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Original article

2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides: Synthesis, reactions and biological activity

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Abstract

2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides (**1**–**17**) were prepared from 3-(4-phenoxy-benzoyl)propionic acid and aromatic aldehydes. Some of the selected butenolides were reacted with ammonia and benzylamine to give corresponding 3-arylidene-5-(4-phenoxy-phenyl)-2(3*H*)-pyrrolones (**18**–**23**) and 3-arylidene-5-(4-phenoxy-phenyl)-1-benzyl-2(3*H*)-pyrrolones (**24**–**29**) respectively, which were characterized on the basis of ^{1}H-, ^{13}C-NMR, Mass spectrometric data and elemental analysis results. These compounds were tested for anti-inflammatory and antimicrobial actions. The compounds, which showed significant anti-inflammatory activity, were screened for their analgesic and ulcerogenic activities. Five new compounds (**5**, **6**, **7**, **25** and **26**), out of 29 showed very good anti-inflammatory activity in the carrageenan induced rat paw edema test, with significant analgesic activity in the acetic acid induced writhing test together with negligible ulcerogenic action. Antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* as well as antifungal activity against *Candida albicans* were expressed as the corresponding minimum inhibitory concentration (MIC) values. Compound **21**, **22** and **23** showed excellent activity against *C. albicans* with MIC-10 μg/ml. Out of the above-mentioned compounds, **22** and **23** also showed good activity against *S. aureus* with MIC-20 and 15 μg/ml respectively.
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Keywords: Butenolide; Aroylpropionic acid; Pyrrolone; Anti-inflammatory; Analgesic; Ulcerogenic; Antimicrobial activity

1. Introduction

The butenolide system as present in many cardiac glycosides shows strong oral cardiotonic activity [1]. Physiological activity of the natural lactones is known ever since santonin was used as an important anthelmintic and ascaricidal agent [2,3]. Besides the whole group of butenolide antibiotics [4], this moiety has been found to have some interesting activities [5–9] such as anticonvulsant, anti-inflammatory, analgesic, antitumor, antiviral, anticancer etc. The reactivity of γ-lactone ring present in the butenolide derivatives has been further exploited for the synthesis of nitrogen heterocycles of potential biological activity [10,11].

3-(4-Phenoxy-benzoyl) propionic acid is an example of well known aroyl propionic acid class of anti-inflammatory drugs [12] and some of them are available in the market (fenbufen, bucloxic acid, furobufen etc.), they have been reported to have comparatively more gastrointestinal side effects as compared to other NSAIDs [13–15]. We had examined in these laboratories the anti-inflammatory activity of a number of 2-arylidene-4-substituted phenyl butenolides and the results were encouraging [16,17]. 3-(4-Phenoxy-benzoyl) propionic acid is a good anti-inflammatory agent associated with gastrointestinal side effects [13]. It was therefore considered worthwhile to study various butenolide derivatives of 3-(4-phenoxy-benzoyl) propionic acid for their anti-inflammatory action. These butenolides were further exploited for the synthesis of nitrogen heterocycles (pyrrolones). In view of the

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reported antimicrobial activity of butenolides and pyrrolones, these compounds were also tested for their antibacterial and antifungal activity against some selected microbes.

2. Chemistry

Overall 29 new compounds **1**–**29** were prepared as outlined in Scheme 1. 2-Arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides (**1**–**17**) were synthesized from 3-(4-phenoxy-benzoyl) propionic acid by reacting with aromatic aldehydes in presence of triethylamine in acetic anhydride. The required 3-(4-phenoxy-benzoyl) propionic acid was prepared by condensing diphenyl ether with succinic anhydride in presence of anhydrous aluminum chloride following Friedel-Craft's acylation reaction conditions. The 3-arylidene-5-(4-phenoxy-phenyl)-2(3*H*)-pyrrolones (**18**–**23**) were prepared by reacting butenolides with ammonia in absolute ethanol. The 3-arylidene-5-(4-phenoxy-phenyl)-1-benzyl-2(3*H*)-pyrrolones (**24**–**29**) were synthesized by reacting appropriate butenolides with benzylamine in dry benzene to give γ-ketobenzylamides, which were then lactamized in 6 N HCl to give the corresponding *N*-benzylpyrrolones. Calculations of δ values using incremental parameters for the hydrogen (semicyclic double bond) seems to suggest (*E*)-configuration. The structures assigned to the compounds **1**–**29** were supported by the results of elemental analysis as well as ^{1}H- and ^{13}C-NMR and Mass spectral data (Scheme 1).

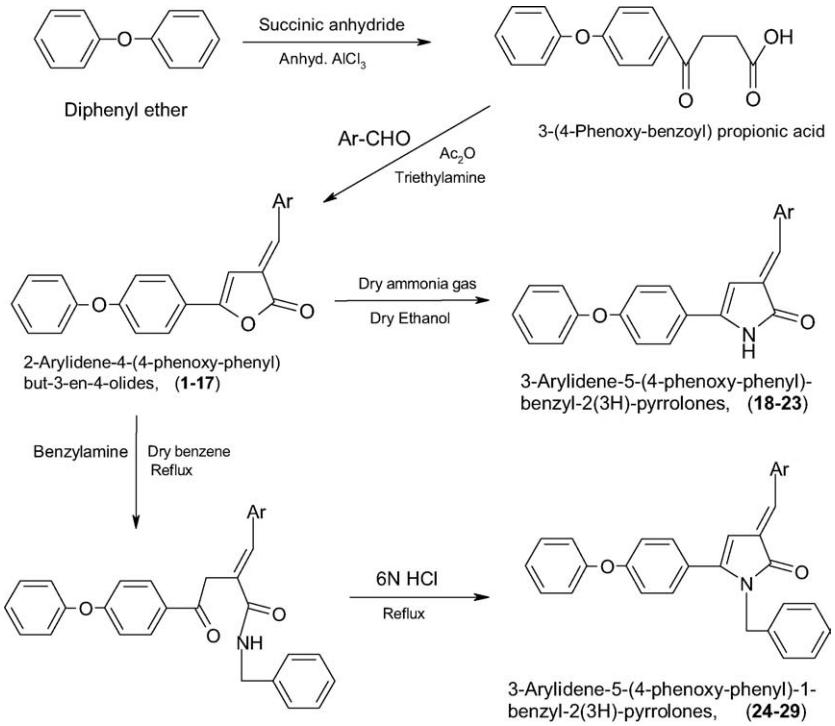
In the ^{1}H-NMR spectral data all the compounds showed two singlets of one proton each around δ 6.5 and δ 7.4 which could be assigned to the ring βH and the olefinic hydrogen of the arylidene substituent. However, deviations are observed when the Ar moiety is 2,6-dichlorophenyl and 9-anthracenyl. In these cases the ring hydrogen gets shifted upfield while the olefinic hydrogen is downfield possibly due to non-planarity of the Ar ring. In the ^{13}C-NMR spectral data all the compounds showed a peak around δ 98.5 that could be assigned to the olefinic carbon (C-5). Other peaks were observed at appropriate places.

The fragmentation pattern observed on electron impact mass spectrum can be summarized as follows:

The 2-arylidene-4-(4-phenoxy-phenyl)but-3-en-4-olides gave M^+ peak in reasonable intensities. The major fragment appears to be C_6H_5–O–C_6H_4–C≡O^+ arising from the heterocyclic oxygen and γ-carbon with its substituent. Subsequently it loses CO to give C_6H_5–O–$C_6H_4^+$. There appeared a peak at *m*/*z* 77 that corresponds to $C_6H_5^+$ Occasionally the aryl ring of the arylidene moiety also appeared as Ar^+. In the case of pyrrolones, the major fragmentation is through C_6H_5–O–C_6H_4–C≡N^+H, which is followed by loss of HCN to give C_6H_5–O–$C_6H_4^+$.

In case of *N*-benzylpyrrolones, loss of 91 mass units corresponding to benzyl moiety from the molecular ion is observed along with peaks at *m*/*z* 91, 77. Other pathway is via C_6H_5–O–C_6H_4–C≡N^+H arising from C-2 and its substituent, which appears to be novel. This also loses HCN to give C_6H_5–O–$C_6H_4^+$.

In case of aryl groups having chloro-substituent(s), the molecular ion peak or their fragments having halogen(s) appeared as cluster of peaks.



Scheme 1.

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