Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 2011–2014

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

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 intermediare 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

Fentanyl[1] 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] lofentanil[1] and remifentanil,[1] (Fig. 1), have been used clinically as narcotic analgesics, other structurally closely related compounds exhibit different pharmacological activities, e.g., antihistaminic (astemizole,[1] levocabastine[1]), tranquillising (droperidol[1]), antidiarrheal (loperamide[1]) and antiarrhythmic (lorcainide[1]).

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 groups[2f] as diverse as carbomethoxy, methoxymethyl, hydroxymethyl, methylketo and aryl[3] 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.

This hypothesis can be readily proven by the synthesis of 4-alkyl fentanyl analogues, where the analgesic potency would depend entirely on the steric factor. In addition, this novel series would provide better SAR for fentanyl analogues in general and possibly, some new, promising opioid analgesics.

Results and Discussion

Here we report the synthesis of the first member of this series, 4-methyl fentanyl **6**, as well as the synthetic approach[4] suitable for the preparation of higher homologues, (Scheme 1). First, *N*-benzyl 4-piperidone was converted[5] to carbamate **1**[6] 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 reaction[7] (concd H_2SO_4, 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 reaction[8] (PhBr, K_2CO_3, cat. CuBr) were unsuccessful. Similarly, when amide **3** or the model amide were first *N*-metalated (KH, diglyme, 20°, 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*-metalated amides was effected with

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0960-894X/00/$ - see front matter
PII: S0960-894X(00)00394-2

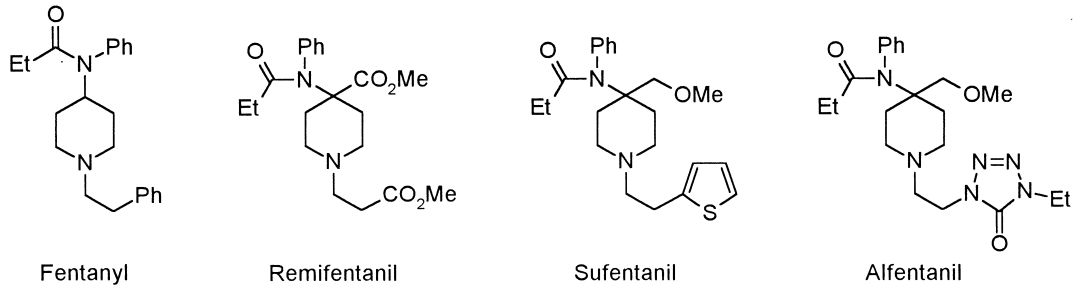
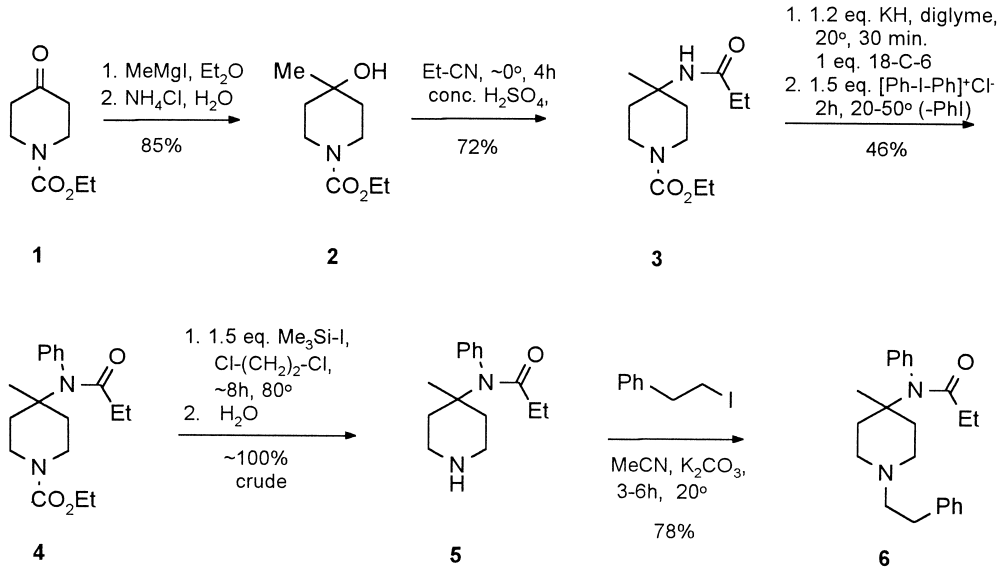


Figure 1.



Scheme 1.

diphenyliodonium chloride.[10] The addition of 18-crown-6 ether (~100 mol%) substantially accelerated the metalation 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_3SiI[11] in boiling dichloroethane (1.5 equiv 80°C, 8 h). A number of other deprotection procedures[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_3SiCl, NaI, MeCN[13]) either caused complete decomposition or failed[13] to effect the cleavage. Remarkably, the ethyl carbamate group was stable towards both a strong nucleophile (MeMgI) and in concd H_2SO_4. The intermediary secondary piperidine **5** was isolated without purification and smoothly alkylated with phenethyl iodide to afford 4-methyl fentanyl **6** (~20% overall yield from **1**). Spectral data (IR, ^1H NMR (250 MHz), ^{13}C NMR (APT, 60 MHz), and MS [EI]), were fully consistent with the assigned structure.

The 4-methyl fentanyl **6** was precipitated as monooxalate salt and tested for analgesic activity using rat tail withdrawal test[14] and fentanyl citrate as a standard. The ED_{50} and 95% confidence limits were estimated from dose-response curve using the standard computer program.[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 ($>8\times ED_{50}$ for analgesia) produced fentanyl-like neurotoxic effects such as stiffness of the tail (Straub tail), catalepsy and

Table 1. Analgesic activity of intraperitoneal 4-methyl fentanyl in rat[a]

	4-Methyl fentanyl ($n=24$)	Fentanyl ($n=23$)
ED_{50} (mg/kg of free base)	0.0028	0.0105
Confidence limits	0.0023–0.0033	0.006–0.018
Time of peak action of ED_{50} (min)	10–15	10–15
Duration of action of ED_{50} (min)	30–40	30–40

[a]n = Number of animals employed to produce dose–response curve.

loss of righting reflex.[16] 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 corelation with the activity of known compounds possesing other substituents (carbomethoxy, methoxymethyl etc.) in the same possition.

Experimental

Amide 3. Alcohol **2** (2.0 g, 10.5 mmol) in propionitrile (40 mmol) is added dropwise to a stirred mixture of H_2SO_4 (96%, 20 mL) and propionitrile (15 mmol, −5°C, 10 min). After 4 h ($t < 0$°C), the mixture is added to 10% K_2CO_3 solution (foaming, pH >7), extracted (CH_2Cl_2), dried ($MgSO_4$) and concd. The residue is purified by dry flash chromatography (30 g SiO_2, 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 stirred suspension of KH (35%, 4.4 mmol, 10 mL diglyme) under Ar. After 10 min (H_2 evolution), solid diphenyliodonium chloride (1.90 g, 6.0 mmol) is added in one portion (mildly exothermal reaction, yellow coloration). After 4 h (40–50°C, external heating) the mixture is poured into H_2O (200 mL), extracted (toluene), concd (10 torr, 90°C) and purified (dry flash chromatography, 20 g SiO_2, hexane/EtOAc gradient). Amide **4** is obtained as yellow glassy solid (0.61 g, 46%). Unreacted amide **3** is eluted with MeOH.

4-Methyl fentanyl 6. A mixture of amide **4** (50 mg, 0.16 mmol) and Me_3SiI (0.1 g, 0.50 mmol) in dichloroethane (2 mL) under Ar is stirred and heated (80°C, 8 h), then treated successively with concd HCl (0.5 mL) and 10% K_2CO_3 solution (10 mL), and concd. The crude product **5** (oil, ~40 mg, ~100%) is mixed together with Et_3N (32 mg, 0.32 mmol) and phenethyl iodide (60 mg, 0.26 mmol) in dry acetonitrile (1 mL) under Ar, stirred (5 h, 20°C), treated with 10%, K_2CO_3 solution (2 mL), extracted (Et_2O) and concentrated. The residual oil[17] (>98% purity, cap. GC) was precipitated as monooxalate salt from anh. Et_2O. Yield: 55 mg (78%), white powder.

The pharmacological testing was performed according to the methodology published earlier.[16]

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17. Spectral data for **6**. **IR** (cm^{-1}): 3061, 3026, 2933, 2810, 2774, 1659, 1594, 1493, 1477, 1453, 1420, 1373, 1351, 1311,

1247, 1159, 1111, 1078, 1028, 996, 811, 750, 701. ^{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).