The Synthesis and Preliminary Pharmacological Evaluation of 4-Methyl Fentanyl

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Received 4 May 2000; revised 27 June 2000; accepted 3 July 2000

Abstract—The synthesis of 4-methyl fentanyl, a prototype of a novel class of fentanyl analogues has been effected in 5 steps, starting from N-ethoxycarbonyl-4-piperidone (~20% overall yield). In the key step, N-phenylation of secondary aliphatic amide intermediate was achieved by a novel reaction, using diphenyliodonium chloride for the phenyl group transfer. Preliminary pharmacological results indicate that 4-methyl fentanyl is a super potent narcotic analgesic, about four times more potent than fentanyl.

Introduction

Fentanyl1 is a well known and clinically widely used narcotic analgesic, about 50–100 times more potent than morphine in humans. Due to its high potency and generally favourable pharmacological profile, numerous analogues have been synthesised in the past three decades.2 While sufentanil,1 alfentanil,1 lofentanil1 and remifentanil1 (Fig. 1), have been used clinically as narcotic analgesics, other structurally closely related compounds exhibit different pharmacological activities, e.g., antihistaminic (astemizole,1 levocabastine1), tranquillising (droperidol1), anti diarrheal (loperamide1) and antiarrhythmic (lorcainide1).

Analgesic activity of the anilidopiperidines is greatly enhanced by the presence of a substituent in the position 4 of the piperidine ring.2f The chemical nature of the substituent apparently has little influence on the activity, since groups2f as diverse as carbomethoxy, methoxymethyl, hydroxymethyl, methylketo and aryl3 all produce significant increase (2–30 times) in the potency compared to fentanyl. Rather it seems that the activity depends primarily on the voluminosity of the substituent.

Results and Discussion

Here we report the synthesis of the first member of this series, 4-methyl fentanyl 6, as well as the synthetic approach4 suitable for the preparation of higher homologues, (Scheme 1). First, N-benzyl 4-piperidone was converted5 to carbamate 1 using ethyl chloroformate, then it was reacted with MeMgI to yield alcohol 2 (85%). Next, the reaction of 2 with propionitrile (via tert carbocation intermediate) under the conditions of Ritter reaction7 (concd H2SO4, 0°C, 4 h), afforded amide 3 (70% yield after dry flash chromatography). Attempts to N-phenylate this amide, or the model compound, N-(1-methyl-cyclohexyl)-acetamide, using various modification of Goldberg reaction8 (PhBr, K2CO3, cat. CuBr) were unsuccessful. Similarly, when amide 3 or the model amide were first N-metallated (KH, diglyme, 20°C, 30 min), then treated with triphenylbismuth carbonate,9 a highly efficient phenylating reagent for enolate anions, only the starting compound was isolated. Finally, the phenylation of N-metallated amides was effected with
diphenyliodonium chloride.\textsuperscript{10} The addition of 18-crown-6 ether (100 mol%) substantially accelerated the metatation and phenylation step and improved the yields. Thus, \(N\)-(1-methyl-cyclohexyl)-\(N\)-phenyl-acetamide and the amide \(4\) were isolated in \(70\) and 40–50\% yields respectively, after dry flash chromatography. The main contaminant in both cases was the starting secondary amide (20–50\%). The procedure appears to be of a more general scope and it is currently being investigated. Interestingly, the phenylation is completely unsuccessful if a tertiary amino group is present in the molecule, although no explanation is available presently. Thus, when 1-\(N\)-benzyl or 1-\(N\)-phenethyl analogues of \(3\) were subjected to the same procedure, only a complete decomposition was observed. In the last steps of the synthesis, the carbamate moiety in amide \(4\) was removed quantitatively, using Me\textsubscript{3}SiI\textsuperscript{11} in boiling dichloroethane (1.5 equiv 80°C, 8 h). A number of other deprotection procedures\textsuperscript{12} (KOH, ethylene glycol, 100°C; KOH, i-PrOH, 18-C-6, 80°C; n-PrOK, n-PrOH, 18-C-6, 100°C; HBr (48\%), 80°C; Me\textsubscript{2}SiCl, NaI, MeCN\textsuperscript{13}) either caused complete decomposition or failed\textsuperscript{13} to effect the cleavage. Remarkably, the ethyl carbamate group was stable towards both a strong nucleophile (MeMgI) and in concd H\textsubscript{2}SO\textsubscript{4}. The intermediary secondary piperidine \(5\) was isolated without purification and smoothly alkylated with phenethyl iodide to afford 4-methyl fentanyl \(6\) (\(\sim\)20\% overall yield from \(1\)). Spectral data (IR, \textsuperscript{1}H NMR (250 MHz), \textsuperscript{13}C NMR (APT, 60 MHz), and MS [EI]), were fully consistent with the assigned structure.

The 4-methyl fentanyl \(6\) was precipitated as mono-oxalate salt and tested for analgesic activity using rat tail withdrawal test\textsuperscript{14} and fentanyl citrate as a standard. The ED\textsubscript{50} and 95\% confidence limits were estimated from dose-response curve using the standard computer program.\textsuperscript{15}

The relative potency of 4-methyl fentanyl was found to be 3.8 (3.2–4.4) times higher than fentanyl, while the time peak of the activity as well as the duration of the action seemed to be equal to fentanyl (Table 1). Also, higher doses of 4-methyl fentanyl (>8\times ED\textsubscript{50} for analgesia) produced fentanyl-like neurotoxic effects such as stiffness of the tail (Straub tail), catalepsy and

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<th>4-Methyl fentanyl ((n=24))</th>
<th>Fentanyl ((n=23))</th>
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<tr>
<td>ED\textsubscript{50} (mg/kg of free base)</td>
<td>0.0028</td>
<td>0.0105</td>
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<tr>
<td>Confidence limits</td>
<td>0.0023–0.0033</td>
<td>0.006–0.018</td>
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<td>Time of peak action of ED\textsubscript{50} (min)</td>
<td>10–15</td>
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<td>Duration of action of ED\textsubscript{50} (min)</td>
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\(n\) = Number of animals employed to produce dose–response curve.
loss of righting reflex. Since all of the observed effects were reversed by s.c. injection of naloxone hydrochloride (1 mg/kg) it was concluded that they were opioid-receptor mediated.

Conclusion
A simple and efficient synthesis of 4-methyl fentanyl, a super potent narcotic analgesic, was accomplished. The compound is a prototype of a novel class of fentanyl analogues, 4-alkyl fentanyls, which are currently being prepared by the same methodology and will provide further insights into the SAR. In the key step, a novel method for the N-phenylation of secondary aliphatic amides was disclosed, providing access to various tertiary N-phenyl amides not readily accessible by other routes. Finally, it has been proven that the central analgesic activity in this series of anilidopiperidines is influenced only by the steric requirements of a group in the position 4 of the piperidine ring rather than its chemical nature. Further examples with more voluminous 4-alkyl substituents (Et, Pr, i-Pr etc.) are expected to provide clear correlation with the activity of known compounds possessing other substituents (carbomethoxy, methoxymethyl etc.) in the same position.

Experimental
Amide 3. Alcohol 2 (2.0 g, 10.5 mmol) in propionitrile (40 mmol) is added dropwise to a stirred mixture of H2SO4 (96%, 20 mL) and propionitrile (15 mmol, −5°C, 10 min). After 4 h (t < 0°C), the mixture is added to 10% K2CO3 solution (foaming, pH > 7), extracted (CH3Cl2), dried (MgSO4) and concentrated. The residue is purified by dry flash chromatography (30 g SiO2, hexane/ EtOAc gradient) yielding pure amide 3 as oil. Yield: 1.83 g (72%).

Amide 4. A typical phenylating procedure. A solution of dried amide 3 (1.0 g, 4.1 mmol) and 18-crown-6 (distilled from NaH, 1.3 g, 5 mmol) in diglyme (5 mL) is injected to the methodology published earlier. The pharmacological testing was performed according to the methodology published earlier. The pharmacological testing was performed according to the methodology published earlier.

References and Notes
17. Spectral data for 6. IR (cm−1): 3061, 3026, 2933, 2810, 2774, 1659, 1594, 1493, 1477, 1453, 1420, 1373, 1351, 1311,
$^1$H NMR (δ, CDCl$_3$): 0.96 (t, $J=7.30$, CH$_3$), 1.68 (s, CH$_3$), 1.71–1.81 (m), 1.85 (q, $J=7.50$, CH$_2$), 2.04–2.08 (m), 2.19 (td, $J_d=2.40$, $J_t=12.0$), 2.52–2.58 (m); 2.74–2.81 (m); 7.1–7.42 (m, 10H Ar).

$^{13}$C NMR (ppm, CDCl$_3$, APT): 9.45 (CH$_3$); 21.05 (CH$_3$); 30.76 (CH$_2$); 33.75 (CH$_2$); 37.15 (2CH$_2$); 50.42 (2CH$_2$); 59.14 (CH$_2$); 60.53 (CH$_2$); [125.99; 127.98; 128.35; 128.62; 128.95; 130.53 (CH$_{Ar}$)]; 140.33 (C$_{Ar}$); 141.33 (C$_{Ar}$); 174.37 (C=O) MS (EI): 350 (M$^+$; 0.4); 260 (18); 259 (100); 110 (34); 106 (22); 105 (10).