Synthesis of 1α and 1β-Acylamino and Alkylamino-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines and Related Compounds

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The synthesis of series of 1α and 1β-alkylamino-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines from the corresponding acylamino intermediates is described. Cyclization of the 1β-chloromethylamido derivative **20** to the novel bridged benzomorphan **21** occurred whereas the corresponding 1β-chloromethylamido derivative **19** failed to cyclize for steric reasons. In addition several related 1α-acylamidomethyl- and 1β-alkylaminomethyl benzomorphans are reported.

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Analgesics that behave pharmacologically like opiates all possess a basic nitrogen center usually as a phenylethylamine, either as a part of an alicyclic system or terminating a short carbon chain [3]. The nitrogen center is believed to be the initial point of attachment to the opiate receptor(s), mainly in its cationic form [4-6] but perhaps also as the free base [7,8].

1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocines (6,7-benzomorphans) afford a versatile, sterically constrained series of compounds for investigating the nature of opiate binding to their receptors. Previously [9,10], in considering the nitrogen pharmacophore, we have studied the influence of substituents α to nitrogen on analgesic responses. Also pertinent to this present work was the report, in 1979, [11] that an arylcyclohexylamine bearing a benzylamine rather than a phenylethylamine moiety exhibited high opiate analgesic potency.

1-Aminobenzomorphans were prepared during an earlier investigation [12] of the Beckmann rearrangement of a corresponding 1-oxime. As a prelude to pharmacological studies, we describe here the synthesis of a series of 1α-and 1β-acylamino- and alkylaminobenzomorphans and some related compounds.

The introduction of a second basic center into a benzomorphan molecule would alter significantly both *in vivo* drug distribution and receptor binding options. In addition, an amino substituent at C-1 would offer the prospect of bridging from C-1 and N-3 in benzomorphans thus fixing the non-binding electron orientation at N-3.

The 1α and 1β-amino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines **2** and **3**, key intermediates in this investigation, were prepared stereoselectively by reduction of the corresponding oxime **1**. Reduction of **1** with LAH gave exclusively the β-amine **3**. The ^{1}H nmr data provided evidence of configuration. The spectrum of **3** exhibited a doublet at δ 4.05 (JH_1, H_2 = 6 Hz) assignable to the 1α-hydrogen. According to the Karplus relationship [13], this coupling value corresponds to a dihedral angle of approximately 30° consistent with **3**. Although LAH with **1** might be expected to afford both α- and β-amines **2** and **3**, it is clear that the approach of the metal hydride to the piperidine bridge face of **1** is severely hindered.

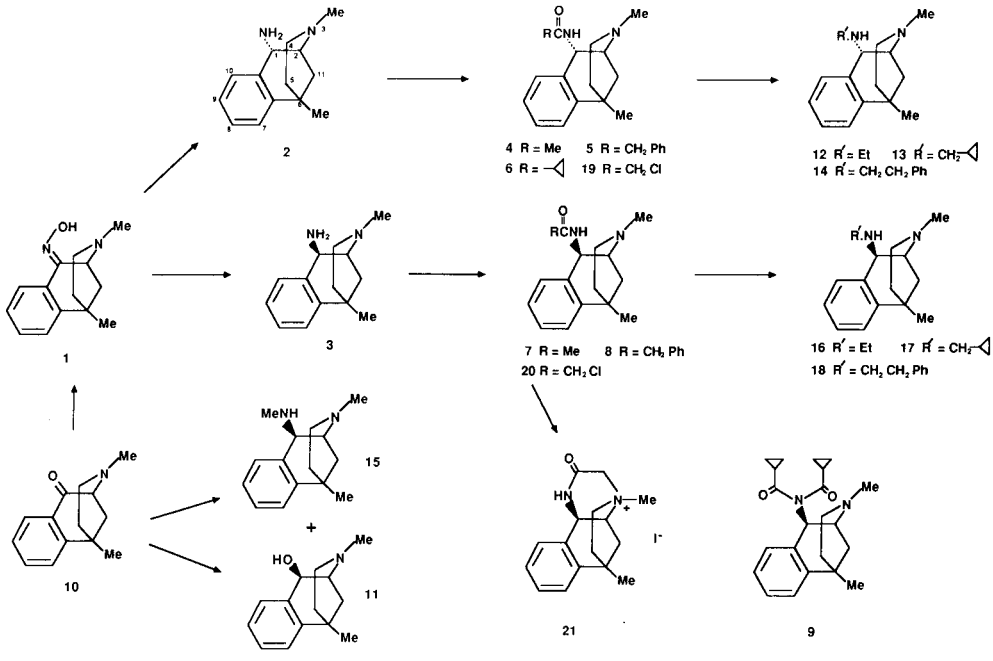
In contrast, reduction of **1** by nickel-aluminium alloy in aqueous alkaline gave predominantly 1α-amino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**2**) which was refined as the oxalate salt. Traces of the β-amine **3** were detected in ^{1}H nmr spectra of crude reaction mixtures. The ^{1}H nmr spectrum of **2** (free base) showed the C-1 benzylic proton as a broad singlet at δ 4.0. A dihedral angle of 80°, commensurate with the 1α-amino configuration, corresponds to a low coupling constant JH_1H_2 of 1-2 Hz.

The 1α-aminobenzomorphan (**2**) was also prepared in good yield by hydrogenation of **1** over platinum oxide.

Amides **4-8** of the 1α- and 1β-amines **2** and **3** were prepared in good yields by their reaction with an appropriate acid chloride in the presence of base according to standard procedures. Spectral data were consistent with the structures assigned.

Unlike its 1α-amino- counterpart **2**, the 1β-aminobenzomorphan **3** failed to yield with cyclopropylcarbonyl chloride in the presence of triethylamine the simple amide corresponding to **6**, but instead gave a compound assigned the unusual 1β-bisamide structure **9**. In its ir spectrum **9** exhibited two strong carbonyl absorptions at 1660 and 1712 cm^{-1}. No NH stretching bands were observed. A broad multiplet in the region δ 0.8-1.4 corresponded to the proton signals from two cyclopropyl moieties. The C-1 benzylic ^{1}H signal appeared as a doublet shifted to lower field at δ 6.08. The mass spectrum (ei) of **9** had M^+ of m/z 352 and an ion at m/z 283 corresponding to the loss of one cyclopropylcarbonyl group. The remaining fragmentation pattern was similar to that of **6**.

It is possible that reaction with a second cyclopropane carbonylchloride to form **9** resulted from anchimeric assis-



tance by the non-bonding electrons of the tertiary amine center.

1-Alkylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines **12-18** were prepared either by reductive alkamination of 3,4,5,6-tetrahydro-3,6-dimethyl-2,6-methano-3-benzazocin-1(2*H*)-one (**10**), or by reduction of the corresponding amide. The benzomorphan-1-one **10** reacted with anhydrous methylamine and sodium cyanoborohydride to furnish a poor yield of 1β-methylaminobenzomorphan **15** together with 1β-hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**11**) [14] as a by-product. The mixture was separated on silica, the products characterized and their stereochemistry about C-1 was assigned from ir and ^{1}H nmr spectra. As anticipated hydride transfer from sodium cyanoborohydride occurred to the more accessible α-face of the benzomorphan leading to 8β-OH and 8β-HNMe epimers. The consistently poor yield from reductive alkamination suggested difficulty in initial imine formation.

1-Alkylaminobenzomorphans **12-14** and **16-18** were prepared by reduction of the corresponding amides with LAH in ether or THF [15]. The 1-phenacyl compounds **5** and **8** required forcing conditions to afford even poor yields of the corresponding 1α- and 1β-phenylethylaminobenzomorphans **14** and **18**. LAH treatment of 1β-dicyclopropionamidobenzomorphan **9** resulted in reductive removal of one acyl moiety to give the 1β-cyclopropylmethyl derivative **17**.

The ir, ^{1}H nmr, and ei-ms characteristics of compounds **12-18** were consistent with the structures assigned.

Acylation of the 1α and 1β-aminobenzomorphans **2** and **3** afforded the opportunity of forming a bridge from C-1 to the piperidine tertiary nitrogen (N-3) with a resultant directing of the piperidine *N*-substituent. Previously benzomorphans with alkane bridges to N-3 have been reported [16-18]. Bridging from C-1 to N-3 resulted in a loss of antinociceptive activity [18], whereas when bridging was from C-11 to N-3 high potency was recorded [16,17].

The 1α and 1β-chloracetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines **19** and **20** were prepared by reacting **2** and **3** respectively with chloroacetyl chloride in the presence of triethylamine in acetone and under nitrogen. It was important to remove precipitated triethylamine hydrochloride prior to work-up. Spectroscopic data confirmed both structures.

Examination of Dreiding molecular models of both **19** and **20** suggested that the 1β-chloracetamidobenzomorphan **20** had the C-1 group and the piperidine tertiary nitrogen (N-3) favorably disposed to permit cyclization. On the other hand the disposition of the corresponding groups in the 1α-chloracetamido epimer **19** was not favorable for cyclization.

Attempts at intramolecular quaternization of **20** in a variety of solvents failed, however, prior treatment of the chloracetamide **20** with sodium iodide in cold acetone and removal of precipitated sodium chloride afforded the corresponding iodoacetamide which was not isolated. The improved leaving properties of iodine over chlorine facilitated the intramolecular nucleophilic displacement reaction and evaporation of the solvent gave the quaternary salt **21**.

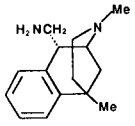
An examination of the mass spectrum of **21** showed a weak molecular ion at m/z 257 and the expected loss of MeI gave a strong (60%) ion at m/z 242.

The stereochemistry of 1α-chloracetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**19**) precluded intramolecular quaternization even under the most forcing of conditions.

Recently [19] we reported a stereospecific route to 1α-aminomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**22**). This intermediate afforded the opportunity to prepare a series of benzomorphans corresponding to **4**, **5**, **6** and **12**, **13**, **14**, but possessing a second phenethylamine moiety rather than a benzylamine moiety.

The amides **23**, **24** and **25** were made by unexceptional methods and had spectral properties commensurate with the structures assigned. LAH reduction of these amides afforded the corresponding alkylamines **27**, **28** and **29**.

The 1α-chloracetamidomethylbenzomorphan (**26**) was prepared in a manner similar to that described for **19** and **20**. As anticipated, because of the unfavorable 1α stereochemistry, intramolecular quaternization of **26** failed.



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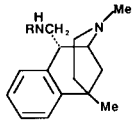

23 R = $-\overset{O}{\overset{\|}{C}}Me$ 27 R = Et

24 R = $-\overset{O}{\overset{\|}{C}}-\triangleleft$ 28 R = $CH_2-\triangleleft$

25 R = $-\overset{O}{\overset{\|}{C}}CH_2Ph$ 29 R = CH_2CH_2Ph

26 R = $-\overset{O}{\overset{\|}{C}}CH_2Cl$

EXPERIMENTAL

Melting points (uncorrected) were taken in open capillary tubes on a Townsend and Mercer apparatus. The ir spectra were recorded (liquid films or nujol mulls) on a Unicam SP-200 Spectrophotometer. The ^1H nmr spectra were recorded on a JEOL PS 100 Spectrometer operating at 100 MHz. Samples were prepared in 5 mm o.d. tubes as approximately 10% solutions in deuteriochloroform with TMS as reference. Mass spectra (ei) were recorded on a VG 7070E mass spectrometer.

1β-Amino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**3**).

The oxime **1** (1.0 g, 4.3 mmoles) was added very slowly, with stirring, to a mixture of lithium aluminum hydride (0.89 g, 21 mmoles) in dry ether (100 ml) under nitrogen. The mixture was stirred overnight, cooled and water (3.2 ml) and sodium hydroxide (5*N*, 6.0 ml) were added dropwise with cooling and stirring. The solid was removed by filtration and washed well with water. The organic phase was washed with water (50 ml), dried (magnesium sulfate) and evaporated to give **3** as a colorless oil (0.60 g, 64%); ^1H nmr (base) (deuteriochloroform): δ 1.33 (s, 3 H, C_6-CH_3), 2.40 (s, 2 H, NH_2, exchangeable), 2.62 (s, 3 H, N-CH_3), 4.0 (d, 1 H, C -H, J = 6 Hz), 7.08-7.4 (m, 3 H, Ar-H); ms: m/z 216 (M^+).

Compound **3** had mp 212-213° (ethanol).

Anal. Calcd. for $C_{14}H_{22}Cl_2N_2$: C, 58.1; H, 7.7; N, 9.7. Found: C, 58.0; H, 7.5; N, 9.7.

1α-Amino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**2**).

Method A.

Raney nickel alloy (1.5 g, 13 mmoles) was added in small portions to a stirred solution of the oxime **1** (1.0 g, 4.3 mmole) in ethanol (20 ml) and 2*N* sodium hydroxide (20 ml). The mixture was stirred at ambient temperature for 5 hours and then filtered. The filtrate was extracted with dichloromethane (3 × 75 ml), washed with water (50 ml), dried (magnesium sulfate) and evaporated to give the product 2 as a colorless oil (0.65 g, 69%). The oil was converted into its dioxalate and this was crystallized from ethanol to furnish colorless needles, mp 202-203°. The free base obtained from the oxalate salt showed the following spectral characteristics: ^1H nmr (deuteriochloroform): δ 1.45 (s, 3 H, C_6-CH_3), 1.56 (s, 2 H, NH_2, exchangeable), 2.42 (s, 3 H, N-CH_3), 4.0 (apparent s, C_1-H), 7.0-7.4 (m, 4H, Ar-H); ms: m/z 216 (M^+).

Anal. Calcd. for $C_{18}H_{22}N_2O_8$: C, 54.8; H, 5.6; N, 7.1. Found: C, 54.7; H, 5.5; N, 7.2.

Method B.

A mixture of the oxime **1** (0.59 g, 2.2 mmoles) and platinum oxide (50 mg, 0.2 mmole) in absolute ethanol (80 ml) containing concentrated hydrochloric acid (4 ml) was hydrogenated at 50 psi in a rocking Parr apparatus at room temperature for 3 hours. The catalyst was removed by filtration and the filtrate evaporated to give a white solid which was dissolved in water (50 ml). The solution was made basic with ammonium hydroxide, extracted with dichloromethane (3 × 150 ml) and dried (magnesium sulfate). Removal of solvent under reduced pressure afforded 2 as a colorless oil (0.34 g, 74%). The product was identical in all respects with the product of method A.

1α-Acetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**4**).

Acetyl chloride (0.30 ml, 4.2 mmoles) was added dropwise, with stirring, to a solution of the 1α-aminobenzomorphan **2** (0.50 g, 2.3 mmoles) and triethylamine (1.0 ml) in dry ether (100 ml). The solution was stirred for 6 hours, washed with water (2 × 50 ml) and extracted with hydrochloric acid (0.5 *N*, 2 × 50 ml). The acid extracts were basified with ammonium hydroxide and extracted with ether (3 × 100 ml). The ethereal phase was washed with water (50 ml), dried (magnesium sulfate) and evaporated to give **4** as white solid (0.42 g, 70%); ν max (base): 3300 (NH), 1640 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 1.40 (s, 3 H, C_6-CH_3), 1.92 (s, 3 H, CO-CH_3), 2.60 (s, 3 H, N-CH_3), 7.0-7.4 (m, 4 H, Ar-H); ms: m/z 258 (M^+), 243 (M^+ -CH_3), 199 (M^+ -NH_2COCH_3).

The hydrochloride had mp 212-213° (ethanol).

Anal. Calcd. for $C_{16}H_{22}ClN_2O$: C, 65.2; H, 7.9; H, 9.5. Found: C, 64.8; H, 7.8; N, 9.2.

1β-Acetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**7**).

The 1β-Amine **3** was acylated by the same procedure as that described for the preparation of **4** to furnish the amide **7** as an oil (68%); ν max (base): 3345 (NH), 1660 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 0.9 (m, 1 H, C_4-H), 1.37 (s, 3 H, C_6-CH_3), 2.14 (s, 3 H, $COCH_3$), 2.62 (s, 3 H, N-CH_3), 5.3 (dd, 1 H, C_1-H, J = 6 Hz, 10 Hz, with deuterium oxide dd → d), 7.0-7.35 (M, 3 H, Ar-H), 7.4 (m, 1 H, C_2-H); ms: m/z 258 (M^+), 243 (M^+ -CH_3), 199 (M^+ -NH_2COCH_3).

The hydrochloride had mp 229-230° (ethanol).

Anal. Calcd. for $C_{16}H_{23}ClN_2O{\cdot}H_2O$: C, 61.0; H, 8.0; N, 8.9. Found: C, 61.5; H, 7.8; N, 8.9.

1α-Phenylacetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**5**).

Phenylacetyl chloride (0.5 ml, 3.8 mmoles) was added dropwise to a stirred suspension of the 1α-amine **2** (0.5 g, 2.3 mmoles) and potassium carbonate (0.5 g, 3.6 mmoles) in methanol (25 ml) and water (3 ml). The mixture was stirred for 4 hours and the solvent removed by evaporation. The residue was dissolved in ether (200 ml), washed with water (3 × 50 ml) and extracted with hydrochloric acid (0.3*N*, 3 × 50 ml). The acid extracts were basified with ammonium hydroxide extracted with dichloro-

methane (3 × 100 ml). The dichloromethane phase was washed with water, dried (magnesium sulfate) and evaporated to give the product, **5** (0.55 g, 71%) which was crystallized from ethanol-ether as colorless plates, mp 172-173°; ν max (base): 3290 (NH), 1630 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 1.36 (s, 3H, C_6-CH_3), 2.6 (s, 3 H, N-CH_3), 3.5 (s, 2 H, $COCH_2Ph$), 5.16 (d, 1 H, C_1-H, J = 8 Hz), 7.0-7.4 (m, 9 H, Ar-H); ms: m/z 334 (M^+), 319 (M^+ -CH_3).

Anal. Calcd. for $C_{22}H_{26}N_2O$: C, 79.0; H, 7.8; N, 8.4. Found: C, 78.9; H, 8.0; N, 8.2.

1β-Phenylacetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**8**).

The amide **8** was prepared from the β-amine **3** in 69% yield by the same procedure as that described for compound **5**. Compound **8** was obtained as colorless needles, mp 76-78° (ethyl acetate); ν max (base): 3330 (NH), 1640 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 1.32 (s, 3 H, C_6-CH_3), 2.62 (s, 3 H, N-CH_3), 3.68 (s, 2 H, $PhCH_2CO$), 5.17 (dd, 1 H, C_1-H), 7.0-7.42 (m, 10 H, Ar-H + NH, reduced to 9 H on deuterium oxide exchange); ms: m/z 334 (M^+).

Anal. Calcd. for $C_{22}H_{26}N_2O$: C, 79.0; H, 7.8; N, 8.4. Found: C, 79.1; H, 8.0; N, 8.3.

1α-Cyclopropionamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**6**).

To a solution of the 1α-amine **2** (1.1 g, 5.1 mmoles) in dichloromethane (100 ml) and triethylamine (3.5 ml) was added cyclopropane carboxylic acid chloride (1.3 g, 15 mmoles). The mixture was heated under reflux for 12 hours and the solvent evaporated. The oily residue was dissolved in ether (200 ml), washed with water (2 × 75 ml) and extracted with aqueous hydrochloric acid (0.5*N*, 3 × 50 ml). The aqueous layer was basified with ammonium hydroxide and extracted with dichloromethane (3 × 100 ml). The dichloromethane layer was washed with water (50 ml), dried (magnesium sulfate) and evaporated to give a white amorphous solid. Recrystallization from acetate-petroleum ether (40-60°) gave **6** (0.9 g, 62%) as colorless needles, mp 203-205°; ν max (base): 3295 (NH), 1670 cm^{-1} (CO); ^1H nmr (deuteriochloroform): 0.6-1.36 (m, 5 H, CO-*c*-C_3H_5), 1.4 (s, 3 H, C_6-CH_3), 2.56 (s, 3 H, N-CH_3), 7.1-7.4 (m, 4 H, Ar-H); ms: m/z 284 (M^+), 249 (M^+ -CH).

Anal. Calcd. for $C_{18}H_{24}N_2O$: C, 76.0; H, 8.5; N, 9.8. Found: C, 75.7; H, 8.5; N, 9.5.

1β-Dicyclopropionamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**9**).

Following the procedure described for the preparation of the 8α-cyclopropionamide **6** the 8β-amino derivative **3** was heated to give **9** as a colorless oil (67%); ν max (base): 3300 (NH), 1712, 1660 cm^{-1} (CO); ^1H nmr (deuteriochloroform): δ 0.7-1.2 (m, 10 H, 2 × *c*-C_3H_5), 1.32 (s, 3 H, C_6-CH_3), 2.52 (s, 3 H, N-CH_3), 3.04 (m, 1 H, C_2-H), 6.08 (d, 1 H, C_1-H, J = 6 Hz), 6.9-7.3 (m, 4 H, Ar-H); ms: m/z 352 (M^+), 283 (M^+ -CO-*c*-C_3H_5), 226, 198 (283 -NHCO-*c*-C_3H_5, base peak). The hydrochloride was crystallized from 2-propanol to furnish colorless plates, mp 140-141°.

Anal. Calcd. for $C_{22}H_{28}N_2O_2$·HCl: C, 67.9; H, 7.5; N, 7.2. Found: C, 67.5; H, 7.7; N, 6.9.

1β-Methylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**15**) and 1β-Hydroxy-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**11**).

To a solution of anhydrous methylamine (2.3 g, 7.2 mmoles) in methanol (25 ml) was added 5*N* methanolic hydrogen chloride (4.8 ml), followed by 3,6-dimethyl-1-oxobenzomorphan (**10**) (2.6 g, 12 mmoles) and sodium cyanoborohydride (0.45 g, 7.1 mmoles). The solution was stirred at 40° for 72 hours, acidified with concentrated hydrochloric acid to *p*H 2 and the methanol removed under reduced pressure. The residue was taken up in water (50 ml) and extracted with ether (2 × 30 ml). The aqueous layer was basified with ammonium hydroxide and extracted with dichloromethane (3 × 50 ml). The dichloromethane layer was dried (magnesium sulfate) and evaporated to give an oil which chromatographed on silica gel, eluting with methanol-chloroform (1-10%) to give starting material **10**, 1β-methylamino-3,6-dimethylbenzomorphan, **15** (8%) and 1β-hydroxy-3,6-dimethylbenzomorphan, **11** (14%).

Compound **15**.

This compound had ν max (base) 3350 cm^{-1} (NH); ^1H nmr (deuteriochloroform): δ 1.33 (s, 3 H, C_6-CH_3), 2.05 (s, 1 H, NH, exchangeable), 2.53 (s, 3 H, NCH_3), 2.60 (s, 3 H, $NHCH$), 3.2 (m, 1 H, C_1-H), 3.65 (d, 1 H, C_1-H, J = 6 Hz), 7.0-7.35 (m, 3 H, Ar-H), 7.7 (m, 1 H, Ar-H); ms: m/z 230 (M^+).

The hydrochloride had mp 261-263° (ethanol).

Anal. Calcd. for $C_{15}H_{24}Cl_2N_2$: C, 59.4; H, 7.9; N, 9.2. Found: C, 59.7; H, 8.0; N, 9.0.

Compound **11**.

This compound had mp 89-91° (acetone) (lit [20], mp 88-90°).

Alkyl Derivatives of 1α- and 1β-amino 3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine **12-14**, **16-18**.

General Procedure.

A solution of the appropriate amide (10 mmoles) in freshly distilled THF (50 ml) was added dropwise with stirring at room temperature to a suspension of $LiAlH_4$ (30 mmoles) in THF (100 ml). The solution was then heated under reflux for 5-8 hours, cooled in ice, and then water (4.2 ml) followed by 5*N* sodium hydroxide (0.75 ml) was added dropwise with stirring. The precipitated solid was removed by filtration and was washed with ether several times. The ether phase was washed with water, dried (magnesium sulfate) and combined with the filtrate. The combined non-aqueous phase was evaporated under reduced pressure and the residue converted to the hydrochloride and recrystallized.

1α-Ethylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**12**).

The product was isolated in 36% yield; ^1H nmr (deuteriochloroform): δ 1.04-1.3 (t, 3 H, CH_2CH_3, J = 8-10 Hz), 1.4 (s, 3 H, C_6-CH_3), 2.5 (s, 3 H, N-CH_3), 2.7-3.0 (q, 2 H, CH_2CH_3), 3.08 (t, 1 H, C_2-H), 3.87 (s, 1 H, C_1-H), 7.0-7.45 (m, 4 H, Ar-H); ms: m/z 244 (M^+).

The hydrochloride had mp 260-261° (2-propanol).

Anal. Calcd. for $C_{16}H_{26}Cl_2N_2$·$2H_2O$: C, 54.4; H, 8.6; N, 7.9. Found: C, 54.5; H, 8.3; N, 7.9.

1β-Ethylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**16**).

The product was isolated in 38% yield; ^1H nmr (deuteriochloroform): δ 1.1-1.3 (t, 3 H, CH_2CH_3), 1.4 (s, 3 H, C_6-CH_3), 2.3 (s, 1 H, NH, exchangeable), 2.6 (s, 3 H, N-CH_3), 2.68-3.04 (m, 2 H, CH_2CH_3), 3.17 (m, 1 H, C_2-H), 3.74 (d, 1 H, C_1-H, J = 6 Hz), 7.0-7.4 (m, 3 H, Ar-H), 7.75 (m, 1 H, C_4-H); ms: m/z 244 (M^+).

The hydrochloride had mp 254-255° (2-propanol-ether).

Anal. Calcd. for $C_{16}H_{26}Cl_2N_2$: C, 60.6; H, 8.3; N, 8.8. Found: C, 60.4; H, 8.5; N, 8.8.

1α-Cyclopropylmethylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**13**).

The product was isolated in 43% yield; ^1H nmr (deuteriochloroform): δ 0-1.4 (m, 5 H, *c*-C_3H_5), 1.4 (s, 3 H, C_6-CH_3), 2.5 (s, 3 H, N-CH_3), 2.68 (d, 2 H, $NHCH_2$, J = 7 Hz), 3.8 (s, 1 H, C_1-H), 7.1-7.5 (m, 4 H, Ar-H); ms: m/z 270 (M^+).

The hydrochloride had mp 208-209° (ethanol-ether).

Anal. Calcd. for $C_{18}H_{28}Cl_2N_2$: C, 63.0; H, 8.2; N, 8.2. Found: C, 62.8; H, 8.4; N, 8.2.

1β-Cyclopropylmethylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**17**).

The product was isolated in 40% yield; ^1H nmr (deuteriochloroform): δ 0-1.1 (m, 5 H, *c*-C_3H_5), 1.35 (s, 3 H, C_6-CH_3), 2.60 (s, 3 H, N-CH_3), 2.68 (m, 2 H, $NHCH_1$), 3.76 (d, 1 H, C_1-H, J = 6 Hz), 7.0-7.8 (m, 4 H, Ar-H); ms: m/z 290 (M^+).

The hydrochloride had mp 188-189° (ethanol-ether).

Anal. Calcd. for $C_{18}H_{28}Cl_2N_2$: C, 63.0; H, 8.2; N, 8.2. Found: C, 63.4; H, 7.9; N, 8.4.

1α-Phenylethylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**14**).

The product was isolated in 23% yield; ^{1}H nmr (deuteriochloroform): δ 1.34 (s, 3 H, C_6-CH_3), 2.47 (s, 3 H, N-CH_3), 2.7-3.3 (m, 5 H, PhCH_2CH_2 and C_2-H), 6.8-7.6 (m, 10 H, Ar-H + NH); ms: m/z 320 (M^+).

The hydrochloride had mp 186-187° (2-propanol-ether).

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2 \cdot H_2O$: C, 64.9; H, 7.8; N, 6.8. Found: C, 65.3; H, 7.8; N, 7.0.

1β-Phenylethylamino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**18**).

The product was isolated in 18% yield; ^{1}H nmr (deuteriochloroform): δ 1.33 (s, 3 H, C_6-CH_3), 2.55 (s, 3 H, N-CH_3), 2.8-3.4 (m, 5 H, PhCH_2CH_2 + C_2-H), 3.75 (d, 1 H, C_1-H, J = 6 Hz), 7.0-7.7 (m, 9 H, Ar-H); ms: m/z 320 (M^+).

The hydrochloride had mp 171-173° (ethanol-ether).

Anal. Calcd. for $C_{22}H_{30}Cl_2N_2 \cdot H_2O$: C, 64.9; H, 7.8; N, 6.8. Found: C, 64.9; H, 7.9; N, 6.8.

1α-Chloroacetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**19**).

To a stirred suspension of **2** (0.5 g, 2.3 mmoles) and triethylamine (1 ml) in dry acetone (50 ml) at 0° was added chloroacetyl chloride (0.75 ml, 9.4 mmoles). The mixture was kept, with stirring, at 0° for 3 hours, the solid removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in ether (100 ml) and the solution was extracted with dilute aqueous hydrochloric acid (0.25*N*, 3 × 50 ml). The extracts were washed with ether (30 ml), basified with NH_4OH and extracted with dichloromethane (3 × 50 ml), the dichloromethane dried (magnesium sulfate) and evaporated to dryness *in vacuo*. The white residue was crystallized from ethyl acetate and gave the product **19** (0.42 g, 63%) as colorless needles mp 210-214° dec; ν max (base) 3350 (NH), 1660 cm^{-1} (CO); ^{1}H-nmr (deuteriochloroform): δ 1.4 (s, 3 H, C_6-CH_3), 2.6 (s, 3 H, N-CH_3), 4.0 (s, 2 H, CO CH_2Cl); ms: m/z 292 and 294 (M^+).

Anal. Calcd. for $C_{16}H_{21}ClN_2O$: C, 65.6; H, 7.2; N, 9.6. Found: C, 66.0; H, 7.5; N, 9.6.

1β-Chloroacetamido-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzazocine (**30**).

According to the method described for **19**, 1β-amino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**3**) (1.0 g) gave the product **20** as a colorless oil (0.72 g, 53%); ν max (base): 3330 (NH), 1670 cm^{-1} (CO); ^{1}H nmr (deuteriochloroform): δ 1.37 (s, 3 H, C_6-CH_3), 2.6 (s, 3 H, N-CH_3), 4.15 (s, 2 H, CO·CH_2Cl); ms: m/z 292 and 294 (M^+). The hydrochloride crystallized as colorless prisms mp 206-208° from ethanol.

Anal. Calcd. for $C_{16}H_{22}Cl_2N_2O \cdot H_2O$: C, 55.3; H, 7.0; N, 8.1. Found: C, 55.7; H, 6.8; N, 7.9.

2-Oxo-4,7-dimethyl-1,2,3,4,5α,6,7,12α-octahydro-4,6-ethanobenz[*f*]quinoxalinium Iodide (**21**).

A solution of **20** (0.1 g, 0.3 mmole) in dry acetone (5 ml) at 0° was added dropwise to a stirred solution of sodium iodide (0.065 g, 0.4 mmole) in dry acetone (10 ml) also at 0°. The mixture was allowed to warm to ambient temperature and then stirred for 2 hours. The deposited sodium chloride was removed and the filtrate evaporated to a white solid that crystallized from ethanol to afford the quaternary salt **21** (0.09 g, 51%) mp 238-240°; ^{1}H nmr (DMSO-d_6): δ 1.47 (s, 3 H, C_6-CH_3), 3.32 (s, 3 H, $\overset{+}{N}$ CH_3), 3.42 (s, 2 H, CO $CH_2\overset{+}{N}$).

Anal. Calcd. for $C_{16}H_{21}IN_2O$: C, 50.0; H, 5.7; N, 7.2. Found: C, 49.7; H, 5.7; N, 7.2.

1α-Acetamidomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**23**).

1α-Aminomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**22**) (0.8 g, 3.4 mmoles) was acetylated according to the procedure described for **4**. It gave the product **23**, as a colorless oil (0.67 g, 71%). The hydrochloride crystallized from ethanol as colorless plates mp 228-229°; ν max (base): 3350 (NH), 1660 cm^{-1} (CO); ^{1}H nmr (deuteriochloroform): δ 1.38 (s, 3 H, C_6-CH_3), 2.04 (s, 3 H, COCH_3), 2.37 (s, 3 H, N CH_3); ms: m/z 272 (M^+).

Anal. Calcd. for $C_{17}H_{24}N_2O$: C, 75.0; H, 8.9; N, 10.3. Found: C, 74.7; H, 9.2; N, 10.4.

1α-Cyclopropionamidomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**24**).

Compound **24** was prepared (63%) from **22** according to the procedure described for **6**. The hydrochloride crystallized from ethanol-ether and had mp 207-209°; ν max (base): 3350 (NH), 1665 cm^{-1} (CO); ^{1}H nmr (deuteriochloroform): δ 0.8-1.1 (m, 4 H, cyclopropane CH), 1.4 (s, 3 H, C_6-CH_3), 2.36 (s, 3 H, N-CH_3); ms: m/z 298 (M^+).

Anal. Calcd. for $C_{19}H_{27}ClN_2O$: C, 68.1; H, 8.1; N, 8.4. Found; C, 68.0; H, 8.3; N, 8.4.

1α-Phenylacetamidomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**25**).

According to the procedure described for **5**, compound **22** gave 1α-phenylacetamidomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**25**) in 81% yield. The base crystallized as colorless plates from ether, mp 110-111°; ν max (Nujol): (base) 3360 (NH), 1643 cm^{-1} (CO); ^{1}H nmr (deuteriochloroform): δ 1.34 (s, 3 H, C_6-CH_3), 2.18 (s, 3 H, N CH_3); ms: m/z 348 (M^+).

Anal. Calcd. for $C_{23}H_{28}N_2O$: C, 79.3; H, 8.1; N, 8.0. Found: C, 79.2; H, 8.2; N, 8.0.

1α-Chloroacetamidomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**26**).

Compound **26** was prepared according to the method described for **19**. The product (53%) was isolated as a colorless oil. The hydrochloride was crystallized from ethanol and had mp 212° dec; ν max (base): 3350 (NH), 1660 cm^{-1} (CO); ^{1}H nmr (deuteriochloroform): δ 1.4 (s, 3 H, C_6-CH_3), 2.36 (s, 3 H, N-CH_3); ms: m/z 306 (M^+).

Anal. Calcd. for $C_{17}H_{24}Cl_2N_2O$: C, 59.5; H, 7.1; N, 8.2. Found; C, 59.4; H, 7.4; N, 7.9.

1α-Ethylaminomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**27**).

The product was prepared in 28% yield according to the general procedure described for the preparation of alkyl derivatives of 1α- and 1β-amino-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines **12-14**, **16-18**. The hydrochloride crystallized from isopropanol-ether and had mp 270-274°; ν max (base): 3350 cm^{-1} (NH); ^{1}H nmr (deuteriochloroform): δ 1.04-1.24 (t, 3 H, CH_2CH_3, J = 8 Hz), 1.37 (s, 3 H, C_6-CH_3), 2.40 (s, 3 H, N CH_3); ms: m/z 258 (M^+).

Anal. Calcd. for $C_{17}H_{28}Cl_2N_2$: C, 61.7; H, 8.5; N, 8.5. Found: C, 61.3; H, 8.5; N, 8.0.

1α-Cyclopropylmethylaminomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**28**).

Compound **28** was prepared in 31% yield according to the general procedure described for **12-14** and **16-18**. The hydrochloride crystallized from isopropanol-ether had mp 236-238°; ν max (base): 3340 cm^{-1} (NH); ^{1}H nmr (deuteriochloroform): δ 0.0-1.1 (m, 5 H, *c*-C_3H_5), 1.38 (s, 3 H, C_6-CH_3), 2.4 (s, 3H, N-CH_3); ms: m/z 284 (M^+).

Anal. Calcd. for $C_{19}H_{30}ClN_2$: C, 63.9; H, 8.5; N, 7.8. Found: C, 63.8; H, 8.6; N, 7.5.

1α-Phenylethylaminomethyl-3,6-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**29**).

Compound **29** was prepared in 15% yield according to the general procedure described for **12-14** and **16-18**. The hydrochloride crystallized from ethanol-ether and had mp 235-236°; ν max (base): 3340 cm^{-1} (NH);

^{1}H nmr: δ 1.4 (s, 3 H, C_6-CH_3), 2.4 (s, 3 H, N-CH_3); ms: m/z 334 (M^+).

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2$: C, 67.8; H, 7.9; N, 6.9. Found: C, 67.3; H, 7.9; N, 6.6.

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