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Heterocyclic and Piperonylic Acid Esters of 1-Methyl-4-piperidinol as Analgesics[1]

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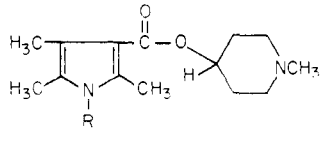
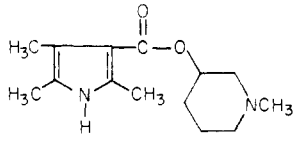
Heterocyclic and piperonylic acid esters of 1-methyl-4-piperidinol were synthesized and evaluated for analgesic activity. 1-Methyl-4-piperidinol 4-piperonylate (**14**) exhibited activity in the codeine range (mouse hot plate). In monkeys, **14** acted neither as a typical narcotic agonist nor as a typical antagonist and it showed no physical dependence liability of the morphine type. The nonquaternary C-4 piperidinol esters **1a**, **4**, **8**, and **14** exhibited marginal to virtually no binding to the opiate receptor in rat brain homogenates. The interaction of various functional groups of this series with potential binding sites of a nonopiate type receptor is discussed.

In a recent study of pyrrolecarboxylates of various cyclic amino alcohols as potential analgesics, 1-methyl-4-piperidinol 4-(2,4,5-trimethylpyrrole-3-carboxylate) (**1a**) was observed to have activity in the codeine–morphine range in the mouse hot-plate assay.[2] More significantly, **1a** did not exhibit a physical dependence syndrome of the morphine type in monkeys. An important structural feature of **1a** that differs from that of the pethidine or alphaprodine analgesics is that it does not have quaternary phenyl substitution at C-4 of the piperidine ring. Since



1a, R = H
b, R = CH_3



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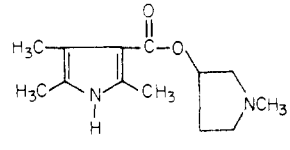


3

the heterocyclic moiety of the ester may play an important role in drug–receptor interaction, CNS concentration, and metabolism, it was of interest to replace the 2,4,5-trimethylpyrrole ring of **1a** with other heterocycles that would confer different electronic, steric, and lipophilic properties to this class of compounds.

In this study, nitrogen-, oxygen-, and sulfur-containing heterocyclic esters **4**–**13**, piperonylic acid esters **14** and **15**, and related 4-piperidinol esters **16**–**18** were prepared by the acid chloride method (Table I and Experimental Section) and evaluated for analgesic activity (Table II). Selected compounds were assayed for binding affinity to the opiate receptor (Table III) and for physical dependence liability in Rhesus monkeys.

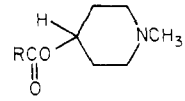
Results and Discussion

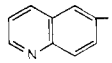
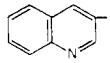
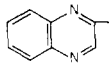
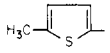
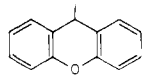
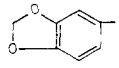
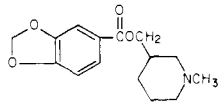
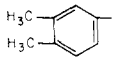
Compounds from each of the three groups of heterocyclic carboxylates (N, S, and O) and piperonylates showed activity in the mouse hot-plate assay[3] (Table II). Quinoline carboxylates **4** and **5** were moderately active (ED_{50} 9.3 and 11.2, respectively), whereas the pyridine and quinoxaline derivatives **6** and **7** were only marginally active and inactive, respectively. The 2-thiophene and 2-furan esters (**8** and **10**) exhibited one-half the potency of codeine by the hot-plate assay. Compound **8** was inactive in the Nilsen assay,[4a] whereas morphine and related drugs are nearly equipotent in the two systems.[4a] Esters **9** and **11**, substituted by electron-donating (methyl) and -withdrawing (bromo) groups, were both less active than the parent compounds. 1-Methyl-4-piperidinol 4-piperonylate (**14**) was the most active compound in this study, showing a potency equivalent to that of codeine (hot plate). It was three times more active than piperonylate **15**. Evidently the 4-piperidinol ring system in **14** is preferred over that of the 3-piperidinemethanol in **15**, even though the carbonyl oxygen and piperidine nitrogen atoms are separated by three carbons in both cases. The potential interaction of certain functions in **1a** and **14** with a receptor will be discussed later.

Compound **14** showed no morphine-like dependence liability in monkeys.[5] In single-dose suppression experiments, it caused only a slight increase in the severity of abstinence signs at 6.0 mg/kg. In nonwithdrawn monkeys it produced only very mild abstinence signs and very mild CNS depression at 6.0 mg/kg. At a higher dosage (12 mg/kg), piloerection, tremors, retching, and increased respiration were observed, but it was not a typical morphine withdrawal syndrome.

Quinolinecarboxylate **4**, thiophenecarboxylate **8**, and piperonylate **14** showed very marginal to essentially no binding to the opiate receptor as shown by their inability to reduce [^{3}H]dihydromorphine binding to rat brain homogenates[6] (Table III). The binding affinity of pyrrole

Table I. Esters of 1-Methyl-4-piperidinol and 1-Methyl-3-piperidinemethanol



No.	R	Mp, °C	Formula	Recrystn solvent[a]	Yield, %	Analyses
4		228-229.5	$C_{16}H_{18}N_2O_5 \cdot HCl \cdot 0.5H_2O$	C	74	C, H, N
5		220-221	$C_{16}H_{18}N_2O_2 \cdot 2HCl$[c]	B	49	C, H, N
6		145-148	$C_{12}H_{16}N_2O_2 \cdot C_4H_4O_4$[d]	A	40	C, H, N
7		214.5-216.5	$C_{15}H_{17}N_3O_2 \cdot HCl \cdot 0.5H_2O$	B	49	C, H, N
8		215.5-216.5	$C_{11}H_{15}NO_2S \cdot HCl$	C	53	C, H, N
9		184.5-185	$C_{12}H_{17}NO_2S \cdot HCl$	E	53	C, H, N
10		210-212	$C_{11}H_{15}NO_3 \cdot C_4H_4O_4$[d]	A	9	C, H, N
11		249-251	$C_{11}H_{14}BrNO_3 \cdot HCl \cdot 0.5CH_2Cl_2$[e]	B	23	C, H, N
12		128-129	$C_{11}H_{15}NO_3 \cdot C_4H_4O_4$[d]	A	20	C, H, N
13		225-230	$C_{20}H_{21}NO_3 \cdot HCl$	C	52	C, H, N
14		229-230	$C_{14}H_{17}NO_4 \cdot HCl$	C	43	C, H, N
15[b]		179.5-180	$C_{15}H_{19}NO_4 \cdot HCl$	D	23	C, H, N
16		233-235	$C_{15}H_{21}NO_2 \cdot HCl$	D	35	C, H, N
17	C_2H_5-	153-154	$C_9H_{17}NO_2 \cdot HCl$	A	80	C, H, N
18		218-219	$C_{17}H_{27}NO_2 \cdot HCl \cdot 0.25H_2O$	A	46	C, H, N

[a] A, acetone; B, MeOH; C, acetone-MeOH; D, acetone-EtOH; E, acetone-ether. [b] The complete formula is shown. [c] Dihydrochloride salt. [d] Maleate salt. [e] Solvated during chromatography.

ester **1a** (ED_{50} = 1000), though comparable to that displayed by pethidine (ED_{50} = 700), was far less efficient (>300-fold) than morphine (ED_{50} = 3). Several hypotheses have been presented[7,8] to explain discrepancies in the binding affinities of opiate and the less rigid nonopiate drugs and these are relevant in the discussion of these nonquaternary C-4 piperidinol esters. First, receptor sites that have an affinity for these esters may be different from those that bind the opiates, or there may be a completely different receptor or family of receptors that accept nonopiate analgesics. Second, the high degree of conformational mobility of these compounds, due in part to free rotation about the carbonyl bond, may result in inefficient bonding interactions. In vivo brain level concentrations of analgesics may also play an important role here. Pethidine has been observed to achieve greater brain level concentrations in comparison with morphine after iv administration in mice,[9,10] thus accounting for the analgesic potency and marginal receptor affinity in vitro of the former. Brain level concentrations of N-substituted pethidine homologues have also been studied.[11]

In a structure–activity comparison of pyrrole ester **1a** and piperonylic acid ester **14**, it is apparent that a suitable heterocyclic or aromatic ring can be interchanged in esters of this type. A nonopiate type receptor is proposed for these nonquaternary C-4 piperidinol esters. A priori, **1a** and **14** could exhibit van der Waals type bonding to a receptor site via their aromatic π electrons. In pyrrole, the lone pair of electrons of the nitrogen atom conjugates with the 4π electrons to form the aromatic sextet. Compounds lacking aromatic π-electron systems were synthesized, namely, propionate **17** and adamantoate **18**, to determine if aromaticity was more effective than alkyl groups in promoting analgesic activity. Compounds **17** and **18** were three to four times less potent that **1a** and two to three times less potent than **14**. The heterocyclic rings of **1a** and **14** could also be involved in binding to an accessory site via hydrogen bonding interactions. The heteroatom of pyrrole could undergo NH···O bonding, as well as NH···π bonding,[12] while an oxygen atom(s) of the methylenedioxy group of **14** could be involved in hydrogen bonding with a different accessory site but in the general proximity of the NH site. In the previous publication,[2] it was shown that the NCH_3 pyrrole ester **1b** was only marginally active at 20 mg/kg in the hot-plate assay (Table II), whereas the NH pyrrole ester **1a** had an ED_{50} of 4.9, thus lending

Table II. Analgesic Activity of 1-Methyl-4-piperidinol and 1-Methyl-3-piperidinemethanol Esters

Compd[a]	ED_{50}, mg/kg sc[b] Hot plate	Nilsen
1a[c,d]	4.9 (3.6-6.5)	7.1 (5.3-9.4)
1b	Marginally act. at 20	
2	Inactive	
3	64.3 (39.6-104.4)	
4[e]	9.3 (5.8-15.0)	29.7 (19.7-45.0)
5[f]	11.2 (7.5-16.5)	
6	44.2 (25.0-78.2)	
7	Inactive	
8[g]	13.3 (8.3-21.2)	Inactive
9	Inactive	
10[h]	12.5 (8.5-18.3)	
11	17.7 (11.8-26.5)	
12	27.9 (17.9-43.3)	
13	35.0 (21.6-56.7)	
14[i]	7.3 (4.7-11.4)	
15	22.7 (13.6-38.0)	
16	Marginally act. at 20	
17	20.2 (8.4-28.4)	
18	15.9 (10.5-24.3)	
Codeine	7.5 (6.7-8.3)	4.5 (2.7-7.6)
Morphine	1.2 (0.9-1.3)	0.8 (0.6-1.2)

[a] Tested subcutaneously as water-soluble salts as indicated in Table I. [b] Numbers in parentheses are the 95% confidence limits obtained by probit analysis. [c] ED_{50} 15.1 mg/kg sc and marginally active at 10 mg/kg sc in the mouse tail-flick and *p*-phenylquinone abdominal-stretching (PPQ) assays,[4b] respectively. [d] No toxicity noted at 20 mg/kg. [e] No toxicity noted at 40 mg/kg; slight toxicity at 50 mg/kg. [f] No toxicity noted at 60 mg/kg. [g] No toxicity noted at 40 mg/kg; one-half of the mice exhibited toxicity at 50 mg/kg. [h] No toxicity noted at 50 mg/kg. [i] No toxicity noted at 30 mg/kg.

Table III. Relative Potencies of Compounds in Reducing Stereospecific [^{3}H]Dihydromorphine Binding

Compd	ED_{50}, nM[a]	Compd	ED_{50}, nM[a]
1a	1 000	14	30 000
4	>100 000	Pethidine	700
8	>100 000	Morphine	3

[a] Refers to nanomolar concentration of drug required to reduce [^{3}H]dihydromorphine binding to rat brain homogenates by 50% (ref 6).

support to possible pyrrole NH group involvement at an accessory site. In a preliminary assessment of the potential binding of a methylenedioxy oxygen atom, 3,4-dimethylbenzoate **16** was synthesized. It was only marginally active at 20 mg/kg, whereas the methylenedioxybenzoate **14** showed an ED_{50} of 7.3. The carbonyl and the protonated nitrogen of piperidine are also potential groups for receptor binding sites, as postulated for the pethidine and prodine series.[13,14] There exists some evidence that the distance between the carbonyl group and protonated nitrogen, as well as geometrical factors, present in the 4-piperidinol esters **1a** and **14**, is essential for receptor binding. This is shown by the reduced activities of the 3-piperidinol ester **2**[2] (inactive), the 3-pyrrolidinol ester **3**[2] (ED_{50} 64.3), and the 3-piperidinemethanol ester **15** (ED_{50} 22.7), in comparison to the 4-piperidinol ester **1a** (ED_{50} 4.9). Additional structure–activity correlations are in progress to further delineate these proposed binding sites. In connection with this discussion, it should be pointed out that the metabolic disposition and the ability to cross the blood–brain barrier, as discussed earlier, may also play important roles in the activity of these compounds.

Electron-inductive groups, as present in **9** and **11**, can significantly alter the pK_a values[15] of the parent heterocycle. Since methyl-substituted **9** and bromo-substituted **11** (containing electron-donating and -withdrawing groups, respectively) both showed reduced activities in comparison with the corresponding unsubstituted esters, this parameter was not determined for this series. Also, correlations concerning the steric influence of the heterocyclic ring were not very promising. For example, monocyclic (**1a, 8, 10**) and bicyclic (**4, 5**) systems did not show significant differences in their analgesia. However, the activity of the large tricyclic system (**13**) was approximately one-third that of the other two systems showing activity.

Further work on aromatic carboxylates of 1-methyl-4-piperidinol and isomeric 4-piperidinols, including substituent effects and additional CNS evaluation of **1a**, is also in progress.

Experimental Section

Melting points were taken on a Kofler hot stage and are corrected. Analytical results obtained were within ±0.4% of theoretical values. Infrared spectra were obtained on a Perkin-Elmer Spectrometer Model 237B. Chloroform was used as a solvent, unless otherwise indicated.

1-Methyl-4-piperidinol and 1-Methyl-3-piperidinemethanol Carboxylates. All of the esters were prepared via the acid chloride. Propionate **17** was prepared by refluxing 691 mg (6 mmol) of 1-methyl-4-hydroxypiperidine and 1.387 g (1.31 mL, 15 mmol) of propionyl chloride in 20 mL of dry benzene under a nitrogen atmosphere for 3 h. The copious, white precipitate was removed by suction filtration and recrystallized two times from acetone to give propionate **17** as the hydrochloride salt (needles) as designated in Table I. The remainder of the esters were prepared by the general procedure as described. A solution of 6 mmol of the carboxylic acid in 10–16 mL of thionyl chloride was refluxed for 30 min. Excess thionyl chloride was removed in vacuo and the residue was mixed with dry benzene (over 3A molecular sieves) and evaporated. No attempts were made to isolate and purify the acid chlorides. To the crude acid chloride was added 3 mmol of 1-methyl-4-piperidinol or 1-methyl-3-piperidinemethanol in 15 mL of dry pyridine (over 4A molecular sieves) and the mixture was then refluxed for 4–6 h. The pyridine was removed in vacuo and the residue mixed and evaporated two times with CH_2Cl_2. The crude reaction mixture was chromatographed on 40 g of silica gel, 70–230 mesh ASTM (elution with increasing percentages of MeOH in CH_2Cl_2), unless otherwise stated. The compounds were eluted from the column at the percentages of MeOH indicated: **4**, 25–50%; **5**, 15–50%; **6**, 8–25%; **7**, crystallized from the reaction mixture; **8**, 7–10%; **9**, 7–10%; **10**, 7–10%; **11**, 6–8%; **12**, 7–12%; **13**, 7–10%; **14**, 4–10%; **15**, crystallized from the reaction mixture; **16**, crystallized from the reaction mixture; **18**, 5–12%. Homogeneous fractions were indicated by TLC [$CHCl_3$–MeOH (9:1), silica gel GF, regular development] and appropriate ester bands in the infrared as listed (**4**, 1704 cm^{-1}, Nujol; **5**, 1715 cm^{-1}, Nujol; **6**, 1730 cm^{-1}, Nujol; **7**, 1727 cm^{-1}; **8**, 1709 cm^{-1}; **9**, 1704 cm^{-1}; **10**, 1712 cm^{-1}; **11**, 1715 cm^{-1}; **12**, 1712 cm^{-1}; **13**, 1733 cm^{-1}; **14**, 1712 cm^{-1}; **15**, 1706 cm^{-1}; **16**, 1712 cm^{-1}; **17**, 1736 cm^{-1}; **18**, 1721 cm^{-1}). Fractions were combined and evaporated and the residues recrystallized from the designated solvent (Table I) to yield the esters as hydrochloride salts (ester **5** as the dihydrochloride salt). Esters **6**, **10**, and **12** were difficult to crystallize as the hydrochloride salts and, hence, were converted to the free bases, dissolved in ether, and converted to maleate salts by slow addition of a dilute solution of maleic acid in ether.

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References and Notes

(1) Presented in part before the Medicinal Chemistry Division, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Aug 30, 1976, MEDI 24.

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Dibenz[*b*,*e*]oxepinalkanoic Acids as Nonsteroidal Antiinflammatory Agents. 3. ω-(6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)alkanoic Acids

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ω-(6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-yl)butyric, -hexanoic, and -octanoic acids were evaluated in the carrageenan paw edema assay. The most active compound, the butyric acid analogue, was 1.80 times more potent than the hexanoic compound, 1.15 times more potent than the octanoic analogue, and 0.43 times as potent as indomethacin.

In earlier papers we reported on the synthesis of 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetic acid[1] (**7**) and 4,10-dihydro-10-oxothieno[3,2-*c*][1]benzoxepin-8-acetic acid[2] which were found to possess potent antiinflammatory activity. We now wish to report on the synthesis and pharmacological activity of a series of related dibenz[*b*,*e*]oxepinalkanoic acids.

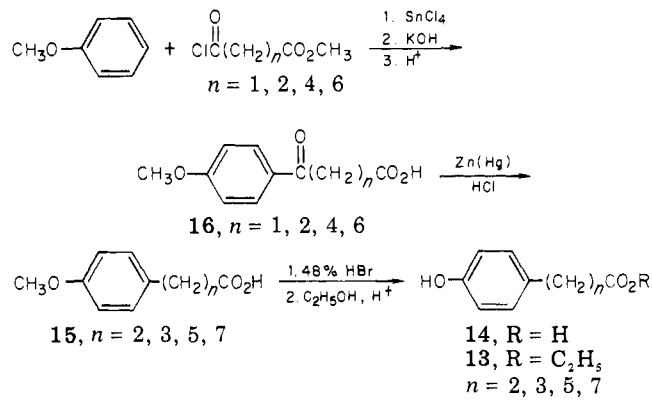
The synthetic approach used in the preparation of the required precursor alkyl ω-(4-hydroxyphenyl)alkanoates is depicted in Scheme I. Anisole was allowed to react with the acid chlorides of monomethyl esters of alkanedioic acids in the presence of stannic chloride to provide the ω-(4-methoxybenzoyl)alkanoic acids (**16**). Application of the Martin[3] modification of the Clemmensen reduction gave the ω-(4-methoxyphenyl)alkanoic acids (**15**). Demethylation of these intermediates with 48% hydrobromic acid according to the method of Fieser et al.[4] afforded the desired ω-(4-hydroxyphenyl)alkanoic acids (**14**) which were then esterified under Fischer–Speier[5] conditions to yield the esters **13**.

As shown in Scheme II, the ethyl ω-(4-hydroxyphenyl)alkanoates were then condensed with ethyl α-bromo-*o*-toluate in the presence of potassium carbonate to provide the diesters which were hydrolyzed with potassium hydroxide to yield the diacids **8**–**11**. Cyclization of the intermediates **9**–**11** was effected by using the polyphosphoric–acetic acid mixture, while the diacid **8** was cyclized using a phosphorus pentoxide–ethanol reagent in sulfolane.

Compounds **1**–**10** were evaluated for antiinflammatory activity in the carrageenan paw edema test in rats.[1] A minimum of three different doses was administered orally using groups of ten rats at each dose level. The ED_{50} values were determined according to the method of Litchfield and Wilcoxon.[6] Activity data for these compounds as well as for indomethacin are presented in Tables I and II.

As shown in Table I, increasing the chain length of the acid from two carbons (**7**) to three carbons (**1**) somewhat

Scheme I



surprisingly[7] results in a complete loss of antiinflammatory activity. However, an increase in chain length from two carbons (**7**) to four (**2**), six (**3**), or eight (**4**) carbons still provides analogues with good antiinflammatory effects. The butyric acid analogue **2** is the most potent of the group **2**–**4**, being 0.63 times as potent as **7** and 0.43 times as potent as indomethacin. The possibility exists that an in vivo β-oxidation[8] to the acetic acid compound **7** is occurring which would be blocked in the case of the propionic acid derivative **1**. This explanation may, however, be somewhat of an oversimplification for while minor differences do exist, the potencies of **2**–**4** are rather similar. If β-oxidation to **7** were the chief operant mechanism, one might expect larger potency differences between **2** and **4** given the limited test period for such metabolism to occur. An alternative explanation could involve the ability of the antiinflammatory receptor(s) for steric reasons to accommodate only dibenzoxepins bearing alkanoic acid chains shorter or longer than three carbons. Further work is necessary to clarify these results.

Both the methyl (**5**) and the isopropyl (**6**) esters were less potent than the parent compound **2**. The diacid precursors were inactive in the carrageenan assay.