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Original paper

Synthesis and antinociceptive activity of 9-phenyl-oxy or 9-acyl-oxy derivatives of xanthene, thioxanthene and acridine

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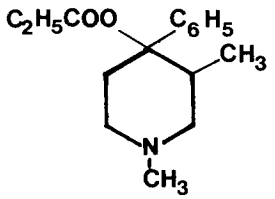
Summary — The synthesis of 9-alkyl-oxy or 9-acyl-oxy derivatives of xanthene, thioxanthene and acridine is reported. A potent antinociceptive activity was confirmed for the 9-phenyl-9-propionyl-oxy derivative bearing an oxygen or sulfur atom in the heteroaromatic structure.

Résumé — Synthèse et activité antinociceptive de dérivés phényl-9-alkoxy-9 ou acyl-oxy-9 de xanthène, thioxanthène et acridine. *Synthèse de dérivés phényl-9-alkoxy-9 ou acyl-oxy-9 du xanthène, thioxanthène et de l'acridine. Une forte activité antinociceptive se manifeste lorsque le dérivé phényl-9-propionyl-oxy-9, porte un oxygène ou un soufre dans la structure hétéroaromatique.*

xanthene derivatives / thioxanthene derivatives / acridine derivatives / trimeperidine analogues / antinociceptive activity

Introduction

The so-called "reversed ester" series of meperidine (ethyl 1-methyl-4-phenyl-4-piperidine carboxylate) derivatives of 4-phenyl-piperidinyl-4-ol, has yielded compounds of greater analgesic effectiveness than the parent substance [1]. Further, among the many other ramifications in the structure of the phenylpiperidinols, the introduction of a methyl group in the 3 position of the piperidine ring has been found to be the most noteworthy [2, 3].



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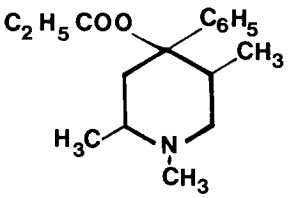

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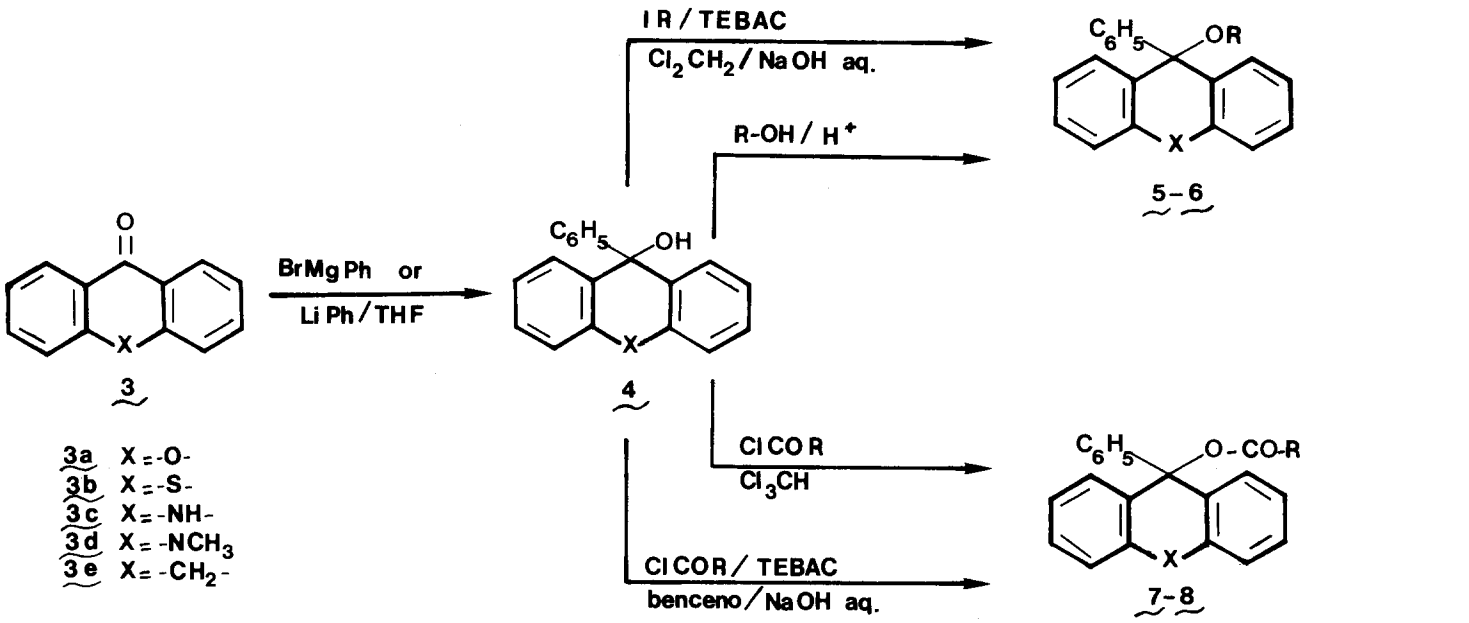
Thus, the resulting α and β-prodines **1** and trimeperidines **2** (1,2,5-trimethyl-4-phenyl-4(propionyloxy)piperidine), are promising analgesic agents and have been used clinically. Data for some reversed ester analogues of meperidine, all of which carry the C-4 oxygen substituent propionyloxy, are now presented in a follow-up of an earlier report [4]. However, in these materials, the substituent on the piperidine ring gives rise to an asymmetric center which often results in the formation of a complex mixture of stereoisomers, rendering the synthetic route more problematical. Consequently, regarding potential potent analgesics, we examined the pharmacological properties of 9-phenyl-9-alkyl-oxy or 9-acyl-oxy derivatives of xanthene, thioxanthene and acridine. This work examines the synthesis of these compounds; and the results of their biological evaluation are given.

Chemistry

The compounds were prepared by the methods shown in Scheme 1. The alcohols **4** were prepared by treating the appropriate ketone **3** with phenyl magnesium bromine or phenyl lithium, which is generally preferred to a phenyl Grignard as the organometallic reactive. The *O*-alkylation and *O*-acylation of **4**, carried out with or without phase transfer catalysts yielded ethers **5**–**6** and esters **7**–**8**.

The *N*-alkylation of the acridone **3c** has been reported under phase-transfer conditions. The method requires an excess of alkylating agent, a high boiling point solvent and a reaction time of several days, when a mixture of *N*- and *O*-alkylation products are obtained [5]. We report here a more simple method for *N*-alkylation of **3c**, using dimethyl sulfate in tetrahydrofuran; only the *N*-alkylation product **3d** was obtained.

The corresponding alcohols **4** can be *O*-alkylated or *O*-acylated under phase transfer catalysed conditions in which triethyl-benzylammonium chloride (TEBAC) is used as the phase-transfer agent. The phase transfer cata-



Scheme 1.

lysis may be an efficient means of avoiding hydrolytic decomposition that was sometimes observed, as it allows alkylation or acylation to be carried out at low temperatures. At room temperature, satisfactory yields were obtained for ethers **5–6** and esters **7–8** (Scheme 1).

The ^1H NMR analysis of samples from the reaction mixture showed that acridones **3c** and **3d**, react more slowly than xanthone and thioxanthone derivatives. On the other hand, the low reactivity of **4e** in comparison with the hydroxy analogues **4** suggested that this reaction may be effected through the carbonium ion, the activation of which requires higher energy [6]. The results of the *O*-alkylation and *O*-acylation procedures carried out in this work are summarized in Tables I and II.

Biological activity

The LD_{50} was first evaluated, utilizing the arithmetic method of Reed–Muench. The results are reported in Table III. Generally these compounds did not present any significant toxicity.

Opiate activity was also tested by suppression of the coaxially-stimulated contractions of guinea pig ileum *in vitro* [7, 8]. Opiate agonists reduce electrically stimulated contractions; and their action was fully reversed by the specific opiate antagonist naloxone (1 μg ml^{-1}); *i.e.*, compounds whose effects were totally antagonised by naloxone were assumed to be opiate agonists.

Anti-nociceptive activity *in vivo* was assessed by the acetic acid-induced writhing test in mice [9]. This peripherally selective analgesic test was chosen rather than a centrally mediated anti-nociceptive model (*e.g.*, hot plate) since polar derivative salts would not readily penetrate the blood–brain barrier into the CNS. The use of writhing assays to detect peripherally mediated anti-nociceptive effects of opioids has been discussed elsewhere [10]. For comparative purposes, meperidine and fentanyl were investigated in the same assays. The effects of meperidine on guinea pig ileum did not appear to be wholly mediated *via* opiate receptors, since naloxone brought about only a partial inhibition of the twitch; this finding is in agreement with that of Paton [11].

Results and Discussion

The meperidine analogues retained biological activity in guinea pig ileum, the ED_{50} s for the inhibition of the electrically-stimulated contractions ranging from 0.10–21.3 μM (Table IV). For comparison, the activity of meperidine also lies within this range: ED_{50} = 2.80 μM.

The results of our experiments demonstrated that the compounds **8a** and **8b** share practically the same pharmacological activities. In the same dose range, both compounds elicit evident *in vivo* and *in vitro* anti-nociceptive effects and similar toxicologic symptoms.

Table I. Products of *O*-alkylation and *O*-acylation of alcohols **4**.

Compd.	R	X	Substrate	mp °C*	Yield % **	Formula
5a	CH_3	O	2a	142–144[a]	60%	$C_{20}H_{16}O_2$
5b	CH_3	S	2b	158–160[a]	65%	$C_{20}H_{16}OS$
5c	CH_3	NH	2c	165–167[b]	40%	$C_{20}H_{17}NO$
5d	CH_3	NCH_3	2d	143–145[b]	55%	$C_{21}H_{19}NO$
6a	CH_2CH_3	O	2a	147–149[a]	55%	$C_{21}H_{18}O_2$
6b	CH_2CH_3	S	2b	170–172[a]	60%	$C_{21}H_{18}OS$
6c	CH_2CH_3	NH	2c	137–138[b]	35%	$C_{21}H_{19}NO$
6d	CH_2CH_3	NCH_3	2d	152–154[a]	50%	$C_{22}H_{21}NO$
7a	CH_3CO	O	2a	128–130[c]	70%	$C_{21}H_{16}O_3$
7b	CH_3CO	S	2b	175–177[d]	65%	$C_{21}H_{16}O_2S$
7c	CH_3CO	NH	2c	135–137[a]	55%	$C_{21}H_{17}NO_2$
7d	CH_3CO	NCH_3	2d	153–154[a]	65%	$C_{22}H_{19}NO_2$
8a	CH_3CH_2CO	O	2a	150–152[d]	70%	$C_{22}H_{18}O_3$
8b	CH_3CH_2CO	S	2b	142–144[d]	65%	$C_{22}H_{18}OS$
8c	CH_3CH_2CO	NH	2c	133–134[a]	65%	$C_{22}H_{19}NO_2$
8d	CH_3CH_2CO	NCH_3	2d	160–162[a]	55%	$C_{23}H_{21}NO_2$

*Recrystallization solvent [a]methanol; [b]ethanol; [c]diethyl ether; [d]hexane.
**Without phase transfer catalysts.

The *O*-acyl derivatives **7** and **8** elicit anti-nociceptive effects, which are generally stronger than those of the *O*-alkyl derivatives. In general therefore, the replacement in opiates by the 9-propionyloxy ($OCOC_2H_5$) group produces a major increase in anti-nociceptive activity. The aza-compounds allow the anti-nociceptive activity to decrease as compared to oxa and thia derivatives; this may be due to the major lipophilicity of these compounds in relation to the aza-analogues. Finally, the fact that the greater part of these derivatives share anti-nociceptive activity indicates that the substitution by aromatic rings and variation of heteroatom does not suppress the anti-nociceptive property of these molecules.

Experimental protocols

Chemistry

The melting points were determined on a Kofler block and are uncorrected. IR spectra were taken on a Perkin–Elmer 570 spectrophotometer. ^1H NMR were recorded on a Hitachi–Perkin–Elmer R 24-B spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent and tetramethylsilane as an internal standard, spectra of all compounds were evaluated as being completely consistent with given structures. The results of elemental analyses (C,H,N,O) were within ±0.3% of theoretical values and were performed on a Carlo–Erba 1106 or Perkin–Elmer 240.

10-Methyl-acridan-9-one ***3d***
Dimethyl sulfate, 10 ml, was added dropwise to a mixture of ketone **3c**, 5 g (0.027 mol), potassium carbonate 2.7 g (0.027 mol) in dry tetrahydrofuran (500 ml). The mixture was stirred for 48 h at reflux; after filtration, the solvent was evaporated *in vacuo*, the residue was recrystallized from ethanol to give **3d** (3.7 g, 70%) mp: 202–204° C ([12] 197°C) IR (KBr) 1640 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.70 (3H, s); 7.90–7.00 (6H, m). Anal. $C_{14}H_{11}NO$ (C, H, N).

General procedure for synthesis of alcohols ***4***
A solution of the corresponding ketone **3** (0.1 mol) in benzene (200 ml) was added to a suspension of the organometallic reagent (1 mol) in THF (450 ml). The mixture was stirred 24 h at room temperature. Saturated ammonium chloride solution (200 ml) was added to the mixture, and the pH of the solution was adjusted 10 with 20% aqueous sodium hydroxide. The organic extracts were washed with water (250 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified by recrystallization.

9-Phenyl-9-hydroxy-xanthene ***4a***
Yield 85%. mp 156°C. IR (KBr) 3560 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.70 (1H, s); 7.60–7.10 (13H, m). Anal. $C_{19}H_{14}O_2$ (C, H).

9-Phenyl-9-hydroxy-9-thioxanthene ***4b***
Yield 80%. Sirup. IR (film) 3520 (OH) and 3300 ((OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.00 (1H, s); 7.60–6.90 (11H, m); 800–7.80 (2H, m); Anal. $C_{19}H_{14}OS$ (C, H, S).

9-Phenyl-9-hydroxy-acridine ***4c***
Yield 80%. Sirup. IR (film) 3540 (OH) and 3300 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (1H, s); 7.70–6.70 (13H, m). Anal. $C_{19}H_{15}NO$ (C, H, N).

Table II. Phase transfer *O*-alkylation and *O*-acylation of alcohols **4**.

Compd.	Substrate	Alkylating or acylating agent	Reaction conditions (Temp. °C / time min)	Yield %
5a	2a	I-CH_3	20–25°C / 60	75%
5b	2b	I-CH_3	20–25°C / 60	70%
5c	2c	I-CH_3	30–40°C / 90	65%
5d	2d	I-CH_3	30–40°C / 90	60%
6a	2a	I-CH_2–CH_3	20–25°C / 60	70%
6b	2b	I-CH_2–CH_3	20–25°C / 60	80%
6c	2c	I-CH_2–CH_3	30–40°C / 120	60%
6d	2d	I-CH_2–CH_3	30–40°C / 120	70%
7a	2a	$ClCOCH_3$	20–25°C / 30	85%
7b	2b	$ClCOCH_3$	20–25°C / 30	80%
7c	2c	$ClCOCH_3$	25–30°C / 90	85%
7d	2d	$ClCOCH_3$	30–40°C / 90	75%
8a	2a	$ClCO\,CH_2CH_3$	20–25°C / 60	85%
8b	2b	$ClCO\,CH_2CH_3$	20–25°C / 60	80%
8c	2c	$ClCO\,CH_2CH_3$	30–40°C / 90	85%
8d	8d	$ClCO\,CH_2CH_3$	30–40°C / 120	70%

9-Phenyl-9-hydroxy-10-methylacridine ***4d***
Yield 75%. Sirup. IR (film) 3560 (OH) and 3320 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 and 1. (3H, 2s); 4.70 (1H, m). Anal. $C_{20}H_{17}NO$ (C, H, N).

9-Phenyl-9-hydroxyantracen ***4e***
Yield 70%. mp 190–191°C. IR (KBr) 3560 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.70–7.10 (13H, m) 8.40 (1H, s). Anal. $C_{20}H_{16}O$ (C, N).

O-*Alkylation of alcohols* ***4*** *with phase transfer catalysis (PTC)*
General procedure. A mixture of alcohol **4** (1 mmol), triethyl-benzyl-ammonium chloride (0.1 mmol), 20% aqueous sodium hydroxide (10 ml) in dichloromethane (15 ml) was added to the alkylating agent (3 mmol). The reaction mixture was stirred for 60–120 min, at the temperature given in Table II, and then washed with dilute hydrochloride acid (20 ml) and water (20 ml). The organic layer was dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified by recrystallization.

O-*Alkylation of alcohols* ***4*** *without PTC*
General procedure. Sulfuric acid (1 ml) was added to a solution of alcohol **4** (0.04 mol) in methanol or ethanol. The mixture was stirred and refluxed for 24 h. The reaction was then made basic with 22% aqueous ammonium hydroxide and extracted with dichloromethane. The organic extracts were dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified by recrystallization.

9-Phenyl-9-methoxyxanthene ***5a***
IR (KBr) 1280 and 1070 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.35 (3H, s); 7.40–6.90 (13H, m).

9-Phenyl-9-methoxythioxanthene ***5b***
IR (KBr) 1270 and 1070 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.00 (3H, s); 7.60–6.90 (13H, m).

9-Phenyl-9-methoxyacridine ***5c***
IR (KBr) 1235 and 1030 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 (1H, s); 3.05 (3H, s); 7.60–6.70 (13H, m).

9-Phenyl-9-methoxy-10-methylacridine ***5d***
IR (KBr) 1290 and 1070 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 and 1.20 (3H, 2s); 3.10 and 3.00 (3H, 2s); 7.50–6.60 (13H, m).

9-Phenyl-9-ethoxyxanthene ***6a***
IR (KBr) 1290 and 1060 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.15 (3H, t); 3.10 (2H, q); 7.50–7.00 (13H, m).

9-Phenyl-9-ethoxythioxanthene ***6b***
IR (KBr) 1290 and 1060 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 (3H, t); 3.00 (2H, q); 7.60–7.00 (13H, m).

9-Phenyl-9-ethoxyacridine ***6c***
IR (KBr) 1270 and 1050 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (3H, t); 1.40 (1H, s); 2.20 (2H, q); 7.70–6.70 (13H, m).

9-Phenyl-9-ethoxy-10-methylacridine ***6d***
IR (KBr) 1270 and 1040 (C-O-C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.00 (3H, t); 1.30 and 1.40 (3H, 2s); 2.10 (2H, q); 7.50–6.90 (13H, m).

O-*Acylation of alcohols* ***4*** *with PTC*
General procedure. The alkylating agent (2 mmol) was added to a mixture of alcohol **4** (1 mmol), triethyl-benzylammonium chloride (0.1 mmol), 20% aqueous sodium hydroxide (10 ml) in benzene (20 ml). The reaction mixture was stirred for 30–120 min at the temperature given in Table II. The organic layer washed with dilute hydrochloric acid (20 ml) and water (20 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue purified by recrystallization.

O-*Acylation of alcohols* ***4*** *without PTC*
General procedure. A molar excess of the corresponding acyl chloride

Table III.

Compound[a]	LD_{50} mg / kg
5a	780
5b	730
5c	725
5d	800
6a	740
6b	750
6c	690
6d	750
7a	675
7b	760
7c	740
7d	780
8a	700
8b	690
8c	700
8d	745
Meperidine	590

[a]All compounds were administered intraperitoneally as an aqueous solution of the hydrogen citrate salt.

was added to the alcohol **4** (4 mmol), and pyridine (10 mmol) in dry dichloromethane (50 ml) and the mixture poured into water and extracted with dichloromethane. The solvent was evaporated under reduced pressure and the residue washed with dilute sulfuric acid. The aqueous layer was extracted with diethyl ether and dried ($MgSO_4$) and the solvent evaporated under reduced pressure; the residue was purified by recrystallization.

9-Phenyl-9-acetyloxyxanthene ***7a***
IR (KBr) 1830 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.70 (3H, s); 7.40–6.70 (13H, m).

9-Phenyl-9-acetyloxythioxanthene ***7b***
IR (KBr) 1740 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.95 (3H, s); 7.70–7.00 (13H, m).

9-Phenyl-9-acetyloxyacridine ***7c***
IR (KBr) 1730 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.40 (1H, s); 2.00 and 1.95 (3H, 2s); 7.60–6.90 (13H, m).

9-Phenyl-9-acetyloxy-10-methyl-acridine ***7d***
IR (KBr) 1750 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.60 and 1.40 (3H, 2s); 2.30 and 2.00 (3H, 2s); 7.80–6.80 (13H, m).

9-Phenyl-9-propionyloxyxanthene ***8a***
IR (KBr) 1820 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.80 (3H, m); 2.75 and 2.00 (2H, 2q); 7.30–6.50 (13H, m).

9-Phenyl-9-propionyloxythioxanthene ***8b***
IR (KBr) 1760 (COO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 (3H, m); 2.35 (2H, m); 7.50–7.00 (11H, m); 8.10–7.80 (2H, m).

9-Phenyl-9-propionyloxyacridine ***8c***
IR (KBr) 1760 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (3H, m); 1.70 and 2.40 (2H, 2m); 7.60–6.90 (13H, m).

9-Phenyl-9-propionyloxy-10-methyl-acridine ***8d***
IR (KBr) 1750 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.20 (3H, m); 1.35 and 1.50 (3H, 2s); 2.35 (2H, m); 7.60–7.00 (13H, m).

Hydrogen citrates
General procedure. A solution of a base in ether was added dropwise to a solution of an equivalent amount of citric acid in methanol and the resulting precipitates collected. Recrystallization from methanol gave analytical samples.

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Table IV. Biological activities.

Compound	GPI[a] ED_{50} (μM)	Naloxone antagonism[b]	AAW[c] (sc) ED_{50} (mg / kg)
5a	16.4	No	25.3
5b	15.3	No	NE at 10
5c	0.55	Yes	NE at 10
5d	21.3	No	22.2
6a	8.4	Partial	NE at 10
6b	6.6	Partial	NE at 10
6c	1.1	Yes	NE at 10
6d	10.3	Partial	NE at 10
7a	18.01	No	24.3
7b	8.6	Partial	NE at 10
7c	2.05	Yes	NE at 10
7d	3.3	Yes	23.3
8a	0.18	Yes	12.8
8b	0.10	Yes	11.7
8c	11.4	Partial	20.5
8d	5.4	Yes	22.4
Meperidine	2.80	Partial	12.8
Fentanyl	0.020	Yes	0.04

[a]Inhibition of electrically-induced contractions of the guinea pig ileum.
[b]Antagonism of ileum effect by naloxone at 1 $\mu g\ ml^{-1}$.
[c]Acetic acid-induced writhing in mice. NE = < 20% inhibition at the stated dose.

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