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Synthesis and Anti-inflammatory Activity of Some 1-Methyl-5-(4-substituted benzoyl)imidazole-2-acetates

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Abstract

1-Methyl-5-(4-X-benzoyl)imidazole-2-acetates were synthesized and tested for anti-inflammatory activity. Tolmetin and aspirin were used as reference drugs.

The most active compound against carrageenan-induced oedema in rat hindpaw was a 4-chlorobenzoyl derivative, which was almost 1·5-times more active than the reference drug aspirin. In addition, it had half the activity of tolmetin.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of certain rheumatic disorders. These agents inhibit the biosynthesis of prostaglandins from arachidonic acid (Vane 1971). Some anti-inflammatory receptor models for NSAIDs show the interaction of these agents with the active site of the key enzyme in prostaglandin biosynthesis namely prostaglandin synthetase (Gund & Shen 1977; Salvetti et al 1981). These receptor models indicate that most NSAIDs, possess the common structural features of an acidic center, an aromatic or heteroaromatic ring, and an additional center of lipophilicity in the form of either an alkyl chain or an additional aromatic ring. The proposed receptor to which indomethacin was postulated to bind consisted of a cationic site to which the carboxylate anion would bind, a flat area to which the indole ring would bind to Van der Waals' forces, and an out-of-plane trough to which the benzene ring of the *p*-chlorobenzoyl group binds through hydrophobic or charge–transfer interactions.

We designed and synthesized a series of 1-methyl-5-(4-X-benzoyl)imidazole-2-acetates. In-vivo anti-inflammatory activity was assessed by the carrageenan-induced oedema test in rat hindpaw.

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Materials and Methods

Chemical procedures

The 1-methyl-5-(4-X-benzoyl)imidazole-2-acetates, as sodium salts **5a–d**, were synthesized as outlined in Figure 1. 1,2-Dimethyl-imidazole-5-carboxaldehyde (**1**) was prepared according to the procedure described by Godefroi et al (1972). Reaction of compound **1** with the appropriate aryl magnesium bromide in anhydrous tetrahydrofuran at 20°C gave compounds **2a–d**. Oxidation of compounds **2a–d** with MnO_2 in chloroform afforded compounds **3a–d**. Condensation of **3a–d** with ethyl chloro-formate in triethylamine–acetonitrile medium, at room temperature (Macco et al 1975) gave the required compounds **4a–d**. These were converted by hydrolysis with 2 M NaOH into the desired sodium 1-methyl-5-(4-X-benzolyl)imidazole-2-acetates **5a–d**.

The physicochemical data of the intermediates **2a–d**, **3a–d** and **4a–d** are given in Tables 1, 2 and

Table 1. Physicochemical properties of 1,2-dimethyl-5-(α-hydroxy-4-X-benzyl)imidazoles.

Compound	X	Yield (%)	Crystallization solvent	Mp (°C)
2a[a]	H	87	THF	194–195
2b	Cl	92	THF	189–191
2c	CH_3	75	THF	224–225
2d	OCH_3	96	THF	158–160

[a]Previously reported by Godefroi & Greenan (1975).

Table 2. Physicochemical properties of 1,2-dimethyl-5-(4-X-benzoyl)imidazoles.

Compound	X	Yield (%)	Crystallization solvent	Mp (°C)
3a	H	91	Ether	52–53
3b	Cl	96	Ether	153
3c	CH_3	93	Ether	79–81
3d	OCH_3	75	Ether	115

Table 3. Physicochemical properties of ethyl 1-methyl-5-(4-X-benzoyl)imidazole-2-acetates.

Compound	X	Yield (%)	Crystallization solvent	Mp (°C)
4a	H	24	Ether	98–99
4b	Cl	23	Ether	159–162
4c	CH_3	39	Ether	147–149
4d	OCH_3	45	Ether	119–120

3, respectively. The compounds were characterized by ^{1}H NMR, IR and microanalysis. The purity of all products was determined by thin-layer chromatography using several solvent systems of different polarity.

Evaluation of pharmacological activity

The anti-inflammatory activity of the synthesized compounds was determined by the carrageenan-induced oedema test in rat hindpaw, according to the modified method described by Maeda et al (1984).

Male Wistar rats, 150–180 g, were maintained at room temperature. Food was withdrawn 12 h before the start of the experiment. A 1% suspension of carrageenan (Sigma Co.) in 1% carboxymethylcellulose was prepared and a volume of 50 μL was injected into the plantar side of the left hindpaw of each rat.

Compounds **5a–d** (50–350 mg kg^{-1}) and tolmetin sodium (12·5–50 mg kg^{-1}) (Sigma Co.) were dissolved in water and administered

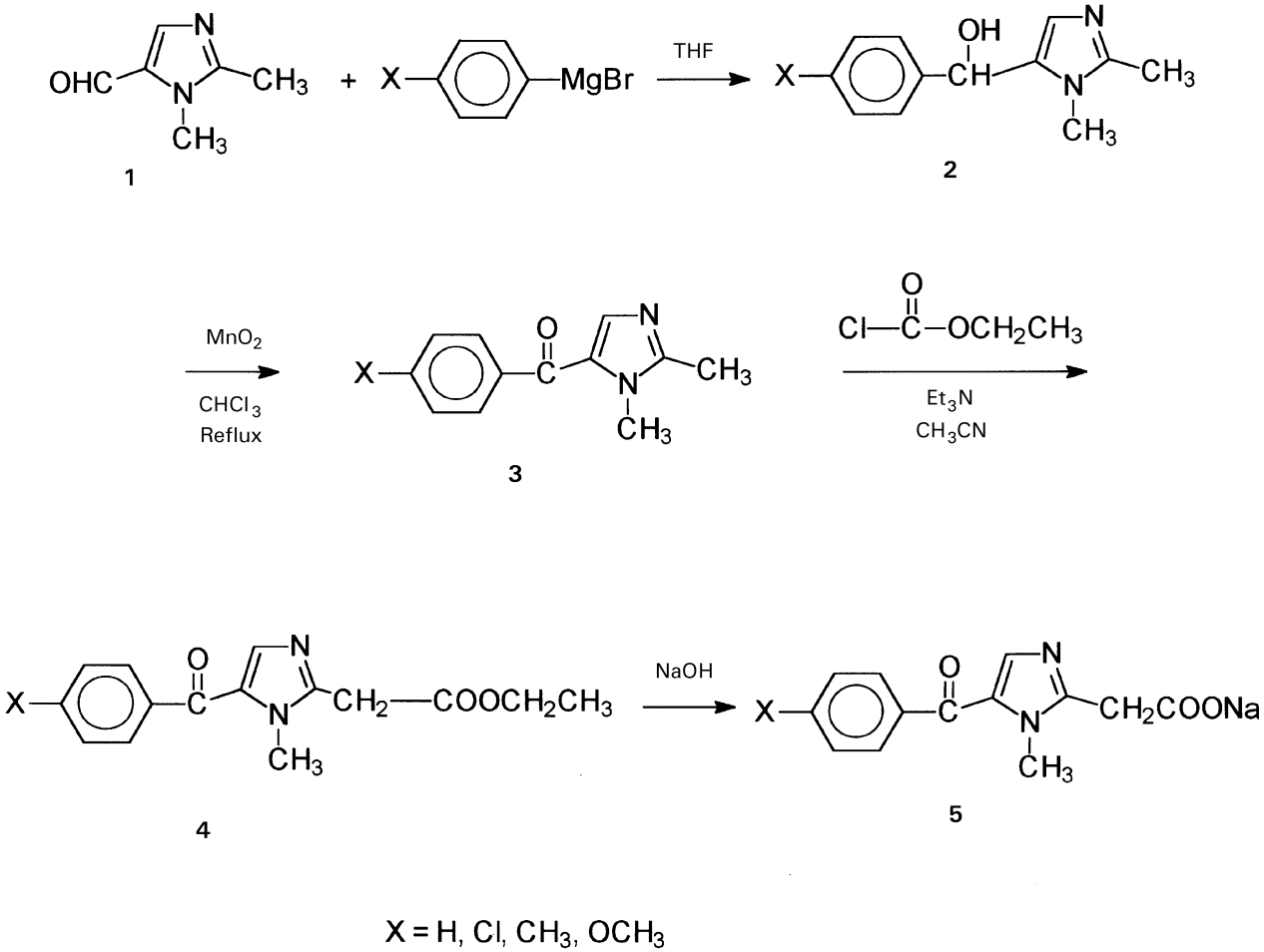

Figure 1. Synthesis of sodium 1-methyl-5-(4-X-benzoyl)imidazole-2-acetates.

Table 4. Anti-inflammatory activity of 1-methyl-5-(4-X-benzoyl)imidazole-2-acetates.

Compound	X	ED50 mg kg^{-1}
5a	H	301 ± 14
5b	Cl	83 ± 1·5
5c	CH_3	137 ± 2
5d	OCH_3	214 ± 3·5
Tolmetin		44 ± 2
Aspirin		116 ± 10

Values are mean ± s.e.m., n = 6.

intraperitoneally. Controls received only saline (10 mL kg^{-1}, i.p.). Drugs and saline were given 1 h before carrageenan treatment and the volume of the paw was measured just before (V_0) and 3 h after (V_3) the carrageenan injection by a water displacement technique. The percentage inhibition of the oedema volume was calculated according to the following formula (Maeda et al 1984):

$$\text{Inhibition (\%)} = (1 - (V_3 - V_0)_{\text{test}}/(V_3 - V_0)_{\text{control}}) \times 100$$

Results and Discussion

Anti-inflammatory activity (ED50) of compounds **5a–d** was determined as the dose required to produce 50% inhibition of carrageenan-induced oedema in the rat hindpaw. The results are presented in Table 4. Comparison of the activity of compounds **5a–d** indicates that the order of potency was $X = Cl > CH_3 > OCH_3 > H$. The presence of a substituent in the 4 position of the benzoyl moiety therefore increases anti-inflammatory activity. The electron-withdrawing substituent, Cl, showed the greatest activity in the carrageenan test. It was almost 1·5 times more active than aspirin (Samin et al 1995). In addition, it had half the activity of tolmetin.

Acknowledgements

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