Synthesis and Analgetic Activity of 1,2,3,4,5,6-Hexahydro-1,6-methano-3-benzazocines

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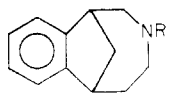
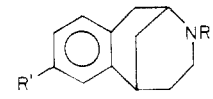
1,2,3,4,5,6-Hexahydro-1,6-methano-3-benzazocine (1) has been synthesized via a four-step sequence from benzonorbornadiene. This compound and its *N*-methyl derivative are more active than codeine in the mouse hot-plate antinociceptive assay and will not support morphine dependence in Rhesus monkeys.

Certain molecules based on condensed ring substructures of morphine have shown desired analgesic activity but are devoid of physical dependence liability of the opiate type in monkey species, the most serious side effect of morphine-like drugs. The best known tricyclic ring system which has yielded compounds of this sort is the 6,7-benzomorphan system. Analgesic activity has also been found in a number of homologues of the 6,7-benzomorphans including the lesser known *B*-norbenzomorphans,[1] *C*-norbenzomorphans,[2] and *C*-homobenzomorphans.[3-6] Several members of the bicyclic 1,2,3,4,5,6-hexahydro-3-benzazocines have also been prepared and tested.[7-9] For 6,7-benzomorphan derivatives, separation of analgesic activity from physical dependence liability is often achieved by substitution of certain saturated or unsaturated side chains[10] on the nitrogen atom or by optical resolution of a racemic mixture. It is well documented[11,12] that the substitution of such groups as allyl, cyclopropylmethyl, and 3-methyl-2-butenyl for methyl confers a combination of agonist (analgetic) and antagonist (precipitates withdrawal in morphine-dependent animals) properties on not only 6,7-benzomorphans and their homologues but also on morphine and related systems.[12] Such agonist–antagonist activity renders these molecules much less prone to abuse with, in some cases, substantial retention or enhancement of analgetic potency.[11] In general, however, increase in antagonistic action is accompanied by an increase in another undesirable property, the "psychotomimetic effect".[13]

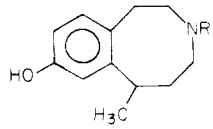
We wish to report the synthesis of several members of a previously unknown ring system, the 1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocines **1a–g**. A number of



1a, R = H
b, R = CH_3
c, R = $CH_2CH_2C_6H_5$
d, R = CH_2-c-C_3H_5
e, R = $CH_2CH_2CH_3$
f, R = $CH_2CH{=}CH_2$
g, R = $CH_2CH{=}C(CH_3)_2$



2a, R = H; R′ = H
b, R = CH_3; R′ = H
c, R = CH_3; R′ = OH

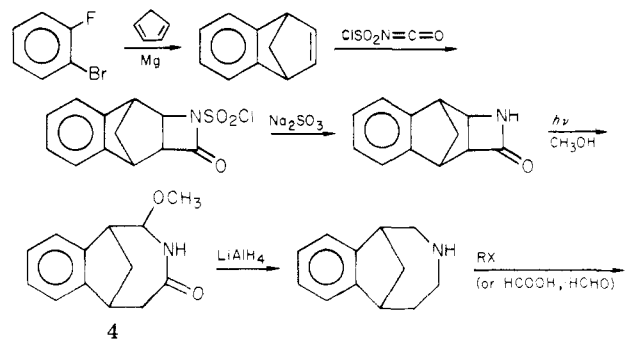


3a, R = H
b, R = CH_3

these materials appear to have strong analgesic activity and lack physical dependence liability (as ascertained from monkey studies); they appear to have no properties of antagonism and, therefore, probably no psychotomimetic effects.

Chemistry. The synthetic sequence utilized in the preparation of **1a–g** is outlined in Scheme I. The synthesis

Scheme I



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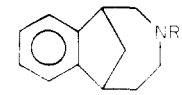

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of **4** by this route has previously been reported.[14] Compounds **1a–g** were obtained in overall yields of 2–10% (from *o*-fluorobromobenzene) by reduction of **4** with lithium aluminum hydride in refluxing tetrahydrofuran followed by alkylation with the appropriate halide, acylation followed by reduction with lithium aluminum hydride, or methylation by formic acid–formaldehyde.

Pharmacology. Analgetic potencies were determined by the Eddy hot-plate method.[15] Compounds **1a** and **1b** have more than twice the analgetic potency of the corresponding 6,7-benzomorphans[16] (**2a,b**) and it is noteworthy that **1b** is as active as the 2′-hydroxy-2-methyl-6,7-benzomorphan[16] (**2c**). Compounds **1a–c** are also more active than the *N*-methyl derivative of **3** (**3b**).[8]

Discussion

The 1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocines which we have prepared are unsubstituted other than on nitrogen. Their activity is particularly striking considering the absence of the 8-hydroxyl group which is considered one of the necessities in morphine-type structures for strong analgesic activity and, by inference, interaction between drug and receptor.

It can be seen from Table I that maximum analgesic activity is shown by the unsubstituted parent and the *N*-methyl and *N*-phenethyl derivatives; the greater activity of the latter two is predictable by analogy to the 6,7-benzomorphan series. The unusual activity of the parent amine (**1a**) is also analogous to the 6,7-benzomorphan system (e.g., **2a**); generally *nor* analgetics are inactive in vivo due to their inability to pass the "blood brain barrier". The other derivatives, whose N-substituents would ordinarily be expected to confer agonist–antagonist activity on the molecule, are notably less active as analgesics, also in accord with the relative activities of the 6,7-benzomorphans but, in contrast to the 6,7-benzomorphans, these

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Table I. Analgetic Data

	R	Analgesic act., hot-plate, ED_{50} mg/kg	μ-mol/kg
1a	H	4.9 (3.6-6.5)[a]	23.4
1b	CH_3	4.2 (2.6-6.7)[b]	18.8
1c	$CH_2CH_2C_6H_5$	8.8 (6.2-12.5)	28.0
1d	CH_2-c-C_3H_5		
1e	$CH_2CH_2CH_3$	16.2 (11.7-22.4)	64.3
1f	$CH_2CH{=}CH_2$	19.4 (13.1-28.7)	77.7
1g	$CH_2CH{=}C(CH_3)_2$	Inactive	
2a	H	10.2	48.7
2b	CH_3	11.2	50.1
2c	CH_3	4.5	18.8
3a	H		
3b	CH_3	12.5	43.7
Morphine hydrochloride		1.2 (0.9-1.3)	4.1
Codeine		7.5 (6.8-8.3)	20.2

[a] ED_{50} (Nilsen, sc, mg/kg) 6.1 (3.9-9.4). [b] ED_{50} (Nilsen, sc, mg/kg) 8.2 (5.1-13.1).

compounds are not antagonists.[17] Neither **1a** (2–8 mg/kg) nor **1b** (2–4 mg/kg) would support morphine dependence in single dose suppression studies or precipitate withdrawal symptoms in nonwithdrawn Rhesus monkeys addicted to morphine.[17] In addition, it is worth noting that in the three test cases so far reported, 6,7-benzomorphans having carbon 5 unsubstituted (tertiary) have shown mixed agonist–antagonist properties,[18] whereas the 1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocines which we have prepared apparently do not share this characteristic.

A priori it would seem reasonable to assume that in vivo transport properties of the 1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocines reported herein, the 6,7-benzomorphans, and homologues of the 6,7-benzomorphans should all be quite comparable. It is tempting to suggest that, in view of their apparent activity, the hexahydro-1,6-methano-3-benzazocines (**1**) manifest their analgesic effect by interaction at the opiate receptor. Judgment on this point will be reserved until binding studies are complete. The syntheses of other derivatives of **1** are in progress and these results will be reported in due course.

Experimental Section

Melting points (capillary, uncorrected) were determined using a Thomas-Hoover apparatus. Elemental analyses (indicated by C, H, and N when within ±0.4% of calculated values) were performed by Dr. Franz Kasler of the University of Maryland. IR (Beckmann) and NMR (Varian Associates XL 100, A-60 or EM-360) spectra are consistent with all assigned structures.

1,2,3,4,5,6-Hexahydro-1,6-methano-3-benzazocine (1a) Hydrochloride. To a 1-L flask equipped with an addition funnel, condenser, and nitrogen inlet (all predried) were added 250 mL of THF (freshly distilled from CaH_2) and 6.17 g (0.163 mol) of $LiAlH_4$. A solution of 5.7 g (0.0263 mol) of 2-methoxy-2,3,5,6-tetrahydro-1,6-methano-3-benzazocin-4(1*H*)-one in 350 mL of tetrahydrofuran (dried) was added with stirring, and the mixture was heated at reflux for 7 days. The mixture was cooled and hydrolysis was accomplished by successive additions of 6.2 mL of H_2O in 24 mL of THF, 6.2 mL of 15% NaOH, and 19 mL of water in 75 mL of THF. Stirring was continued for 20–30 min and the mixture filtered by suction.

Approximately 100 mL of benzene was added to the filtrate and the mixture concentrated in vacuo. The residue was distilled [90–110 °C bath temperature (0.1 mm)] to give 1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (3.85 g, 86%): IR (neat) 3270, 1140, 1020, 760, 740 cm^{-1}. The free amine was dissolved in Et_2O and HCl gas passed through the solution giving a white flocculent precipitate which was filtered and recrystallized from MeOH–acetone (1:3): mp 272–275 °C dec; IR ($CHCl_3$) 2850–2650, 1590, 1450 cm^{-1}; NMR (D_2O) δ 1.6–3.8 (10 H, m, aliphatic), 7.4 (4 H, s, aromatic). Anal. ($C_{12}H_{16}NCl$) C, H, N.

3-Methyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1b) Hydrochloride. To a 10-mL round-bottom flask were added 1.50 g (0.00867 mol) of **1a**, 2 mL of HCOOH, and 2 mL of 40% HCHO. The mixture was heated at 95–105 °C for 3 h and cooled, 60 mL of 15% NaOH was added, and the aqueous layer was extracted with four 60-mL portions of CH_2Cl_2. The combined extracts were concentrated in vacuo in the presence of benzene to remove H_2O. The residue, 1.55 g (0.00829 mol), was distilled [90–115 °C bath temperature (0.1 mm)] to give colorless 3-methyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1.1 g, 68% yield) which was converted to the hydrochloride: mp 215–216 °C dec (from acetone–Et_2O); *m/e* 187 (M^+ – HCl). Anal. ($C_{13}H_{18}NCl$) C, H, N.

3-Cyclopropylcarbonyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine. To 2.00 g (0.0116 mol) of **1a** in 29 mL of CH_3OH were added 4.3 mL of H_2O and 2.86 g (0.0207 mol) of K_2CO_3. The mixture was stirred in an ice bath while 2.26 g (0.0216 mol) of cyclopropylcarbonyl chloride was added dropwise, and stirring was continued for an additional 3 h.

The solvent was removed in vacuo and the residue treated with 60 mL of H_2O, 40 mL of benzene, and 20 mL of 1-BuOH. The organic layer was separated, washed with two 60-mL portions of 3 N HCl and two 60-mL portions of water, and then concentrated in vacuo; 100 mL of benzene was added and the mixture dried over Na_2SO_4. Filtration and concentration in vacuo afforded 2.1 g of residue which was distilled [220–240 °C bath temperature (0.1 mm)] to give 1.6 g (57%) of colorless product: *m/e* 241 (M^+); IR (CCl_4) 1640 cm^{-1}; NMR ($CDCl_3$) δ 0.2–1.20 (4 H, m, cyclopropyl), 0.65–4.8 (11 H, m, aliphatic), 7.2 (4 H, s, aromatic). Anal. ($C_{16}H_{19}NO$) C, H, N.

3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1d) Hydrochloride. A solution of 1.39 g (0.00576 mol) of 3-cyclopropylcarbonyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine in 14 mL of dry THF was added dropwise to a slurry of 0.69 g (0.0182 mol) of $LiAlH_4$ in 25 mL of dry THF. The reaction mixture was heated at reflux for 3 h, cooled, and hydrolyzed by addition of a solution of 1.3 mL of H_2O in 25 mL of THF. The mixture was filtered, 100 mL of benzene added to the filtrate, and the solution concentrated in vacuo. The residue was distilled [120–160 °C bath temperature (0.1 mm)] to give 0.89 g (68%) of the amine **1d** which was converted to the hydrochloride (Et_2O–HCl gas): mp 228–230 °C dec (CH_3OH–Et_2O); *m/e* 227 (M^+ – HCl); NMR (D_2O) 0.2–1.2 (5 H, m, cyclopropyl), 1.6–4.0 (12 H, m, aliphatic), 7.3 (4 H, m, aromatic). Anal. ($C_{16}H_{22}NCl$) C, H, N.

3-(2-Phenylethyl)-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1c) Hydrochloride. To 1.0 g (0.0058 mol) of **1a** and 1.97 g (0.0143 mol) of K_2CO_3 in 25 mL of DMF (freshly distilled from CaH_2) was added 1.11 g (0.0060 mol) of 2-phenylethyl bromide, and the mixture was heated at 90–110 °C overnight with stirring. The mixture was cooled, DMF was removed in vacuo, and 65 mL of $CHCl_3$ and 30 mL of H_2O were added to the residue. The organic layer was separated, washed with five 60-mL portions of H_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was distilled [bath temperature 190–210 °C (0.1 mm)] and converted to the hydrochloride (ether–HCl gas): mp 275–278 °C dec. Anal. ($C_{20}H_{24}NCl$) C, H, N.

3-Allyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1f) Hydrochloride. To 2.00 g (0.0116 mol) of **1a** and 2.88 g (0.034 mol) of $NaHCO_3$ in 60 mL of absolute EtOH was added 1.4 g (0.0116 mol) of 3-bromopropene. The mixture was stirred at reflux for 19 h, cooled, and filtered and the filter pad was washed with 20 mL of EtOH. The combined filtrates were concentrated in vacuo to leave a residue which was triturated with acetone–Et_2O and filtered through Celite, and the filtrate was concentrated under reduced pressure. Distillation of the residue [118–125 °C bath temperature (0.15 mm)] gave 1.35 g (55%) of amine **1f** which was converted to the hydrochloride (ether–HCl gas): mp 214–216 °C dec (acetone–ether); *m/e* 213 (M^+ – HCl). Anal. ($C_{15}H_{20}NCl$) C, H, N.

3-Propyl-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1e) Hydrochloride. To 1.32 g (0.00763 mol) of **1a** and 2.66 g (0.0193 mol) of K_2CO_3 in 16 mL of DMF (freshly distilled from CaH_2) was added 1.36 g (0.0080 mol) of propyl iodide. The mixture was stirred and heated at 110 °C for 2.5 h, cooled, and filtered. The recovered solid was washed with 15 mL of $CHCl_3$ and the filtrates were combined and concentrated under reduced pressure. Distillation of the residue [90–120 °C bath temperature (0.1 mm)] gave 0.81 g (49%) of free amine. The amine was dissolved in ether, dried over molecular sieves, filtered through Celite, and converted to the hydrochloride (HCl gas): mp 195–197 °C (acetone–Et_2O); *m/e* 215 (M^+ – HCl). Anal. ($C_{15}H_{22}NCl·0.5H_2O$) C, H, N.

3-(3-Methyl-2-butenyl)-1,2,3,4,5,6-hexahydro-1,6-methano-3-benzazocine (1g) Oxalate. To 1.00 g (0.00578 mol) of **1a** were successively added 50 mL of DMF (distilled from CaH_2), 0.86 g (0.00577 mol) of 1-bromo-3-methyl-2-butene, and 0.73 g (0.00869 mol) of $NaHCO_3$. The mixture was refluxed 4.5 h, cooled, filtered through Celite (the filter cake washed with EtOH), and concentrated in vacuo. The residue was triturated with Et_2O and the solution filtered through Celite. After concentration, the residue was distilled [125–135 °C bath temperature (0.05 mm)] and the distillate (0.8 g, 57%) converted to the oxalate salt (ethereal oxalic acid): mp 173–176 °C (from CH_3OH–acetone). Anal. ($C_{19}H_{25}NO_4$) C, H, N.

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Hetacillin (*R*)- and (*S*)-Sulfoxides. Synthesis and Structure–Activity Relationships

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Hetacillin was oxidized with *m*-chloroperbenzoic acid to give the corresponding (*R*)- and (*S*)-sulfoxides. Ozonization of hetacillin not only oxidized the sulfide but caused unexpected oxidation of the imidazolidine ring to a 2*H*-imidazoline. The biological spectrum showed the (*R*)-sulfoxide to be appreciably more active than the (*S*)-sulfoxide.

Hetacillin,[1] a semisynthetic penicillin, offers a unique advantage in preparing penicillin (*R*)-sulfoxides. Other workers have extensively studied the stereochemistry of sulfoxide bond formation[2,3] and have indicated that the preferential formation of penicillin (*S*)-sulfoxides can be attributed to the directing effect of the carboxamido group present in the side chain. As with 6-phthalimidopenicillanic acid, hetacillin has a relatively bulky 6-substituent without an amide hydrogen available for hydrogen bonding. This allows steric effects to dominate and offers a convenient route to the preparation of penicillin (*R*)-sulfoxides. The imidazolidine moiety of hetacillin, however, offers a distinct advantage over the phthalimido group since it can be hydrolyzed easily to an α-aminophenylacetamido group, which is a side chain of a biologically active penicillanic acid derivative. It was our purpose to prepare both the hetacillin (*R*)- and (*S*)-sulfoxides and to compare their biological activities with those of their penicillin precursor, hetacillin.

The oxidation of penicillin derivatives has been extensively studied by other investigators. In contrast to oxidants such as sodium metaperiodate,[4] hydrogen peroxide,[5] and *m*-chloroperbenzoic acid[6] which have led to the isolation of only the (*S*)-sulfoxide, ozone has been found to afford a mixture of the (*R*)- and (*S*)-sulfoxides.[7] Therefore, the oxidation of hetacillin with ozone seemed to be the method of choice for the preparation of the (*R*)-sulfoxide. However, when ozone was found to attack the imidazolidine ring, oxidation with *m*-chloroperbenzoic acid was investigated.

Chemistry. Oxidation of hetacillin with *m*-chloroperbenzoic acid afforded a 7:3 mixture of the isomeric sulfoxides **2** and **3** (Scheme I). These could be easily separated by fractional crystallization, and the major isomer was assigned the (*R*)-sulfoxide configuration, **2**. Treatment of hetacillin with ozone unexpectedly led to oxidation of both the imidazolidine ring and the sulfide, affording compound **1** in high yield. The assignments of sulfoxide configurations on compounds **1–3** are based primarily on the hypothesis that the thermodynamically more stable (*S*)-sulfoxide arises from a strong oxidant directing effect and sulfoxide stabilizing effect by a 6β-

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