SYNTHESIS OF 9α-AMINO-2, 5-DIMETHYL-6, 7-BENZOMORPHAN AS A POTENTIAL ANALGESIC

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ABSTRACT
6, 7-Benzomorphans show pronounce narcotic analgesic activities. Several compounds comprising 6, 7-benzomorphan nucleus have been synthesized. Previous works centered mainly on structure – activity relationship to the effect of oxygen, hydroxyl, alkyl or aryl substituents on various positions of the molecule and variation of N-substituents. This study reports the synthesis of 6, 7-benzomorphan having an amino group at C – 9 of the molecule. The synthesis involved bromination and arrangement of heterocyclic enamines, followed by aqueous basic hydrolysis to yield 9-oxobenzomorphan which was converted to the oxime. Catalytic reduction of the oxime afforded the desired 9α-amino-6, 7-benzomorphan. Its pharmacology demonstrated dose-dependent inhibition analgesia. The intermediates and title compound were analyzed and characterized on the basis of their spectral and chemical properties.

Key words: 6, 7-benzomorphan, analgesic, 9α-amino-2, 5-dimethyl-6, 7-benzomorphan.

INTRODUCTION
The problems of pain and mental anguish, the efficacy of opiates in ameliorating these experiences, and the consequent difficulties of dependence and addiction associated with opiate use have been the subject of extensive study by scientists for many decades. The problems of opiate addiction and associated social trauma have served to intensify the search for a better analgesic which has no harmful side effect and does not induce dependence.

Consequently, numerous modifications of the morphine skeleton have been undertaken. The 6, 7-benzomorphans are one of the most extensively investigated morphine analogues, first prepared by May and Murphy (1955) and several potent analgesics have been reported to have this skeleton (Ziering et al; 1970). However, nearly all these compounds suffer from one side effect or the other. Thus the search for a potent analgesic with morphine’s beneficial properties and attenuated side effects including tolerance and dependence is continuing (Eddy and May, 1973).

For the benzomorphans, configuration at C-9 is important for activity – omission of 9-methyl group being detrimental for activity, suggesting it to be an important pharmacodynamic feature of the molecule (Chignelli and May, 1965; Casy, 1970; Larson and Portoghese, 1973). The possible role of the 9-methyl group in benzomorphans is the enhancement of analgesic activity (Casy, 1970). Thus the effect of replacement of this group by an amino group was explored. We report here
the synthesis of 9α-amino-2, 5-dimethyl-6, 7-enzomorphan (xi). It was anticipated that replacement of the methyl group in benzomorphan by an amino group would give an analgesic with greater affinity for receptor(s), therefore more potent and longer acting, further defining the requirement, mode of interaction, and nature of, analgesic with receptor(s).

**MATERIALS AND METHODS**

**General:** mp was determined on a Gallenkamp mp apparatus and is uncorrected. IR spectra were recorded on a perkin–Elmer IR Spectrophotometer 710B. NMR spectra were recorded on a Varian EM-390 90 MHz NMR spectrometer using CDCl₃ (except oxime-CD₃OD). Chemical shifts are in δ values using TMS as internal reference.

2-Tetralone (2, 3-dihydro-2(1H)-naphthalenone) II

This was done according to the procedure of Soffer et al (1950). Essentially it involved dissolving metal (sodium) reduction of 2-naphthol in ethanol under reflux. This was followed by acid hydrolysis under reflux for 30 minutes and cooled. The mixture was extracted with benzene, washed (H₂O) and benzene removed by distillation. The crude oil was purified via conversion to its bisulphate addition product. Regeneration of 2-tetralone was via basic (Na₂CO₃) treatment in H₂O followed by ether extraction. The organic layer was washed (with 10% HCl, H₂O), dried (MgSO₄) and ether removed by distillation to give II. (Ir (neat): 1710 cm⁻¹ NMR  δₗ: 2.48 (t, 2H, C₄), 2.98, (t, 4H, C₁ and C₃), 7.0-7.12 (m, 4H, ArH).

3, 4-dihydro-1-methyl-2 (1H)-naphthalenone(III)

The method of Stork et al (1963) was used. 1-methyl-2-tetralone was obtained in 72% yield. Ir (neat) cm⁻¹: 1710, 1380. NMR: 1.5 (d, 3H, C₁-CH₃; J = 6.0 Hz); 2.3 (m, 2H, C₄); 2.9 (m, 3H, C₁ and C₃); 7.0-7.12 (m, 4H, ArH).

**Compounds (IV) to (ix):**

These compounds were prepared by methods described in the literature (kavadias et al, 1979).

Ethyl-1-methyl-2-oxo-1, 2, 3, 4-tetrahydro-1-naphthalene acetate (IV) 56% yield, ir (neat): 1740 cm⁻¹ (unresolved ketone and ester bands); NMR: 1.1 and 3.8 (t, q, CO₂CH₂CH₃); 1.5 (s, 3H, C₁ – CH₃); 2.4 (m, 4H, C₃ and C₄); 4.0 (s, 2H, CO – CH₂); 6.8 – 7.18 (m, 4H, ArH).

3, 9b-Dimethyl-3a-hydroxy-2-oxo-2, 3, 3a, 4, 5,9b-hexahydro-1H-benz[e]indole (v) MP 72 – 74°C.ir (nujol): 3250 cm⁻¹ (OH), 1670 cm⁻¹ (lactam); NMR: 1.30 (s, 3H, CH₃); 2.9 (s, 3H, N – CH₃); 4.0 (s, 1H, OH, exchangeable); 6.8 – 7.2 (m, 4H, ArH).

3, 9b-Dimethyl-3-hydroxy-2-oxo-2, 3, 3a, 4, 5,9b-hexahydro-1H-benz[e]indole (VI) Ir (CHCL₃): 1675 cm⁻¹ (N-C= CH), 1725 cm⁻¹ (N – CO). NMR  δₗ: 1.30 (s, 3H, CH₃); 2.8 (s, 2H, CH₂CO); 3.0 (s, 3H, N – CH₃); 5.35 (t, IH, NC = CH); 6.8 – 7.3 (m, 4H, ArH).

4-Bromo-9b-methyl-2, 4, 5,9b-tetrahydro-1H-benz[e]indole Methobromide (viii). Mp: 61-64°C Ir (nujol): 1670 cm⁻¹ (N – C = CH) NMR: 1.25 (s, 3H, CH₃); 2.53 (s, 3H, N – CH₃); 5.15 (t, 1H, NC = CH), 6.9 – 7.3 (m, 4H, ArH)

4–Bromo-9b-methyl-2, 4, 5,9b-tetrahydro-1H-benz[e]indole Methobromide (vii).

Ir (neat): 1670 cm⁻¹ (N – C = CH) NMR: 1.25 (s, 3H, CH₃); 2.53 (s, 3H, N – CH₃); 5.15 (t, 1H, NC = CH), 6.9 – 7.3 (m, 4H, ArH)

4–Bromo-9b-methyl-2, 4, 5,9b-tetrahydro-1H-benz[e]indole Methobromide (viii).

M.p: 61-64°C Ir (nujol): 1658 (C = N⁺); 750 (C-Br) cm⁻¹

2, 5-Dimethyl-9-oxo-6, 7-benzomorphan (ix) 50% yield.

As oxalate salt: mp 91 – 93°C;
As free base: ir (neat): 1725 cm⁻¹ NMR: δ: 1.35 (s, 3H, C₅ – CH₃); 2.28 (s, 3H, N – CH₃); 2.95 (d, 2H, benzylic protons; j=6.1Hz); 3.4 (m, 4H, methylene protons); 3.90 (t, 1H, C₁ – H); 6.7–7.2 (m, 4H, ArH).

2, 5-Dimethyl-9-oxo-6, 7-benzomorphan oxime (x)

A solution of hydroxylamine was prepared by mixing hydroxylamine hydrochloride (1.4 g) and sodium acetate (1.7 g) in 70 ml EtOH. The mixture was filtered after 1hr, and filtrate treated with 2.8 g of 9–oxobenzomorphan (ix). After refluxed for
8hr, the solution was concentrated to 20 ml, cooled and filtered to give the oxime, 1.21 g; 40% yield. mp. 54 – 57°C. NMR (CD3OD)δ: 1.33 (s, 3H, C5 – CH3); 2.30 (s, 3H, NCH3); 3.0, (d, 2H, benzylic protons; J = 6.0Hz); 3.65 (m, 4H, methylene protons); 6.9–7.3 (m, 4H, ArH); 11.30 (s, 1H, OH, exchangeable).

9α-Amino-2, 5-dimethyl-6, 7-benzomorphan (xi)
Raney alloy (1.5 g) was added in small portions to a magnetically stirred solution of oxime (1.0 g) in 20 ml EtOH and 20 ml 2.0 M NaOH. The mixture was stirred at ambient temperature for 5hr and filtered. Filtrate was extracted with DCM (3x75 ml), washed (H2O), dried (MgSO4) and evaporated to give 9α-amino-benzomorphan as almost colorless oil (0.42 g, 45% yield). The dioxalate salt was crystallized from EtOH (mp 192 – 194°C). Ir (neat): 3450 – 3375cm⁻¹ (NH2), 1600cm⁻¹ (C = C).

NMR (CDCl3)δ: 1.4 (s, 3H, C5 – CH3); 1.55 (s, 2H, NH2, exchangeable); 2.4 (s, 3H, NCH3); 2.85 (t, 1H, C1 – H); 3.15 (d, 2H, benzylic protons; J = 5.0 Hz); 3.83 (d, 1H, C9 – H); 7.0–7.4 (m, 4H, ArH).

**Evaluation of Analgesic Activity**
Analgesic activity for title compound (as dioxalate) and morphine (as sulphate) was determined in mice using the hot plate procedure of Portoghese et al (1973).

The top surface of a tin can dipped in a bath containing thermostatically controlled hot water served as hot plate with its temperature maintained at 55°C. Compounds were administered subcutaneously (sc) in aqueous solution (using sterile water). Each mouse received 0.01mg/kg body weight for each dose level tested; doses used were 1mg/kg, 2mg/kg, 4mg/kg and 8mg/kg with sterile water as general control. A group of 10 mice were used for each dose. The mice were placed singly on the hot plate and time taken for it to lick its hind paws (Fennesssy, 1970; Glassman, 1971) or attempts to jump out of the cylinder (Fennesy and Lee, 1975) was recorded. Reaction times were recorded at three 15 – minute intervals prior to drug administration to establish a reaction time control value. A mean value for second and third interval pre-injection reaction times for each mouse were taken as control value, each mouse used as its own control. Mice with mean reaction time more than 30 seconds were excluded as non responders and reaction times were recorded 15, 30, 60, 90, 120, 180, 240 minutes after drug administration. The results of pain threshold response – time were analyzed by means of a plot of response time vs. post treatment time at each dose.
Scheme 1
Fig. 1: Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 2mg/kg. (--- indicates times at which benzomorphan is significant as compared to morphine.)

Fig. 2: Analgesic effect of benzomorphan as compared to morphine and saline at a dose of 1mg/kg. (--- indicates times at which drugs are significant P≤0.05 as compared to saline.)
Fig. 3: Analgesic effect of benzonarphan as compared to morphine and saline at a dose of 4 mg/kg.

Fig. 4: Analgesic effect of benzonarphan as compared to morphine and saline at a dose of 1 mg/kg. (+ indicates time at which morphine is significant compared to benzonarphan.)
RESULTS AND DISCUSSION
The synthetic route to the title compound is as shown in scheme 1. Aqueous alkaline hydrolysis of (viii) in EtOH resulted in (ix) in 50% yield. This compound was purified via formation of the oxalate salt. Its ir spectrum exhibited carbonyl frequency at 1725 cm\(^{-1}\) and nmr spectrum displayed a signal at \(\delta 3.05\) ascribable for methine proton at C\(_1\), which were absent in (viii). 2,5-Dimethyl-9-oxo-6,7-benzomorphan, (ix), was converted into its oxime (X), which on catalytic reduction with Raney alloy in EtOH - NaOH mixture resulted in the title compound, 9\(\alpha\)-amino-2,5-dimethyl-6,7-benzomorphan, (xi), as an almost colorless material in 45% yield. It was purified by dioxalate salt formation, mp 192 – 194\(^\circ\)C. The ir spectrum of (xi), 9\(\alpha\)-amino-6,7-benzomorphan, gave bands at 3450 – 3375 cm\(^{-1}\), ascribable to NH\(_2\) group and that at 1600 cm\(^{-1}\) could be assigned to C=C moiety. Its NMR spectrum gave signals at \(\delta\) 1.4 (singlet, C\(_5\) – CH\(_3\)); 1.55 (singlet, NH\(_2\) exchangeable with D\(_2\)O); 1.8 (multiplet, C\(_4\) – CH\(_2\)); 2.4 (singlet, N – CH\(_3\)). 2.85 (triplet C\(_1\) – H); 3.15 (doublet, J = 5H\(_2\), benzylic protons); 3.83, (doublet, J = 3,1H, C\(_9\) – H).

Reduction of oximes is stereo specific and has been reported to be dependent on nature of the nitrogen atom (May et al., 1961; Kugita and May, 1961; Laidler, 1966). Free base gives \(\alpha\) - isomers whereas quaternary salts yield \(\beta\) - isomers. This perhaps explains our unsuccessful attempt to get \(\beta\) - aminobenzomorphan by direct reduction of the oxime, (x), using lithium aluminum hydride.

The title compound (xi) was tested on mice for analgesic effects in line with procedure given by Portoghese et al (1973), (Figs 1 – 4). It was observed that 9\(\alpha\) - amino – 6, 7-benzomorphan was equipotent with morphine and most potent N – methyl non-phenolic 9\(\alpha\)-amino compound so far (Tor-Anyiin, 1987). Optimum activity was found at 2mg/kg. (Fig 2). Increases in dosage lead to decrease in activity with complete loss of activity at a dose of 8mg/kg, (Fig 4). Preliminary results indicate that this compound 9\(\alpha\)-amino-benzomorphan, (xi), has longer duration of analgesic action than morphine.

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REFERENCES


