1 (0.07-0.14)
						Buprenorphine	0.058 (0.031-0.095)	0.11 (flat)

[a] All compounds were analyzed for C, H, and N; analytical results were within ±0.4% of the theoretical values. [b] Acetylcholine writhing test (mouse), mg/kg sc (95% confidence limits). [c] Phenazocine antagonism (rat), mg/kg sc (95% confidence limits). [d] At screening dose of 80 mg/kg. [e] ED_{50}'s were not calculated for compounds showing less than 50% protection at 25 mg/kg. [f] Questionable activity at the screening dose. [g] R = cyclopropylmethyl.

H and the change to $R^3 = CH_3$ has a dramatic effect on antagonist potency, **4g** being moderately potent and **4h** somewhat more so. Looked at from a different point of view, attachment of a $-CH_2CH_2C(CH_3)(OH)R^1$ group to the 11 position of metazocine (i.e., to give **4g** and **4h**) introduces narcotic antagonist activity at the expense of agonist activity. The alcohol stereochemistry of **4h** seems to be required since its reversal (**4i**) destroys the antagonist effect. Compound **4h** appears to be one of the most potent N-CH_3 narcotic antagonists so far reported.[21] Narcotic antagonism has not been reported for N-CH_3 derivatives of ring C bridged thebaines or oripavines.

Compounds **4j–r** are the N-CPM analogues of **4a–i**, respectively. In the homologous series **4j–m** there is again a slight increase in agonist activity in going from $R^1 = CH_3$ to C_2H_5, and antagonist activity appears to be maximum at $R^1 = C_3H_7$. By contrast, and bearing in mind our proposed stereochemical assignments, in the corresponding homologous series of N-CPM bridged oripavines, antagonism decreases to a minimum at C_3H_7, the n-C_4H_9 compound being a morphine-like agent.[10] Compounds **4j** and **4n** with $R^3 = H$ undergo an approximate tenfold increase in antagonist potency by changing R^3 to CH_3 (**4p** and **4q**, respectively). Or, looked at from the point of view of cyclazocine, introduction of a $-CH_2CH_2(CH_3)(OH)R^1$ at position 11 (i.e., to give **4p** and **4q**) has no or little effect on antagonist activity while greatly weakening the agonist effect. Reversal of alcohol stereochemistry of **4n** and **4q** to give **4o** and **4r**, respectively, decreases but does not abolish antagonist activity while at the same time increases agonist activity relative to **4n** and **4q**. Compound **4r** is our closest analogue to buprenorphine (**2**, $R^1 = t$-C_4H_9; R^2 = CPM). While the two compounds are more or less comparable as antagonists, **4r** is some 150 times less potent as an agonist.

It can be seen that while our compounds may be structurally similar to the bridged oripavine derivatives, there are major differences in the structure–activity profile which has so far emerged. An explanation of these differences is not readily apparent; development of a more complete structure–activity profile is desirable with a view toward finding compounds with greater agonist potency. This work is currently in progress and will form the subjects of future reports.

Experimental Section

Grignard reagents and alkyllithiums were either obtained commercially or prepared by standard procedures. In either case they were titrated before use.[22] Melting points were determined by the capillary method and are uncorrected. IR, NMR, and mass spectra substantiated the structures of all new compounds. Where analyses are indicated by the symbols of the elements, analytical results are within ±0.4% of the theoretical values.

Ethyl 4,8-Dimethyl-3-(4-methoxyphenylmethyl)-2-(phenylmethyl)-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate Hydrochloride (6a). To 2500 mL of a stirred 0.2 M Et_2O solution of 4-$CH_3OC_6H_4CH_2MgCl$ was added 117 g (0.5 mol) of **5a**. Stirring was continued for 4 h followed by quenching in 1 L of saturated aqueous NH_4Cl. The Et_2O layer was washed with H_2O and brine, dried, filtered, and evaporated. The residue was taken up in 500 mL of C_6H_6 and 108 mL (1.0 mol) of ethyl acrylate, refluxed overnight, and evaporated. This residue was dissolved in 250 mL of hexane and cooled in ice to remove the Grignard coupling product. Filtration and evaporation of the filtrate left a residue which was taken up in 200 mL of EtOH, acidified with HCl–Et_2O, and diluted with 800 mL of Et_2O. Cooling and scratching gave after filtration, washing, and drying 66 g (29%) of **6a** of adequate purity for chemical purposes. An analytical sample was obtained

by repeated recrystallization from EtOH–Et_2O: mp 205–207 °C. Anal. ($C_{27}H_{33}NO_3$·HCl) C, H, N.

Ethyl 3-(4-Methoxyphenylmethyl)-8-methyl-2-(phenylmethyl)-2-azabicyclo[2.2.2]oct-7-ene-6-carboxylate Hydrochloride (6b). The same procedure as for **6a** was used to give **6b**: 42%; mp 210–213 °C. Anal. ($C_{26}H_{31}NO_3$·HCl) C, H, N.

Ethyl 1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-4a,5-dimethyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinoline-3-carboxylate (7a). Liquid HF was added to 40.9 g (0.09 mol) of **6a** in a Nalgene screw cap bottle to a total volume of 240 mL. The cap was screwed on tightly and the solution allowed to stand at room temperature for 24 h. The cap was removed and the HF allowed to evaporate. The residue was partitioned between CH_2Cl_2 and dilute NH_4OH. The organic layer was washed with H_2O, brine being added to sharpen phase separation. Drying and evaporation of the solvent left a syrup which crystallized from 180 mL of EtOH to give 29.0 g (77%) of crude **7a**, mp 89–94 °C. An analytical sample was obtained by adding a warm hexane (50 mL) solution of 10 g of the crude solid to a column of 250 g of silica gel containing 20% of H_2O and eluting with hexane. The resulting syrup was crystallized from 43 mL of EtOH to give 8.1 g of pure **7a**, mp 98–100 °C. Anal. ($C_{27}H_{33}NO_3$) C, H, N.

Ethyl 1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-5-methyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinoline-3-carboxylate (7b). The same procedure as for **7a** was used. The product was isolated as the HCl salt from acetone (75%): mp 225–228 °C. Anal. ($C_{26}H_{31}NO_3$·HCl) C, H, N.

1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-4a,5-dimethyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinoline-3-carboxylic Acid (7c). A solution of 27.0 g (0.064 mol) of **7a**, 130 mL of EtOH, 130 mL of H_2O, and 2.8 g (0.07 mol) of NaOH was stirred and refluxed for 3 h, cooled, and washed twice with Et_2O. The aqueous layer was neutralized by addition of 4.0 mL (0.07 mol) of HOAc and extracted thrice with Et_2O. The combined extracts were washed twice with H_2O and then brine. Drying, filtration, and evaporation left 22.9 g (91%) of a powderable foam which could not be induced to crystallize and therefore was analyzed directly. Anal. ($C_{25}H_{29}NO_3$) C, H, N.

1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-5-methyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinoline-3-carboxylic Acid (7d). The same procedure as for **7c** was used, adding an extra equivalent of NaOH. This compound was obtained (82%) crystalline from *i*-PrOAc: mp 158–160 °C. Anal. ($C_{24}H_{27}NO_3$) C, H, N.

1-[1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-4a,5-dimethyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinolin-3-yl]-1-ethanone (7e). To a stirred solution of 11.5 g (0.029 mol) of **7c** in 220 mL of Et_2O was added under N_2 50 mL (0.09 mol) of 1.8 M CH_3Li–Et_2O. Stirring was continued 1 h at room temperature when 1.5 mL (0.015 mol) of EtOAc was added dropwise. The reaction mixture was then poured into aqueous NH_4Cl and the Et_2O layer washed with H_2O, brine being added to sharpen phase separation. Washing with brine, drying, filtering, and evaporating left 10.7 g (94%) of a white solid which could be recrystallized from EtOH: mp 128–131 °C. Anal. ($C_{26}H_{31}NO_2$) C, H, N.

1-[1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-5-methyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinolin-3-yl]-1-ethanone (7f). The same procedure as for **7e** was used (78%): mp 126–128 °C. Anal. ($C_{25}H_{29}NO_2$) C, H, N.

1-[1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-4a,5-dimethyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinolin-3-yl]-2,2-dimethyl-1-propanone (7g). A solution of 83.9 g (0.2 mol) of **7a** in 800 mL of toluene was stirred under N_2 and cooled <–65 °C. Over 1 h 125 mL (0.2 mol) of 1.7 M *t*-BuLi–pentane was added and stirring <–65 °C was continued for 15 min before allowing the reaction to come to room temperature. The mixture was poured into aqueous NH_4Cl and 800 mL of Et_2O was added. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with H_2O and brine, dried, filtered, and evaporated. The crude base was taken up in 265 mL of EtOH and 2650 mL of Et_2O, acidified with ethereal HCl and allowed to crystallize. Two recrystallizations from EtOH–Et_2O gave material which was homogeneous on TLC but showed variable melting behavior and was not further characterized. It was converted to the base with dilute NH_4OH, dried in Et_2O, and crystallized from EtOH to give 46.8 g (54%), mp 112–115 °C. Anal. ($C_{29}H_{37}NO_2$) C, H, N.

1-[1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-5-methyl-1-(phenylmethyl)-2,5-methanobenzo[*g*]quinolin-3-yl]-2,2-dimethyl-1-propanone (7h). The same procedure as for **7g** was used. The crude base was purified by passing a C_6H_6 solution of it through a column of silica gel deactivated with 10% of H_2O and eluting with C_6H_6. The resulting syrup crystallized from EtOH (50%): mp 146–151 °C. Anal. ($C_{28}H_{35}NO_2$) C, H, N.

1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-2,4a,5-trimethyl-1-(phenylmethyl)-3,5-ethenobenzo[*g*]quinoline (8a) and 4-[1,2,3,4,5,6-Hexahydro-8-methoxy-6,11-dimethyl-3-(phenylmethyl)-2,6-methano-3-benzazocin-11-yl]-2-butanone (9a). A mixture of 19.5 g (0.05 mol) of **7e**, 38 mL (1.0 mol) of formic acid, and 1000 mL of mesitylene was stirred and refluxed (internal temperature 115–120 °C) for 48 h. The mixture was cooled and basified with aqueous NaOH. The mesitylene layer was washed with H_2O and brine, dried, filtered, and evaporated leaving 15.9 g of solid. This was dissolved in a minimum of boiling EtOH and cooled to give 11.9 g of crude **9a**. Recrystallization from EtOH gave pure **9a** (59%), mp 132–133 °C. Anal. ($C_{26}H_{33}NO_2$) C, H, N.

The filtrate from the isolation of crude **9a** was evaporated, the residue dissolved in 25 mL of acetone, and 3 g of picric acid added. On cooling, **8a** picrate was obtained: mp 236–239 °C. Anal. ($C_{26}H_{31}NO$·$C_6H_3N_3O_7$) H, N; C: calcd, 63.78; found, 62.95.

1,2,3,4,4a,5,10,10a-Octahydro-7-methoxy-2,5-dimethyl-1-(phenylmethyl)-3,5-ethenobenzo[*g*]quinoline (8b) and 4-[1,2,3,4,5,6-Hexahydro-8-methoxy-6-methyl-3-(phenylmethyl)-2,6-methano-3-benzazocin-11-yl]-2-butanone (9b). The same procedure as for **8a** and **9a** was used. **9b**: 50%; mp 101–102 °C. Anal. ($C_{25}H_{31}NO_2$) C, H, N. **8b** picrate: mp 214–216 °C. Anal. ($C_{25}H_{29}NO$·$C_6H_3N_3O_7$) C, H, N.

5-[1,2,3,4,5,6-Hexahydro-8-methoxy-6,11-dimethyl-3-(phenylmethyl)-2,6-methano-3-benzazocin-11-yl]-2,2-dimethyl-3-pentanone (9c). The same procedure as for **9a** was used except the reflux period was 6 days. The product was purified as the HCl salt (pure by TLC but variable melting point) and then converted back to the base, a syrup (73%). Anal. ($C_{29}H_{39}NO_2$) C, H, N.

5-[1,2,3,4,5,6-Hexahydro-8-methoxy-6-methyl-3-(phenylmethyl)-2,6-methano-3-benzazocin-11-yl]-2,2-dimethyl-3-pentanone (9d). The same procedure as for **9a** was used. The HCl salt had mp 246–249 °C (83%). Anal. ($C_{28}H_{37}NO_2$·HCl) C, H, N.

1,2,3,4,5,6-Hexahydro-8-methoxy-6,11,α,α-tetramethyl-3-(phenylmethyl)-2,6-methano-3-benzazocine-11-propanol (10a). To a stirred, cold solution of 25 mL (0.043 mol) of 1.7 M CH_3Li–Et_2O in 100 mL of C_6H_6 under N_2 was added dropwise a solution of 8.4 g (0.021 mol) of **9a** in 100 mL of C_6H_6. Stirring was continued for 1 h at room temperature, when the reaction was quenched with aqueous NH_4Cl. The aqueous layer was extracted with C_6H_6 and the combined organic layers were washed with H_2O and brine, dried, filtered, and evaporated. The residue was taken up in 20 mL of EtOH and 80 mL of Et_2O, acidified with HCl–Et_2O and cooled in ice to give 6.1 g (64%) of **10a**·HCl salt. A sample recrystallized from EtOH had mp 233–236 °C. Anal. ($C_{27}H_{37}NO_2$·HCl) C, H, N.

1,2,3,4,5,6-Hexahydro-8-methoxy-6,α,α-trimethyl-3-(phenylmethyl)-2,6-methano-3-benzazocine-11-propanol (10b). The same procedure as for **10a** was used. The HCl salt was obtained in 87% yield, mp 256–257 °C, from EtOH. Anal. ($C_{26}H_{35}NO_2$·HCl) C, H, N.

α-(1,1-Dimethylethyl)-1,2,3,4,5,6-hexahydro-8-methoxy-6,11,α-trimethyl-3-(phenylmethyl)-2,6-methano-3-benzazocine-11-propanol (10c-I and 10c-II). The same procedure as for **10a** was used. In one run 27.7 g (98%) of crude base mixture was obtained. This was taken up in 450 mL of EtOH and acidified with HCl–Et_2O to give a crop (20.7 g) of **10c**-II. Two recrystallizations from EtOH gave pure material, mp 246–248 °C. Anal. ($C_{30}H_{43}NO_2$·HCl) C, H, N.

The mother liquor from the crop of crude **10c**-II was evaporated; the residue (10.8 g) was dissolved in 50 mL of MeOH and diluted with 400 mL of Et_2O to give a crop (4.1 g) of **10c**-I. Two recrystallizations gave pure material, mp 250–251 °C. Anal. ($C_{30}H_{43}NO_2$·HCl) C, H, N.

α-(1,1-Dimethyl)-1,2,3,4,5,6-hexahydro-8-methoxy-6,α-dimethyl-3-(phenylmethyl)-2,6-methano-3-benzazocine-11-propanol (10d-I and 10d-II). The same procedure as for **10a** was used. In one run 38.0 g (96%) of crude base mixture was obtained. This was taken up in 190 mL of EtOH and cooled to give a crop (24.1 g) of **10d**-II solvated base. Three recrystallizations from EtOH gave TLC pure material which was converted to the HCl salt from EtOH–Et_2O: mp 246–249 °C after melting ~150 °C and resolidifying ~165 °C. Anal. ($C_{29}H_{41}NO_2$·HCl) C, H, N.

The mother liquor from the crystallization of crude **10d**-II base was evaporated to dryness. The residue (13.3 g) was dissolved in 135 mL each of Et_2O and EtOH and acidified with HCl–Et_2O to give a crop (8.7 g) of crude **10d**-I. Recrystallization from EtOH–Et_2O gave TLC pure material, mp 249 °C dec. Anal. ($C_{29}H_{41}NO_2$·HCl) C, H, N.

Compounds for Biological Evaluation (4a–r). For compounds **4b–d** and **4k–m**, **9b** was allowed to react with the appropriate alkyllithium according to the procedure given for the preparation of **10a**. These intermediates were not isolated and characterized but were used directly in their crude base form, 0.01 mol being dissolved in 50 mL of DMF and 1 equiv of HCl–Et_2O added. For the remaining compounds the HCl salt of the appropriate 10 was used, 0.01 mol being dissolved in 50 mL of DMF. To each DMF solution was added 0.5 g of Pd/C and the mixture was shaken under 50 psi of H_2 until uptake ceased. For the *N*-CH_3 derivatives **4a–i**, 1.5 mL (0.011 mol) of Et_3N and 1.1 mL (0.0145 mol) of 35% aqueous CH_2O were added and the mixture was again shaken under 50 psi of H_2 until uptake ceased. The catalyst was filtered and the filtrate distilled at 1 atm until the head temperature was 150 °C. For the *N*-CPM derivatives **4j–r** the catalyst was filtered, 2.0 g (0.015 mol) of cyclopropylmethyl bromide[23] and 1.7 g (0.02 mol) of $NaHCO_3$ were added, and the mixture was warmed on a steam bath 1 h and then distilled as above for the *N*-CH_3 derivatives. The remainder of the procedure was the same in either case. To the cooled reaction mixture was added under N_2 2.1 g (0.05 mol) of NaH (57% dispersion in oil) and 4.6 mL (0.05 mol) of propanethiol dropwise. The resulting mixture was stirred and refluxed for 4 h, cooled, poured into aqueous NH_4Cl, and extracted with Et_2O. The basic fraction was isolated by extraction with 0.1 M CH_3SO_3H and basification with NH_4OH. Bases were crystallized from EtOAc, CH_3SO_3H salts from MeOH-Et_2O, and the HCl salt from EtOH. Overall yields ranged from 20 to 80%. The physical properties of **4a–r** are given in Table I.

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References and Notes

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