

## SYNTHESIS OF PYRAZOLIDINONE ANTIBACTERIAL AGENTS

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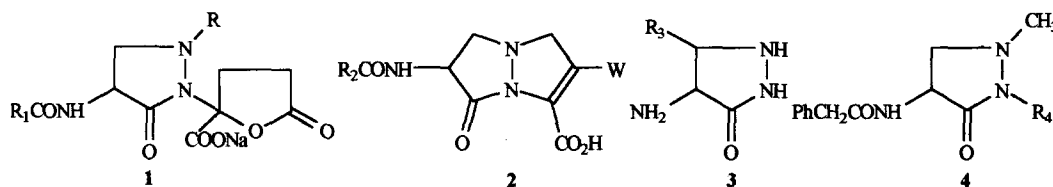
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**Abstract :** The synthesis of monocyclic pyrazolidinones, which show moderate antibacterial activity, are described. © 1999 Published by Elsevier Science Ltd. All rights reserved.

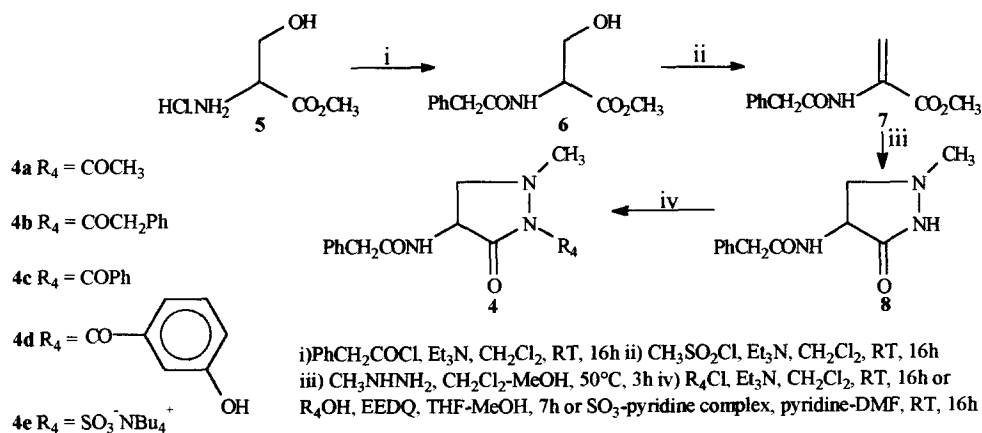
Bacterial resistance to  $\beta$ -lactam antibiotics is increasingly worrying. More often it involves enzymes,  $\beta$ -lactamases<sup>1</sup>, which catalyze the ring opening of  $\beta$ -lactams leading to inactive compounds. One of the possible ways for countering this resistance is to modify the  $\beta$ -lactam ring itself. Molecular modeling suggests that  $\gamma$ -lactams could replace  $\beta$ -lactams in the activity they exert on PBPs, penicillin-binding proteins, required for bacteria cell synthesis. Some lactivicin derivatives<sup>4</sup> **1** and some pyrazolidinones<sup>2</sup> such as **2** and **3** were described, some of them showed excellent antibacterial activity [e.g. R = CH<sub>3</sub>, COCH<sub>3</sub>, W = COCH<sub>3</sub>, CN, SO<sub>2</sub>CH<sub>3</sub>, R<sub>3</sub> = H, Ph].

We have synthesised a few related monocyclic pyrazolidinones **4** and tested their biological activity against bacteria. We chose to prepare compounds possessing electron-withdrawing groups<sup>3</sup> (R<sub>4</sub>) which improve the reactivity of  $\beta$ -lactams and the phenylacetyl side-chain of benzylpenicillin, which heightens the bindings with PBPs.



The key pyrazolidinone<sup>4</sup> **8** was prepared from D,L-serine methyl ester hydrochloride (**5**) which was coupled with phenylacetyl chloride to afford phenylacetylserine methyl ester (**6**). Treatment of **6** with methanesulfonyl chloride gave the acrylic acid derivative **7** which reacted with methylhydrazine and afforded the pyrazolidinone **8** in 48% overall yield from **5**.

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No regioisomer of **8** is observed and this is in accordance with the fact that esters react at the less substituted nitrogen, and with NMR chemical shifts<sup>5</sup>.

Compound **8** was coupled with acetyl chloride, phenylacetyl chloride or benzoyl chloride to afford 1-methyl-2-acetyl-4-N-phenylacetamidopyrazolidin-3-one (**4a**), 1-methyl-2-phenylacetyl-4-N-phenylacetamidopyrazolidin-3-one (**4b**) and 1-methyl-2-benzoyl-4-N-phenylacetamidopyrazolidin-3-one (**4c**) in 40% yield, 60% yield and 92% yield respectively. The coupling of **8** with 3-hydroxybenzoic acid and EEDQ gave 1-methyl-2-(3-hydroxybenzoyl)-4-N-phenylacetamidopyrazolidin-3-one (**4d**) in 40% yield. Electrophilic sulfonation of **8** with  $\text{SO}_3$ -pyridine complex gave the 1-methyl-2-sulphonyl-4-N-phenylacetamidopyrazolidin-3-one (**4e**) isolated as its tetra-n-butylammonium salt in 53% yield.

Compounds **4b** to **4e** showed moderate antibacterial activity [i.e. MICs 128 to 512  $\mu\text{g/ml}$ ] vs *Micrococcus luteus* and/or *Staphylococcus aureus*. In vitro qualitative microbiological testings suggested a positive synergy test of **4a**, **4b** and **4c** with cephalothin against *S. aureus* and *Escherichia coli* while **8** showed no antibacterial activity.

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