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Practical Synthesis of Fenbufen Ethanolamide

The ongoing interest in ethanolamide derivatives of anti-inflammatory drugs as potential synthetic cannabinoids and mechanistic tools for the study of cannabinoid and vanilloid receptors prompted us to develop a practical gram scale synthesis for the hitherto unknown ethanolamide of fenbufen. Dehydration of fenbufen leads to intramolecular ring closure yielding bright pink crystals of the intramolecular enol ester. Reaction of this activated but stable intermediate with ethanolamine leads to the title compound in good yield and purity without the necessity to remove coupling reagents or residual activating groups, such as *N*,*N*-dialkyl ureas and fluorinated phenols.

Keywords: Anandamide; Enol ester; Fenbufen; Acylation

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Introduction

The recently discovered role of AM404, *N*-(4-hydroxyphenyl)-5,8,11,14-eicosatetraenamide, **1** as an active metabolite of paracetamol/acetaminophen sheds new light on the question whether amide conjugates of other known pain-relieving drugs contribute to the mechanism of action of these agents, too [1]. Paracetamol differs from most NSAIDs in that it is a weak anti-inflammatory agent that does not generate the typical side effects related to COX-1 inhibition. Although extensively used as antipyretic and analgesic for more than a century, its mechanism of action is still widely unsolved [2]. Selective inhibition of prostaglandin synthesis in brain, consistent with a central site of action, has been proposed. However, evidence is weak: paracetamol is no potent inhibitor of isolated COX-1 and COX-2. The postulated target COX-3 does not seem to be present in the human brain in sufficient amounts [3].

The endogenous fatty acid anandamide (arachidonoylethanolamide) **2** is hydrolyzed to arachidonic acid and ethanolamine by fatty acid amide hydrolase (FAAH) and, vice versa, ethanolamine and arachidonic acid are reacted to form anandamide [4,5]. It is now hypothesized that paracetamol, following deacetylation to 4-amino phenol, is similarly conjugated with arachidonic acid to form AM404 (**1**) in the CNS [1]. The possible role of FAAH in formation of conjugates of ethanolamine to xenobiotic acids is yet to be explored.

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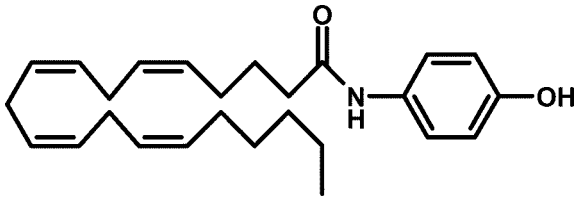
Results and discussion

Recently, it was revealed that AM404 (**1**) interacts with vanilloid and cannabinoid receptors, and it might be strongly anticipated today that interaction with these receptors might help to understand hitherto obscure clinical effects of other analgesic drugs such as fenbufen (**4**). Conjugation of fenbufen (**4**) with ethanolamine might be a prerequisite for a probable contribution to the mode of action of these analgesic drugs [6].

Looking at the structure of the active metabolite AM404 (**1**) formed after ingestion of paracetamol, anandamide (**2**) and the novel fenbufen ethanolamide **3** (see Figure 1), it seems rewarding to develop a high yielding synthesis for this hitherto unknown fenbufen derivative.

The synthesis of the title compound started from commercially available fenbufen (**4**)(Scheme 1). In order to avoid toxic and costly coupling reagents such as *N*,*N*-dialkyl carbodiimides, acylated succinic imides or pentafluoro phenol esters, fenbufen was dehydrated by means of acetic anhydride. The resulting intramolecular enol ester (**5**) could effortlessly be purified by crystallization.

The beautifully glossy, bright pink crystals of compound **5** are shelf-stable at room temperature and can easily be obtained in multi-gram quantities. This is an advantage in comparison to the possible preparation of acid chloride derivatives of the starting material fenbufen. Ring-opening of the enol ester (**5**) by chemoselective reaction with ethanolamine (**6**) as N-nucleophile in dry toluene yielded the desired target compound in good yield and purity (Scheme 2). The development of N-selective acylation procedures that allow for the evasion of protecting groups operations represents a



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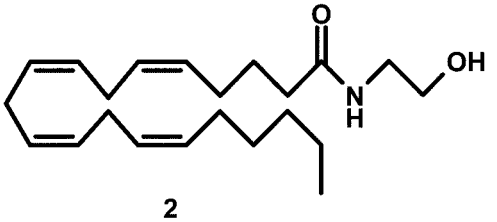

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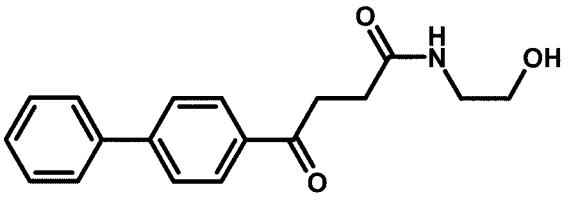

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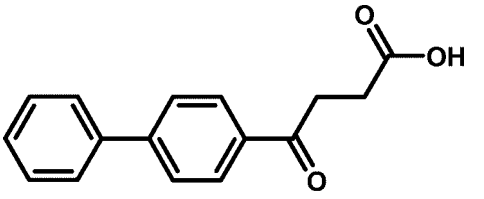
Figure 1. Structural comparison of AM-404 (**1**), anandamide (**2**), and amide **3**.



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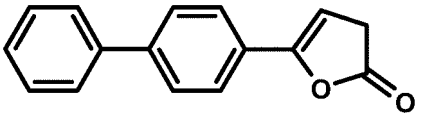

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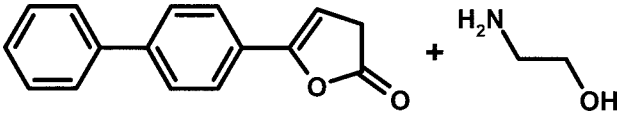
Scheme 1. Preparation of the enol ester **5**; i: a) toluene, reflux, b) acetic acid anhydride, reflux 6 h.



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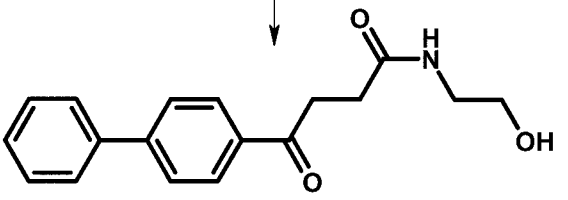

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Scheme 2. Preparation of fenbufen ethanolamide (**3**); i: toluene, room temp.

general concern in the synthesis of natural product-like compounds that are often decorated with reactive primary alcoholic functions. Such approaches have been explored by our group in detail [7–13]. In this case, the absence of the tendency to form esters is a benefit of the moderate reactivity of compound **5**. Comparable to the use of pentafluoro phenol esters for the synthesis of ethanolamides, attack by O-nucleophiles is negligible, the desired amides are the single products, even under forcing conditions.

In comparison to standard procedures for the synthesis of amides using activated esters as coupling reagents or *in situ* formed anhydrides, the lack of sources for impurities using the inner ester **5** is a strong advantage. Since neither formation of diisopropyl urea nor liberation of pentafluoro phenol or pyrrolidine-2,5-dione occur, work-up of the reaction mixture is straightforward. The crude reaction product is already pure and a single crystallization from a standard solvents yields analytically pure material, as proven by combustion analysis and HPLC.

Full Paper

Conclusion

The rapidly growing understanding of the cannabinoid system as an important endogenous regulator of neuronal, cardiac, reproductive, and immune functions demands molecular tools to study specific ligand-receptor interactions, especially, as compounds are currently developed for medical intervention. The convenient, high yielding and practical synthesis of fenbufen ethanolamide **3** is useful for the production of this novel compound in gram scale and shall contribute to investigations concerning the role of ethanolamide conjugation of fenbufen and to evaluate biological activities of this novel fatty acid amide analogue.

Acknowledgments

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Experimental

Structures were assigned by NMR spectroscopy. NMR spectra were recorded on a JEOL ECLIPSE+500 spectrometer (JEOL, Tokyo, Japan), using tetramethylsilane as internal standard. IR spectra were recorded on a Nicolet 510P FT-IR-spectrometer (Nicolet, Madison, MI, USA). TLC reaction control was performed on Macherey-Nagel Polygram Sil G/UV_{254} precoated microplates (Macherey-Nagel, Düren, Germany). Spots were visualized under UV-illumination at 254 nm. Microanalyses were obtained from a Hewlett-Packard CHN-analyzer type 185 (Hewlett-Packard, Palo Alto, CA, USA).

*5-Biphenyl-4-yl-3H-furan-2-one (**5**)*

To a boiling solution of fenbufen (2.54 g, 9.98 mmol) in dry toluene (40 mL), acetic acid anhydride was added dropwise until all of the solid was dissolved and a bright red homogenous liquid was obtained. The reaction was monitored by TLC. Quantitative conversion was observed after 6 h of heating. The reaction mixture was allowed to cool to room temperature and the product precipitated as glossy pink crystals. The resulting suspension was filtered. The solid was recrystallized from ethanol to yield 2.05 g (87%) of analytically pure material. Analytical data were identical to those reported [14].

*4-Biphenyl-4-yl-N-(2-hydroxy-ethyl)-4-oxo-butyramide (**3**)*

To a solution of compound **5** (450 mg, 1.90 mmol) in dry toluene (20 mL) ethanolamine (114.70 μL, 1.90 mmol) was added. The reaction mixture was stirred at room temperature and monitored by TLC. Quantitative conversion was observed after 4 h. The suspension was filtered and the residual solid crystallized from ethanol to yield 429 mg (76%) of yellowish crystals. ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.05 (d, 2H, J = 8.7 Hz), 7.88 (t, 1H, J = 5.4 Hz), 7.83 (d, 2H, J = 8.7 Hz), 7.75 (d, 2H, J = 7.1 Hz), 7.51 (m, 2H), 7.43 (m, 1H), 4.63 (t, 1H, J = 5.5 Hz), 3.41 (q, 2H, J = 6.0 Hz), 3.26 (t, 2H, J = 6.7 Hz), 3.13 (q, 2H, J = 6.0 Hz), 2.51 (d, 2H, J = 6.6 Hz overlapping with DMSO signal.). ^{13}C NMR (126 MHz, DMSO-d_6): δ (ppm) 198.40, 171.18, 144.32, 138.86, 135.40, 128.97, 128.47, 128.23, 126.85, 126.74, 59.87, 41.49, 33.38, 29.23. IR (cm^{-1}): 3298, 1685, 1638, 1560, 759. Combustion analysis: % [C] 72.87 (calc. 72.71), % [H] 6.14 (calc. 6.44), % [N] 4.76 (calc. 4.71). Relative purity as determined by HPLC: 94%. Melting point: 157 °C.

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