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Antimicrobial study of pyrazine, pyrazole and imidazole carboxylic acids and their hydrazinium salts

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Summary

Some new hydrazinium salts of 2-pyrazinecarboxylate, 2,3-pyrazinedicarboxylate, 3,5-pyrazoledicarboxylate and 4,5-imidazoledicarboxylate have been prepared. The *in vitro* antibacterial screening of the free acids and their hydrazinium salts has been carried out against *Escherichia coli, Salmonella typhii* and *Vibrio cholerae*. The antibacterial activities of the prepared hydrazinium salts show more promising activity than the corresponding free acids and the standard positive control antibiotic, Co-trimoxazole.

Introduction

Dibasic acids are known to form N_2H_5HA, $(N_2H_5)_2A$ and $N_2H_5HA.H_2A$ types of salts (H_2A = dibasic acid) with hydrazine. The preparation of hydrazinium salts has become a subject of recent interest due to their wide use as additives in propellants, explosives, and as drugs to treat cancer and Hodgkin's disease (Schmidt 1984). The preparation and thermal behaviour of some of these salts have recently been reported from our laboratory with a few aliphatic (Yasodhai & Govindarajan 1999) and aromatic (Kuppusamy *et al.* 1995) carboxylic acids. However, the antibacterial activity of hydrazinium salts has not been studied to date. It was, therefore, considered interesting to prepare the hydrazinium salts of 2-pyrazinecarboxylic and 2,3-pyrazine-, 3,5-pyrazole- and 4,5-imidazoledicarboxylic acids (Figure 1) and study their antibacterial activity.

Materials and methods

Microorganisms

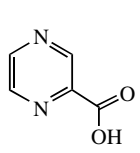
Three pathogenic microorganisms were used to test the biological potential of the free carboxylic acids and their hydrazinium salts. They were (i) *Escherichia coli,* (ii) *Salmonella typhi* and (iii) *Vibrio cholerae,* obtained from the stock cultures of the Microbiology Laboratory of the Department of Environmental Sciences, Bharathiar University, Coimbatore, India.

Activity testing

The antibacterial activity of the compounds was determined by the disc diffusion method (Cruickshank 1968). The bacteria were cultured in nutrient agar medium and used as inoculum for the study. Bacterial cells were swabbed onto nutrient agar medium (prepared from NaCl 5.0 g, peptone 5.0 g, beef extract powder 3.0 g, yeast extract powder 3.0 gagar 20.0 g in 1000 ml distilled H_2O; pH = 7.5 ± 0.2) in Petri dishes.The test solutions were prepared in distilled water to a final concentrations of 1%, 2% and 4% and then applied to filter paper discs (Whatmann No. 4, 5 mm dia).These discs were placed on the already seeded plates and incubated at 35 ± 2 °C for 24 h. The zone of inhibition around the discs were measured after 24 h. Co-trimoxazole was used as a standard positive control.

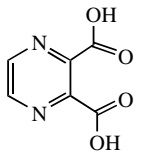
Hydrazinium salts

The monohydrazinium salts such as N_2H_5pyzCOO, N_2H_5pyzCOO·H_2O, N_2H_5Himdc, N_2H_5Himdc·H_2O, N_2H_5Hpyz$(COO)_2$ and N_2H_5 Hpz$(COO)_2$ and dihydrazinium salts, namely, $(N_2H_5)_2$pyz$(COO)_2$, $(N_2H_5)_2$pyz$(COO)_2$·H_2O and $(N_2H_5)_2$pz$(COO)_2$ and also the other kind of acidic salts such as (N_2H_5)Hpyz$(COO)_2$·H_2 pyz$(COO)_2$, (N_2H_5)Hpz$(COO)_2$·H_2pz$(COO)_2$ and (N_2H_5)Hpz$(COO)_2$·$(H_2pz(COO)_2)_3$ have been prepared by neutralization of aqueous hydrazine hydrate with the respective acids in the appropriate molar ratios (Premkumar 2002; Premkumar & Govindarajan 2003).



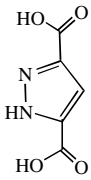
2-pyrazinecarboxylic acid

(HpyzCOO)



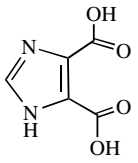
2,3-pyrazinedicarboxylic acid

($H_2pyz(COO)_2$)



3,5-pyrazoledicarboxylic acid

($H_2pz(COO)_2$)



4,5-imidazoledicarboxylic acid

(H_2imdc)

Figure 1. The structures of 2-pyrazinecarboxylic and 2,3-pyrazine-, 3,5-pyrazole- and 4,5-imidazoledicarboxylic acids.

Table 1. Antibacterial activity (the test solution was prepared in distilled water).

Compound	Diameter of inhibition zone (mm)								
	E.coli			*S.typhii*			*V.Cholerae*		
	1%	2%	4%	1%	2%	4%	1%	2%	4%
Hpyz(COO)	–	9	11	–	–	9	6	8	10
$N_2H_5pyz(COO)$	9	10	12	7	8	11	9	11	24
$N_2H_5pyz(COO) \cdot H_2O$	8	9	12	7	7	10	8	10	19
$H_2pyz(COO)_2$	–	9	11	9	9	12	9	11	14
$N_2H_5Hpyz(COO)_2$	9	11	15	–	10	21	9	13	32
$(N_2H_5)_2pyz(COO)_2$	10	13	28	9	16	37	10	14	35
$(N_2H_5)_2pyz(COO)_2 \cdot H_2O$	10	13	29	9	17	36	11	13	34
$N_2H_5Hpyz(COO)_2 \cdot H_2pyz(COO)_2$	10	11	13	9	10	14	11	11	15
$H_2pz(COO)_2 \cdot H_2O$	–	6	8	–	7	9	–	6	7
$N_2H_5Hpz(COO)_2$	–	8	11	6	9	12	6	8	10
$(N_2H_5)_2pz(COO)_2$	9	16	25	10	16	34	10	17	32
$N_2H_5Hpz(COO)_2 \cdot H_2pz(COO)_2$	–	8	10	6	8	12	7	7	11
$N_2H_5Hpz(COO)_2 \cdot (H_2pz(COO)_2)_3$	6	8	10	–	8	8	7	9	10
H_2imdc[a]	–	–	–	–	–	–	–	–	–
N_2H_5Himdc	6	8	11	6	9	12	–	11	12
$N_2H_5Himdc \cdot H_2O$	6	8	11	6	8	11	–	11	12
Co-trimoxazole	6	7	10	6	9	11	7	8	10

Diameter of zone of inhibition is a mean of triplicates.
[a] Insoluble.
–: no activity.

Results

These are reported in Table 1. Antibacterial studies of the simple hydrazinium salts have not previously been carried out. The results suggest that the antibacterial activity of the prepared hydrazinium salts shows more promising effects than the acid and the standard antibiotic, Co-trimoxazole.

Conclusions

It is worthwhile noting that the antibacterial activity increases as the number of hydrazine moieties increases. Thus it is evident that the dihydrazinium salts showed a greater area of inhibition than those of monohydrazinium salts and free acids.

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