Asian Journal of Chemistry Vol. 20, No. 5 (2008), 3949-3953

Antibacterial Activity of New [(2-Hydroxypropyl)-*n*-oximino]pyridines

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The synthesized [(2-hydroxypropyl)-*n*-oximino]pyridine derivatives has been tested against the pathogenic four Gram-positive bacteria *Bacillus cereus* (ATCC 11778), *Staphylococcus aureus* (ATCC 6538), *Sarcina lutea* (ATCC 9341) and *Streptococs mutans* (UCTC 10499) and three Gram-negative bacteria *Salmonella typhimurium* (1,4,5,12:;:1,2), *Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 29998). Generally, all synthesized compounds (**IVa-c**) showed strong activity compared to antibiotic drug (cefalexin). However, among this compounds (**IVa**) showed excellent activity against *Bacillus cereus* (ATCC 11778), *Sarcina lutea* (ATCC 9341), *Salmonella typhimurium* (1,4,5,12:;:1,2) and *Escherichia coli* (ATCC 29998) compared to cefalexin.

Key Words: Pyridinecarbaldehyde oximes, Antibacterial activity, Gram-positive bacteria, Gram-negative bacteria.

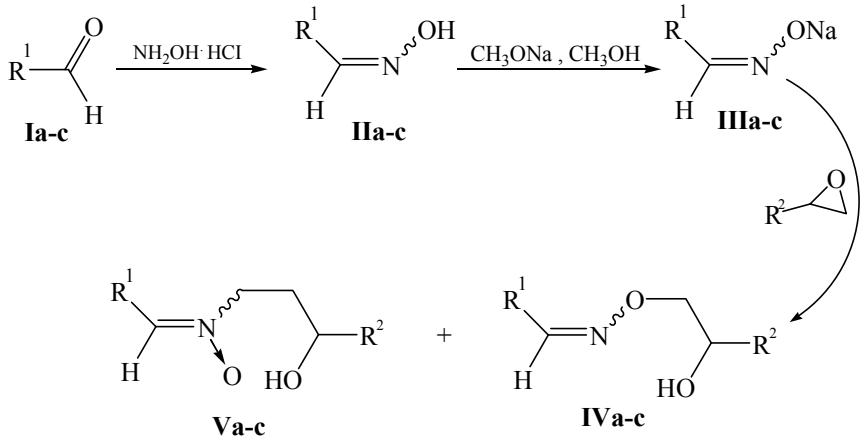
INTRODUCTION

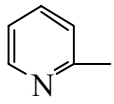
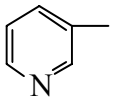
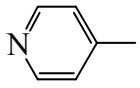
Oximes and their ethers are important intermediates in organic synthesis. Specifically, they are used for protection, alkylation and regeneration of carbonyl compounds[1-4] in the synthesis of hydroxylamines, primary amines, nitrones, nitriles[4-7] and for the preparation of many pharmaceuticals[8,9]. It has been reported in literature that pyridines and a lot of compounds including pyridine ring have owned a number of pharmacological properties, such as cardiotonic[10], β-adrenergic blocking activity[11], antihypertensive[12], anticonvulsant[13,14] and antibacterial activity[15,16]. Recently, in the studies taken by Manna *et al.*[11] and Abele *et al.*[17] some amino alcohols derived from oximes were found to exhibit properties of β-adrenergic blocking and anti-ulcer agents *in vitro*. In view of these observations and in continuation of our related pyridinecarbaldehyde oximes[4], it was realized in the present investigation to undertake the evaluation of whether the antibacterial activities of some new O-alkyl derivatives of pyridinecarbaldeyde oximes (**IVa-c**), *i.e.*, [(2-hydroxypropyl)-2-oximino]pyridine, [(2-hydroxypropyl)-3-oximino]-pyridine and [(2-hydroxypropyl)-4-oximino]pyridine, respectively, against

four Gram-positive bacteria *B. cereus* (ATCC 11778), *S. aureus* (ATCC 6538), *S. lutea* (ATCC 9341) and *S. mutans* (UCTC 10499) and three Gram-negative bacteria *S. typhimurium* (1,4,5,12:;:1,2), *P. aeruginosa* (ATCC 27853) and *E. coli* (ATCC 29998) are different each other or not and to find new and more potent antibacterial agents.

EXPERIMENTAL

Synthesis of [(2-hydroxypropyl)-*n*-oximino]pyridines: In previous work[4], we synthesized a number of pyridine-2-, -3- and -4-carbaldehyde O- and N-alkyl oximes **IVa-c** and **Va-c** by reactions of the corresponding oximes (**IIa-c**) with racemic 1,2-epoxypropane according to following **Scheme-I**.



Substituent	(I-V)a	(I-V)b	(I-V)c
R^1			
	Pyridine-2-yl	Pyridine-3-yl	Pyridine-4-yl
R^2	CH_3	CH_3	CH_3

Scheme-I: Synthesis of new [(2-hydroxypropyl)-*n*-oximino]pyridines

The alkylation of oximes (**IIa-c**) as mixtures of *syn*- and *anti*-isomers with racemic α-epoxides gave mixtures of isomeric O- and N-alkylation products **IVa-c** and **Va-c** at a ratio of 92:8. In the alkylation of the *anti*-isomers, the ratio of the corresponding O- and N-substituted derivatives was 88:12, whereas *syn*-isomers gave rise to O- and N-alkylation products at a ratio of 78:22. Compounds **IV** and **V** can readily be separated due to their different solubilities. O-Alkyl derivatives **IV** are soluble in diethyl ether,

while N-Alkyl oximes are soluble in chloroform. Therefore, compounds **IVa-c** were isolated by extraction with diethyl ether and compounds **Va-c** were extracted into chloroform. Also, the O- and N-substituted isomers can be separated by vacuum distillation (the boiling points of the latter range from 80 to 100 ºC) or by preparative thin-layer chromatography on aluminum oxide (eluent chloroform-diethyl ether, 5:1; R_f 0.46 and 0.78 for the O- and N-alkylated substituted isomers, respectively).

While O-Alkyl derivatives were occurring in high yields between 34-42 %, N-Alkyl derivatives were occurred in low yields (between 6.5-8.5%). The detailed information including synthesis procedure, characterization studies and physico-chemical properties about these synthesized compounds had been given in previous study[4].

***in vitro* Biological assay**

Medium: As a solid media, Muller-Hinton Agar (MHA) was prepared as follows: Beef infusion 300 g/L, casein acid hydrolysate 17.5 g/L, starch 1.5 g/L, agar-agar 17 g/L and distilled water 1000 mL, adjusted to pH 7.4) were used for the biological assay of all of the synthesized compounds.

Test microorganisms: Four Gram-positive bacteria *B. cereus* (ATCC 11778), *S. aureus* (ATCC 6538), *S. lutea* (ATCC 9341) and *S. mutans* (UCTC 10499) and three Gram-negative bacteria *S. typhimurium* (1,4,5,12:;:1,2), *P. aeruginosa* (ATCC 27853) and *E. coli* (ATCC 29998) were used for biological assays.

Antibacterial activity test: To determine the sensitivity of one strain in each bacterial species against four compounds, (**IVa-c**) was carried out by disc diffusion test. The solutions of compounds (**IVa-c**) (0.1 mg/mL) were prepared by dissolving 10 mg of the test compound in pure water (100 mL). Cefalexin (30 µg/disc) and pure water were used as positive and negative controls, respectively. For this activity test, 20 mL of Mueller-Hinton agar (Difco) was melted at 100 ºC and after cooling to 56 °C, it was poured into Petri plates and left on a flat surface to solidify and the surface of the medium was dried at 37 °C. Then, the cultures of each bacterium, after being kept in Muller-Hinton broth (Difco) at 37 °C for 24 h and diluted with Mueller-Hinton broth to 1×10^8 CFU/mL, were pipetted into the Muller-Hinton agar plate prepared as described above. The surface of the medium was allowed to dry. Then, sterile 6 mm diameter filter paper discs were impregnated with 25 µL of each of the test solutions/disc and placed onto the surface of inoculated labeled Petri plates. The Petri plates were placed in an incubator at 37 °C. After 24 h of incubation, the Petri plates were examined and the diameter of the clear zone of growth inhibition around each disc containing the test compound was measured accurately with using a Vernier Caliper and expressed in millimeters as its antibacterial activity (Table-1). Each test was run in triplicate.

TABLE-1
in vitro ANTIBACTERIAL ACTIVITY OF THE COMPOUNDS (**IVa-c**) BY USING DISC DIFFUSION ASSAY TECHNIQUE

Compd.	Diameter of zone of growth inhibition (mm)						
	Bc	Sa	Sl	Sm	St	Pa	Ec
IVa	24	29	39	30	21	31	22
IVb	15	8	24	13	18	28	18
IVc	11	36	37	33	–	29	13
Cefalexin	20	30	44	30	16	–	12

– = no activity; Bc = *B. cereus* (ATCC 11778); Sa = *S. aureus* (ATCC 6538); Sl = *S. lutea* (ATCC 9341); Sm = *S. mutans* (UCTC 10499); St = *S. typhimurium* (1,4,5,12:;:1,2); Pa = *P. aeruginosa* (ATCC 27853) and Ec = *E. coli* (ATCC 29998).

RESULTS AND DISCUSSION

The antibacterial activity of compounds (**IVa-c**) was evaluated by using disc diffusion method[18] against pathogenic four Gram-positive bacteria *Bacillus cereus* (ATCC 11778), *Staphylococcus aureus* (ATCC 6538), *Sarcina lutea* (ATCC 9341) and *Streptococs mutans* (UCTC 10499) and three Gram-negative bacteria *Salmonella typhimurium* (1,4,5,12:;:1,2), *Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 29998) (Table-1). As can be seen, while compounds (**IVa**) and (**IVb**) exhibit activity against all bacteria, (**IVc**) shows all of Gram-positive bacteria and two Gram-negative bacteria *Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 29998). Among all compounds, which (**IVa**) owned the highest activity against *Escherichia coli* (ATCC 29998) as compared to cefalexin was used in the cure of a number of infections such as ears, nose or throat, skin or wound, urinary system, organs (*i.e.*, lungs), *etc*. and least activity against *Staphylococcus aureus* (ATCC 6538) was showed by (**IVb**). In addition, when all compounds were compared with each other, (**IVa**) was generally found more active than (**IVb**) and (**IVc**) against all the strains of bacteria under this study owing to the fact that the electron-withdrawing pyridine nitrogen atom in the *ortho* position with regard to the oximinic group leads to increment of polarization of oximinic group resulting from inductive effect[11]. On the basis of the present results, it is concluded that higher polarization of oximinic group in a compound, higher biological activity of the compound.

In conclusion, a new derivatives of [(2-hydroxypropyl)-*n*-oximino]pyridines have been prepared and their structures were characterized by using spectroscopic data. They were also evaluated for antibacterial activity against both Gram-positive and Gram-negative bacteria *in vitro* comparable to cefalexin.

The antibacterial activity in terms of zone of inhibition was exhibited by all the compounds against all bacteria except for *Salmonella typhimurium* (1,4,5,12:;:1,2). The compound (**IVa**) showed excellent activity against *Bacillus cereus* (ATCC 11778), *Sarcina lutea* (ATCC 9341), *Salmonella typhimurium* (1,4,5,12:;:1,2) and *Escherichia coli* (ATCC 29998) compared to cefalexin. As can be seen from Table-1, the high activity of the compound (**IVa**) reveals that it was suitable for supplemental *in vivo* and *in vitro* studies in order to develop new antibacterial drugs or prodrugs which can be probably used in a number of infection diseases treatments. Moreover, this present work may also provide valuable information to the researchers working on this subject due to the limited study in literature.

ACKNOWLEDGEMENT

This study was supported financially under project number: BAP (2001-1006) by the Foundation of Scientific-Research Projects of Selcuk University.

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(*Received*: 29 October 2007; *Accepted*: 8 February 2008) AJC-6334