Synthesis and Analgesic-Antiinflammatory Activities of Ethyl 2-[3-(1-phenoxy(methoxy)carbonyl-4-aryl-(alkyl)-1,4-dihydropyridyl)]acetates

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Reaction of ethyl 2-(3-pyridyl)acetate **4a** or ethyl 2-methyl-2-(3-pyridyl)acetate **4b**, with phenyl chloroformate or methyl chloroformate, afforded the intermediate pyridinium salt **5** which undergoes regioselective nucleophilic attack at C-4 upon reaction with a Grignard reagent in the presence of a cuprous iodide catalyst at -23° to yield the corresponding ethyl 2-[3-(1-phenoxy(methoxy)carbonyl-4-aryl(alkyl)-1,4-dihydropyridyl)]acetates **6a-f** in 64-96% chemical yield. No product arising from reaction of the ester substituent of the pyridinium salt **5** with the Grignard reagent was observed. The ^{1}H nmr spectra of **6a-f** exhibited dual resonances for the 1,4-dihydropyridyl H-2, H-5 and H-6 protons at 25° in deuteriochloroform. These dual resonaces were attributed to two different rotameric configurations resulting from restricted rotation about the nitrogen-to-carbonyl carbamate bond due to its double bond character. Compound **6** generally exhibited superior analgesic and antiinflammatory activities, compared to the reference drugs aspirin and ibuprofen, respectively. These structure-activity correlations indicate the 1,4-dihydropyridyl ring system present in **6** is a suitable bioisostere for the aryl (heteroaryl) ring present in aryl(heteroaryl)acetic acid non-steroidal antiinflammatory drugs.

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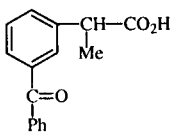
Introduction.

Traditional benzoylaryl, and heteraryl, acetic acids (non-steroidal antiinflammatory drugs) such as ketoprofen **1**, tolmetin **2** and indomethacin **3** are effective analgesic-antiinflammatory agents [1]. However, non-steroidal antiinflammatory drugs, which block arachidonic acid metabolism by inhibition of cyclooxygenase-1 and -2 isozymes, induce gastrointestinal irritation and hemorrhage and provide only interim relief of pain and inflammation symptoms without correction of the underlying disease process. Accordingly, new classes of antiarthritic drugs, that act by a novel mechanism, would be useful in separating the desired antiinflammatory action from undesirable gastrointestinal side effects, and to treat the disease process rather than just alleviating pain and edema caused by inflammation.

Non-steroidal antiinflammatory aryl- and heteroaryl acetic acid derivatives possess several common structural features that include a carboxyl group or its equivalent (ester) separated by one-carbon atom from a flat aromatic nucleus, and one or more large lipophilic groups attached to the aromatic nucleus that is two, three or four carbon or heteratoms removed from the point of attachment of the acetic acid side chain [2]. These structure-activity correlations prompted us to investigate the synthesis and analgesic-antiinflammatory activities of ethyl 2-[3-(1-phenoxy(methoxy)carbonyl-4-aryl(alkyl)-1,4-dihydropyridyl)]acetates **6a-f**, wherein the R^1-substituent is hydrogen or methyl, the R^2-substituent is phenyl or methyl, and the R^3-substituent is phenyl, 4-chlorophenyl, *n*-butyl or methyl (see structures in Scheme 1).



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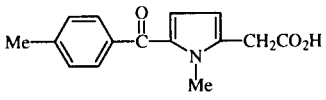

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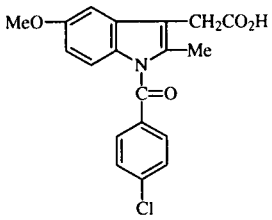

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Chemistry.

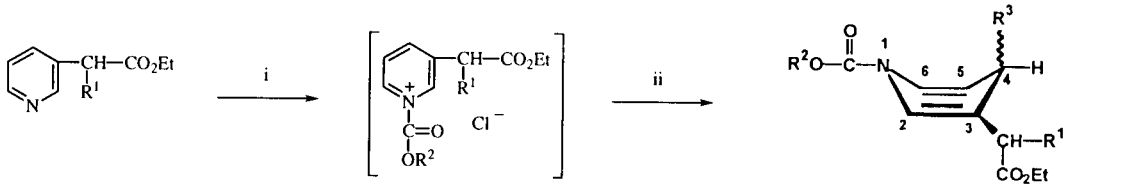
The ethyl 2-[3-(1-phenoxy(methoxy)carbonyl-4-aryl-(alkyl)-1,4-dihydropyridyl)]acetates **6a-f** were synthesized using the procedure illustrated in Scheme 1. The copper-catalyzed regioselective addition of Grignard reagents to 1- acylpyridinium salts is a convenient method for the synthesis of 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines [3]. A similar reaction of ethyl 2-(3-pyridyl)-acetate **4a**, or ethyl 2-methyl-2-(3-pyridyl)acetate **4b**, with phenyl chloroformate or methyl chloroformate gave the intermediate pyridinium salt **5**, which undergoes regioselective nucleophilic attack at C-4 by the Grignard reagent (R^3MgCl; R^3 = phenyl, 4-chlorophenyl, *n*-butyl or methyl) in the presence of a catalytic amount of cuprous iodide at -23° to yield the corresponding 1,4-dihydropyridyl products **6a-f** in 64-96% chemical yield. The observation that no product is produced by reaction of the ester substituent of the pyridinium salt **5** with the Grignard reagent is attributed to the fact that **5** is so reactive to the Grignard reagent in the presence of cuprous iodide that the selective addition at C-4 of **5** takes place even when a reactive substituent, such as an ester, is present at C-3 [4]. The ^1H nmr spectra for **6a-f** exhibited dual resonances for the H-2, H-5 and H-6 protons in deuteriochloroform at 25° in a ratio of about 1:1. The dual resonances observed for **6f**, which contains two asymmetric carbons, could be attributed to diastereomers. However, a ^1H nmr variable temperature study for **6f** in deuteriodimethyl sulfoxide showed that the dual resonances for H-5, and the dual overlapping resonances for H-2 and H-6, coalesced to single resonances at 68°. This latter study shows that the dual resonances observed for **6a-f** is due to two different rotameric configurations attributed to restricted rotation about the nitrogen-to-carbonyl bond of the carbamate moiety, which has a double bond character, as reported previously [5].

Biological Results and Discussion.

The 1,4-dihydropyridyl ring system of **6a-f** possesses conformational and steric characteristics that are significantly different from those present in traditional aryl(heteroaryl)acetic acid non-steroidal antiinflammatory agents such as ketoprofen (**1**). Accordingly, the 1,4-dihydropyridyl ring system is more puckered than the planar aryl(heteroaryl) ring system due to distortion at the 1,4-dihydropyridyl N-1 and C-4 positions. Hoffman and Cimiraglia reported [6], based on ab-initio STO-3G calculations for 4-phenyl-3,5-dicarboxy-1,4-dihydropyridine, that a boat conformation for the 1,4-dihydropyridine ring is favored over a planar ring arrangement, that ring distortion is greater at C-4 than at N-1, and that the C-4 phenyl substituent on the 1,4-dihydropyridine ring having a pseudoaxial orientation relative to the plane of the olefinic bonds was unequivocally favored [7]. These conformational differences, together with steric and physicochemical effects due to the 1,4-dihydropyridyl N-1, C-3 and C-4 substituents would be expected to change the global size of the molecule, distribution of the drug between hydrophilic and hydrophobic sites, and binding of the drug with the antiinflammatory binding site or cyclooxygenase enzyme active site(s).

The compounds **6a-f** were investigated to determine the effect of the acetic acid ester moiety (R^1 = hydrogen, methyl), the 1,4-dihydropyridyl N-1 carbamate moiety (R^1 = phenyl, methyl), and the C-4 substituent (R^3 = phenyl, 4-chlorophenyl, *n*-butyl, methyl) upon analgesic and antiinflammatory activities. Analgesic activity was determined using the 4% sodium choride-induced writhing (abdominal constriction) assay [8], and antiinflammatory activity was determined using the carrageenan-induced rat paw edema assay [9], as reported previously (see results in Table 1).

Scheme 1 [a]



4a, R^1 = H
4b, R^1 = Me

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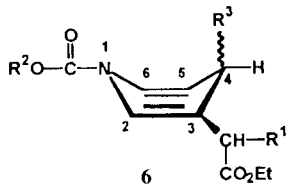
6a, R^1 = H, R^2 = Ph, R^3 = Ph
6b, R^1 = H, R^2 = Ph, R^3 = 4-Cl-C_6H_4-
6c, R^1 = H, R^2 = Ph, R^3 = *n*-Bu
6d, R^1 = H, R^2 = Ph, R^3 = Me
6e, R^1 = H, R^2 = Me, R^3 = Ph
6f, R^1 = Me, R^2 = Ph, R^3 = Ph

[a] Reagents and conditions: i, phenyl chloroformate or methyl chloroformate (R^2OCOCl; R^2 = Ph or Me), dry tetrahydrofuran, 25°, 15 minutes; ii, cuprous iodide, Grignard reagent (R^3MgCl; R^3 = Ph, 4-Cl-C_6H_4-, *n*-Bu, Me), 15 minutes at -23° and then 1 hour at 25°.

Table 1

Analgesic and Antiinflammatory Activites for the Ethyl 2-[3-(1-Phenoxy(methoxy)carbonyl-4-aryl(alkyl)-1,4-dihydropyridyl)]acetates **6a-f**



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Compound	R^1	R^2	R^3	Analgesic Activity % Inhibition [a]	Antiinflammatory Activity % Inhibition [b] 3 Hours	5 Hours
6a	H	Ph	Ph	83.1 ± 3.8	50.2 ± 3.5	31.7 ± 1.5
6b	H	Ph	4-Cl-C_6H_4-	62.4 ± 5.2	7.3 ± 4.8	6.0 ± 2.8
6c	H	Ph	*n*-Bu	73.2 ± 2.6	62.3 ± 2.3	35.4 ± 1.8
6d	H	Ph	Me	80.2 ± 2.4	60.3 ± 3.2	37.3 ± 4.5
6e	H	Me	Ph	58.0 ± 2.5	46.0 ± 1.5	38.0 ± 2.8
6f	Me	Ph	Ph	68.0 ± 1.5	70.5 ± 3.5	45.5 ± 1.6
Aspirin				57.8 ± 2.8	—	—
Ibuprofen				—	43.8 ± 2.3	51.7 ± 3.6

[a] The result is the mean value ± standard error mean (SEM, n = 5) for a 50 mg/kg intraperitoneal dose of the test compound in the rat 4% sodium chloride-induced writhing assay. [b] The result is the mean value ± standard error mean (SEM, n = 4) for a 100 mg/kg oral dose of the test compound in the carrageenan-induced rat paw edema assay.

In the analgesic screen, **6a-f** inhibited writhing by 58-83% compared to the reference drug aspirin (58% inhibition) for a 50 mg/kg intraperitoneal dose. Although the 1,4-dihydropyridyl C-4 R^3-substituent (phenyl, 4-chlorophenyl, *n*-butyl, methyl) of compounds **6a-d** influences analgesic activity, the differences in potency were within a relatively narrow range (62-83% inhibition). In contrast, the carbamate R^2-substituent had a greater effect on analgesic potency (**6a**, R^2 = Ph, 83% inhibition > **6e**, R^2 = Me, 58% inhibition). The R^1-substituent of the acetate moiety was also a determinant of analgesic activity, where the potency profile was **6a** (R^1 = H, 83% inhibition) > **6f** (R^1 = Me, 68% inhibition).

In the antiinflammatory screen (3 hour test data), compounds possessing a C-4 phenyl (**6a**), *n*-butyl (**6c**) or methyl (**6d**) substituent exhibited more potent activity (50-62% inhibition) than the reference drug ibuprofen (44% inhibition). The large difference in antiinflammatory activity between the C-4 phenyl (**6a**, 50% inhibition) and 4-chlorophenyl (**6b**, 7% inhibition) compounds may be due to differences in absorption and/or biodistribution properties. The R^2-carbamate substituent was not a determinant of antiinflammatory activity since the phenyl **6a** and methyl **6e** analogs were approximately equipotent. In contrast, the R^1-acetate substituent was a determinant of activity where the potency profile was **6f** (R^1 = Me, 70% inhibition) > **6a** (R^1 = H, 50% inhibition).

It is highly probable that the compounds **6a-f** investigated act as prodrugs, which undergo *in vivo* cleavage of the ester moiety by esterases, to afford active 2-[3-(1-phenoxy(methoxy)carbonyl-4-aryl(alkyl)-1,4-dihydropyridyl)]acetic acid analogs.

EXPERIMENTAL

Nuclear magnetic resonance spectra (^{1}H nmr) were recorded for solutions in deuteriochloroform with tetramethylsilane as internal standard on a Bruker AM-300 spectrometer. Infrared spectra (ir) were recorded on a Nicolet 5DX FT spectrometer. Column chromatography was performed using Merck 7734 (100-200 mesh) silica gel. All reactions employing Grignard reagents were performed in oven-dried glassware under a nitrogen atmosphere. Tetrahydrofuran was dried over sodium benzophenone and distilled just before use.

Ethyl 2-[3-(1-Phenoxy(methoxy)carbonyl-4-aryl(alkyl)-1,4-dihydropyridyl)]acetates (**6a-f**).

General Procedure.

Cuprous iodide (28 mg, 0.2 mmoles), and then either phenyl chloroformate or methyl chloroformate (3.7 mmoles), was added to a solution of either ethyl 2-(3-pyridyl)acetate or ethyl 2-methyl-2-(3-pyridyl)acetate (3.15 mmoles) in dry tetrahydrofuran (30 ml) under a nitrogen atmosphere at 25° with stirring.

The reaction mixture was cooled to -23° in a dry ice-carbon tetrachloride bath, a solution of the Grignard reagent (3.46 mmoles) in dry tetrahydrofuran (0.65 ml) was added dropwise with stirring over a period of 10 minutes, and the reaction was allowed to continue for 15 minutes at -23°. The reaction mixture was allowed to warm to 25° with stirring during a 1 hour period. A saturated solution of ammonium choride (5 ml) was added to quench the reaction. Ether (30 ml) was added and the mixture was washed successively with 20% ammonium chloride-ammonium hydroxide (1:1, v/v; 2 x 20 ml), water (2 x 10 ml) and then brine (10 ml). The organic fraction was dried (magnesium sulfate), filtered, and the solvent was removed *in vacuo* to give an oil which was purified by silica gel column chromatography using ethyl acetate-hexane (15:85, v/v) as eluent to afford the respective ethyl 2-[3-(1-phenoxy(methoxy)carbonyl-4-aryl-(alkyl)-1,4-dihydropyridyl)]acetate **6a-f** as an oil (mixture of two rotamers in a ratio of about 1:1).

Ethyl 2-[3-(1-Phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-acetate (**6a**).

This compound was obtained as a colorless oil (96%); ir (neat): ν 1745 (CO_2Et), 1730 (CO_2Ph) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.16-7.48 (m, 10H, phenyl hydrogens), 7.00-7.14 (m, 2H, H-2, H-6), 5.05 and 5.12 (two dd, $J_{4,5}$ = 4.0, $J_{5,6}$ = 8.6 Hz, 1H total, H-5), 4.26 and 4.36 (two d, $J_{4,5}$ = 4.0 Hz, 1H total, H-4), 4.1 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.72-2.92 (m, 2H, CH_2CO_2), 1.14-1.32 (m, 3H, CH_2CH_3).

Anal. Calcd. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.77; H, 5.85; N, 3.56.

Ethyl 2-[3-(1-Phenoxycarbonyl-4-(4-chlorophenyl)-1,4-dihydropyridyl)]acetate (**6b**).

This compound was obtained as a colorless oil (75%); ir (neat): ν 1745 (CO_2Et), 1730 (CO_2Ph) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 6.80-7.45 (m, 9H, phenyl hydrogens), 6.76 and 6.80 (two s, 1H total, H-2), 6.76 (d, $J_{5,6}$ = 8.6 Hz, 1H, H-6), 5.00 and 5.08 (two dd, $J_{4,5}$ = 4.0, $J_{5,6}$ = 8.6 Hz, 1H total, H-5), 4.30 and 4.40 (two d, $J_{4,5}$ = 4.0 Hz, 1H total, H-4), 4.08 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.70-2.90 (m, 2H, CH_2CO_2), 1.24 (t, J = 7.0 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{22}H_{20}ClNO_4$: C, 66.42; H, 5.07; N, 3.52. Found: C, 66.30; H, 5.30; N, 3.57.

Ethyl 2-[3-(1-Phenoxycarbonyl-4-*n*-butyl-1,4-dihydropyridyl)]-acetate (**6c**).

This compound was obtained as a colorless oil (82%); ir (neat): ν 1740 (CO_2Et), 1730 (CO_2Ph) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.14-7.50 (m, 5H, phenyl hydrogens), 6.86-7.00 (m, 2H, H-2, H-6), 4.95 and 5.02 (two dd, $J_{4,5}$ = 4.9, $J_{5,6}$ = 8.4 Hz, 1H total, H-5), 4.12-4.22 (m, 2H, $CO_2CH_2CH_3$), 2.92-3.18 (m, 3H, H-4, CH_2CO_2), 1.20-1.65 (m, 9H, $CO_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$), 0.88 (t, J = 7.0 Hz, 3H, $CH_2CH_2CH_3$).

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.94; H, 7.33; N, 4.07. Found: C, 69.86; H, 7.26; N, 4.04.

Ethyl 2-[3-(1-Phenoxycarbonyl-4-methyl-1,4-dihydropyridyl)]-acetate (**6d**).

This compound was obtained as a colorless oil (64%); ir (neat): ν 1740 (CO_2Et), 1730 (CO_2Ph) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.10-7.45 (m, 5H, phenyl hydrogens), 6.84-6.96 (m, 2H, H-2, H-6), 4.90 and 5.02 (two dd, $J_{4,5}$ = 4.3, $J_{5,6}$ = 8.8 Hz, 1H total, H-5), 4.19 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 2.94-3.25 (m, 3H, H-4, CH_2CO_2), 1.28 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.16 (d, $J_{CH,Me}$ = 6.9 Hz, 3H, $CHCH_3$).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.75; H, 6.35; N, 4.64. Found: C, 67.58; H, 6.37; N, 4.32.

Ethyl 2-[3-(1-Methoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]-acetate (**6e**).

This compound was obtained as a colorless oil (87%); ir (neat): ν 1745 (CO_2Et), 1745 (CO_2Me) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.12-7.30 (m, 5H, phenyl hydrogens), 6.90 and 6.93 (two s, 1H total, H-2), 6.74 and 6.78 (two d, $J_{5,6}$ = 8.6 Hz, 1H total, H-6), 4.85 and 4.95 (two broad d, $J_{5,6}$ = 8.6 Hz, 1H total, H-5), 4.16 (broad peak, 1H, H-4), 4.06 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.80 (s, 3H, *OMe*), 2.70 (s, 2H, CH_2CO_2), 1.20 (t, J = 7.0 Hz, 3H, CH_2CH_3).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.75; H, 6.35; N, 4.64. Found: C, 67.63; H, 6.05; N, 4.59.

Ethyl 2-Methyl-2-[3-(1-phenoxycarbonyl-4-phenyl-1,4-dihydropyridyl)]acetate (**6f**).

This compound was obtained as a colorless oil (64%); ir (neat): ν 1742 (CO_2Et), 1730 (CO_2Ph) cm^{-1}; ^{1}H nmr (deuteriochloroform, 25°): δ 7.10-7.60 (m, 10H, phenyl hydrogens), 6.90-7.10 (m, 2H, H-2, H-6), 5.04 and 5.14 (two dd, $J_{4,5}$ = 4.3, $J_{5,6}$ = 8.8 Hz, 1H total, H-5), 4.25 (d, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 4.08 (q, J = 7.0 Hz, 2H, CH_2CH_3), 2.90 (q, $J_{CH,Me}$ = 7.0 Hz, 1H, *CH*Me), 1.10-1.45 (m, 6H, $CHCH_3$, CH_2CH_3); ^{1}H nmr (deuteriodimethyl sulfoxide, 68°): δ 7.20-7.50 (m, 10H, phenyl hydrogens), 6.98-7.10 (m, 2H, H-2, H-6), 5.12 (dd, $J_{4,5}$ = 4.3, $J_{5,6}$ = 8.8 Hz, 1H, H-5), 4.20 (d, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 3.98 and 4.02 (two overlapping q, J = 7.0 Hz, 2H, CH_2CH_3), 2.29 and 2.96 (two overlapping q, $J_{CH,Me}$ = 7.0 Hz, 1H, *CH*Me), 1.06-1.24 (m, 6H, $CHCH_3$, CH_2CH_3).

Anal. Calcd. for $C_{23}H_{23}NO_4 \cdot 1/2H_2O$: C, 71.50; H, 6.26; N, 3.63. Found: C, 71.64; H, 6.16; N, 3.26.

Acknowledgements.

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